Identifiers: NCT05546411

Unique Protocol ID: 22-314

Brief Title: A Trial of NIS793 With FOLFIRINOX in Pancreatic Cancer

Full Title: A Phase 2 study of neoadjuvant NIS793 in Combination with mFOLFIRINOX in resectable and borderline resectable pancreatic adenocarcinoma (PDAC)

Date document downloaded from OncPro portal: 4.26.2024

Document Date: Protocol Version: 03.13.2023

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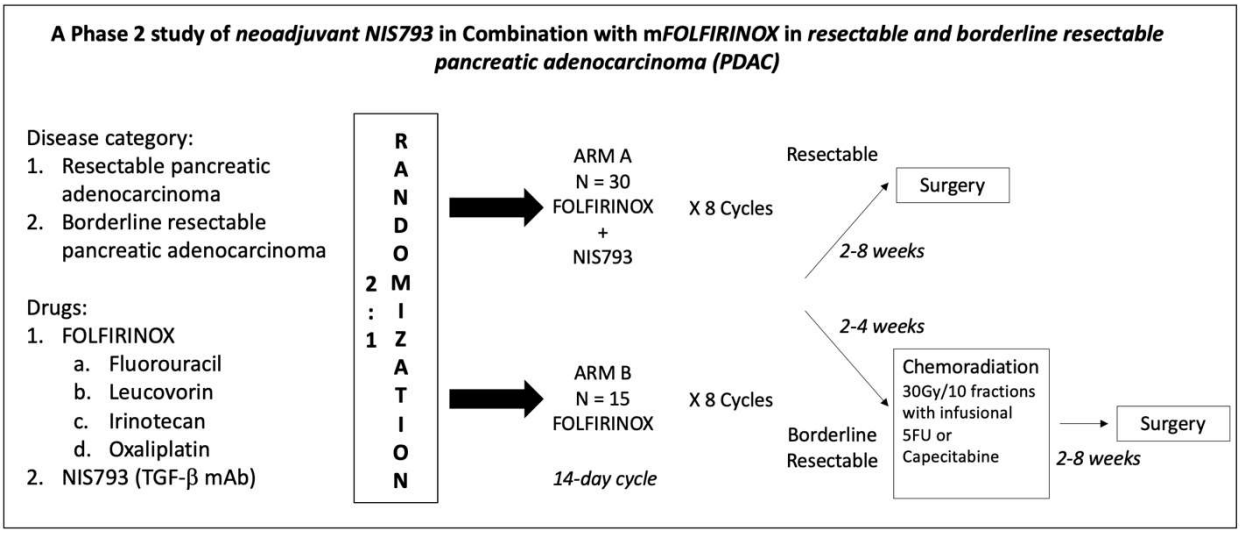
NCI-Supplied Agent: Not applicable
Other Agent: NIS 793, supplied by Novartis Pharmaceuticals Corporation

IND #: 161866
IND Sponsor: Kimberly Perez, MD
Protocol Type / Version # / Version Date: [Revised / Version 3 / March 13, 2023]

SCHEMA


A Phase 2 study of neoadjuvant NIS793 in Combination with mFOLFIRINOX in resectable and borderline resectable pancreatic adenocarcinoma (PDAC)
Disease category:
1. Resectable pancreatic adenocarcinoma
2. Borderline resectable pancreatic adenocarcinoma
Drugs:
1. FOLFIRINOX
a. Fluorouracil
b. Leucovorin
c. Irinotecan
d. Oxaliplatin
2. NIS793 (TGF-β mAb)
RANDOMIZATION 2:1
ARM A
N = 30
FOLFIRINOX
+
NIS793
X 8 Cycles
Resectable
Surgery
2-8 weeks
2-4 weeks
ARM B
N = 15
FOLFIRINOX
X 8 Cycles
14-day cycle
Borderline Resectable
Chemoradiation
30Gy/10 fractions with infusional 5FU or Capecitabine
Surgery
2-8 weeks

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1. OBJECTIVES

1.1 Study Design

This is a randomized phase 2 study which includes subjects with previously-untreated, resectable or borderline resectable pancreatic adenocarcinoma. The study will evaluate the efficacy of NIS793, a TGF-beta inhibitor, when added to a standard chemotherapy program of modified FOLFIRINOX (mFOLFIRINOX) in the neoadjuvant setting. The terms FOLFIRINOX or mFOLFIRINOX are used interchangeably during this protocol. Preoperative radiation therapy will be administered to the subset of patients with borderline resectable disease.

1.2 Primary Objective

To evaluate the efficacy of the addition of NIS973 to the standard chemotherapy program of mFOLFIRINOX, as defined by major pathological response rate (MPR) in patients with resectable or borderline resectable pancreatic adenocarcinoma.

1.3 Secondary Objectives

1.3.1 To evaluate the safety and tolerability of the investigational agent NIS793, a TGF-beta inhibitor, in combination with mFOLFIRINOX, in patients with resectable or borderline resectable pancreatic adenocarcinoma.

1.3.2 To evaluate the progression-free survival (PFS) and overall survival (OS) of the investigational agent NIS793, a TGF-beta inhibitor, in combination with mFOLFIRINOX, in patients with resectable or borderline resectable pancreatic adenocarcinoma.

1.4 Exploratory objectives

By comparing to control Arm B (mFOLFIRINOX alone):

1.4.1 To explore the influence of combined TGF-beta inhibition and mFOLFIRINOX on the

tumor microenvironment and tumor immune cell infiltrate.

1.4.2 To explore the influence of combined TGF-beta inhibition and mFOLFIRINOX on the evolution of various immune cell populations in the peripheral blood during and after completion of therapy.

1.4.3 To explore tumor derived predictive biomarkers for efficacy of combined TGF-beta inhibition and mFOLFIRINOX.

1.4.4 To explore peripheral blood based immune cell and plasma derived predictive biomarkers for efficacy of combined TGF-beta inhibition and mFOLFIRINOX.

1.4.5 To explore radiomics of pancreatic adenocarcinoma for correlations with immune-related endpoints, responses, and clinical outcomes.

2. BACKGROUND

2.1 Study Disease(s)

Pancreatic cancer

Pancreatic cancer is estimated to become the second leading cause of cancer death by 2030, (1) with an overall 5-year relative survival rate of 5.6%(2). Surgery remains the only chance for cure for patients diagnosed with resectable disease, however, only 10-15% of patients present with operable disease. Among the subset of patients who undergo resection and go on to receive adjuvant therapy, the disease free survival (DFS) and the chances of 5- year survival are dismal (13.4 months and 20%, respectively)(3). In recent years, most drug development efforts have been directed towards patients with metastatic disease,(4, 5) and progress in identifying new therapeutic options has been slow. Limitations have been attributed to difficulties permeating the tumor bulk and the growth-permissive, immunosuppressive tumor microenvironment.

Neoadjuvant chemotherapy in pancreatic cancer

Given the prognostic importance of the surgical margins status of localized pancreatic cancers that are treated operatively, these tumors are traditionally classified into two main categories, resectable and unresectable disease. This classification is based on the vessels involvement by the tumor including the superior mesenteric artery, celiac axis, common hepatic artery and superior mesenteric portal vein(6). Resectable pancreatic cancers are cancers for which R0 resection is believed to be technically possible and therefore have been traditionally treated surgically. In contrast, unresectable pancreatic cancers are tumors for which R0 resection is believed to be unlikely and therefore are treated nonsurgical similar to metastatic disease with chemotherapy (6, 7). A subset of potentially resectable pancreatic cancers is defined as "borderline resectable pancreatic cancers". These tumors have a limited involvement of the mesenteric vasculature, and therefore, they are at high risk for margin-positive post resection (6, 7). Based on the Alliance Intergroup Criteria(8) borderline resectable pancreatic cancers are defined radiographically as: localized cancers with 1 or more of: (1) An interface between the primary tumor and SMV-PV measuring 180 degrees or greater of the circumference of the vein wall, and/or (2) short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction, and/or (3) short-segment interface (of any degree) between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction, and/or (4) an interface between the tumor and SMA or celiac trunk measuring less than 180 degrees of the circumference of the artery wall(8). Neoadjuvant therapy has been advocated as a potential way to improve outcomes of patients with resectable or borderline resectable pancreatic cancer (9-16).

Neoadjuvant therapy has theoretical benefits of: allowing a greater proportion of patients to complete a full course of adjuvant therapy; avoiding resection in patients with occult metastatic disease at time of presentation which becomes evident on preoperative staging; and improving the chance of achieving a microscopically negative margin (R0) at resection. The neoadjuvant approach also provides the opportunity to have access to tumor tissue following therapy, giving investigators the opportunity to study the treatment's mechanism of action(14, 17).

A variety of neoadjuvant approaches have been suggested in pancreatic cancer including chemotherapy, chemoradiation therapy or both (9-13). However, no consensus has been reached in regards to which modality is most effective (18).

The choice of chemotherapy in the neoadjuvant setting has been informed by agents that are active in the adjuvant and metastatic setting(3, 19-21). The PRODIGE-24 phase III study, conducted in the adjuvant setting, demonstrated that FOLFIRINOX compared to gemcitabine resulted in an improvement in median overall survival (54.4 vs 35.0 months. HR 0.64; 95% CI, 0.48 to 0.86; P=0.003) (22). In the metastatic setting, where tumor response can be assessed, results from the ACCORD-11 study demonstrated that objective response rate with FOLFIRINOX was 31.6% versus 9.4% in a gemcitabine control (4).

Multiple small phase II studies have evaluated the role of neoadjuvant therapy utilizing a range of chemotherapeutic agents. One study which evaluated FOLFORINOX and radiation in 48 patients with borderline-resectable pancreatic cancer demonstrated a median OS of 37.7 months (95% CI, 19.4 to not reached)(16). Three trials that have compared multi-modality neoadjuvant therapy to surgery followed by adjuvant therapy. The phase III PREOPANC trial compared outcomes with preoperative chemoradiotherapy vs immediate surgery for *resectable or borderline resectable* pancreatic cancer. Chemoradiotherapy consisted of 3 cycles of gemcitabine, combined with 15 fractions of 2.4 Gy radiotherapy. Disease-free survival, locoregional failure-free survival, R0 resection rate (71% v 40%), and pathologic response favored neoadjuvant therapy. PEROPANC used a dated chemotherapy regimen at a modest dose (23), however, the ESPAC-5f trial is comparing upfront surgical exploration for *borderline resectable* pancreatic cancer, to gemcitabine plus capecitabine (GEMCAP), or FOLFIRINOX or 50.4Gy capecitabine-based CRT.(24) Initial results demonstrated survival rates for the specific neoadjuvant regimens were 84% for FOLFIRINOX, 79% for GEMCAP and 65% for CRT (25). In the third trial, Alliance A021501, patients were randomized to either neoadjuvant mFOLFIRINOX or mFOLFIRINOX followed by radiation therapy. Patients who received radiation therapy did not have improved survival and had numerically lower rates of R0 pancreatectomy (42% vs 25%), initiation of postop therapy (33% vs 24%) and completion of all treatment (30% vs 18%). 64% of patients in this study had ≥1 grade 3+ adverse events, and 17% had ≥1 grade 4+ adverse events (26).

Several radiation regimens have also been utilized. Apart from the trials described above, trials have used regimens such as FOLFIRINOX followed by either short-course chemoradiotherapy (5 Gy × 5 with protons) with capecitabine or long-course radiotherapy (50.4 Gy in 28 fractions) with capecitabine or continous 5FU (15, 16). Some centers also apply intraoperative radiation therapy

(IORT) to improve local control (27). Others utilize MRI-guided radiation therapy (28).

Major academic centers, including Dana-Farber Cancer Institute and MD Anderson Cancer Center, have adopted neoadjuvant chemotherapy with 4-8 cycles of mFOLFIRINOX as a standard approach to treat patients with borderline resectable or resectable disease in order to increase the likehood of R0 resection and improve outcomes (14, 15). There are differing and evolving approaches to how best incorporate radiation therapy in the neoadjuvant setting. Radiation therapy is often considered for patients with borderline resectable disease to improve local control rates and R0 resection.

The role of the immune system in pancreatic cancer development and progression

Increasing evidence demonstrates that the immune system plays a major role in controlling tumor progression in a variety of tumors including pancreatic cancer. The tumor microenvironment is composed of tumor cells, cancer associated fibroblasts (CAFs), endothelial cells, and immune cells. The following immune cells are present in the tumor microenvironment: macrophages, dendritic cells (DCs), natural killer cells, mast cells (MCs), granulocytes, B cells and naïve and memory T cells which include cytotoxic CD8+ T cells and different subsets of CD4+ T and regulatory T cells (T-regs)(29-31). The tumor infiltrating immune cells interact with the tumor cells through secretion of chemokine and cytokines playing a regulatory role in tumor progression(32). When cancer develops the immune system plays a dual role: (i) it destroys cancer cells or inhibits their growth and (ii) it promotes tumor progression via production of innate inflamatory cytokines that promote immune suppression and/or directly promote tumor cell survival pathways such as NF-kB (33). Therefore, it is critical to understand the balance between the tumor-promoting innate immune response and the tumor-suppressing adaptive immune response against tumors (34, 35). Pancreatic cancer is unique from immunological perspective. First, intratumoral effector T cells in proximity to tumor cell nests are rare, in contrast to many other solid tumors for which infiltration of effector T cells is often prominent (36). Second, the ras oncogene drives an inflammatory program that establishes immune privilege in the pancreatic tumor microenvironment (37). Third, pancreatic cancer is associated with a massive infiltration of immunosuppressive leukocytes in the tumor microenvironment (36). In addition, the development of pancreatic tumors is usually associated with a strong

desmoplastic reaction that is consists of multiple cell types, molecular factors, and extracellular matrix (38-40). Accordingly, the tumor immune microenvironment and the balance between the effector cell signal and suppressor cell signal in pancreatic cancer deserve to be investigated further in order to develop an effective treatment approach.

The Effect of Neoadjuvant FOLFIRINOX on The Pancreatic Tumor Immune Microenvironment (TIME) Chemotherapeutic agents can increase the immunogenic properties of tumor cells by enhancing MHC class I expression, thereby increasing their vulnerability to cytotoxic T lymphocytes (CTLs). Using multiplexed immunofluorescence (mIF)and digital image analysis, our group has analyzed pancreatic tumors who either underwent upfront resection (n=27) or received neoadjuvant FOLFIRINOX prior to resection (n=33) (Figure 1). We found that neoadjuvant treatment with FOLFIRINOX was associated with higher density of CD8+ T lymphocytes (median CD3+CD8+ 218.7 v.s. 124.7 cells/mm2, p=0.005), while CD4+ T lymphocyte density remained unchanged, resulting in a lower CD4/CD8 ratio (median CD4/CD8 ratio 1.09 v.s. 3.46, p<0.001) in neoadjuvant-treated tumors. Within the CD3+CD8+ subpopulation, naïve CD8+ T lymphocyte density was relatively increased (median CD3+CD8+CD45RO- 34.02 v.s. 4.31 cell/mm2, p<0.001) as compared to memory CD8+ T lymphocyte density (median CD3+CD8+CD45RO+ 178.6 v.s. 120.72 cell/mm2, p=0.04). Analysis of macrophage density and polarization revealed that neoadjuvant FOLFIRINOX was associated with pro-inflammatory

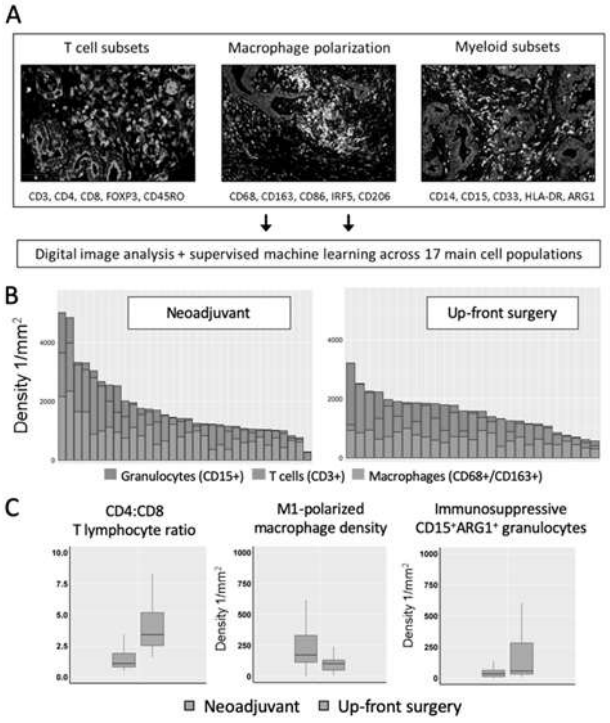

Figure 1. Evaluation of the PDAC TIME. (A) Three 7-plex mIF panels were developed to profile T cell subsets, myeloid cell subsets and macrophage polarization in situ using digital images analysis and supervised machine learning. (B-C) Density distributions for the main immune cell populations in matched neoadjuvant and up-front surgery cases show that neoadjuvant therapy has minimal changes to overall immune cell density and composition, multiple immune cell subpopulations shift to a more pro-inflammatory, anti-tumorigenic state.

M1-like macrophages (median 183.14 v.s. 102.7 cell/mm2, p<0.001), whereas stromal density of immunosuppressive M2-like macrophages was decreased (median 189.49 v.s. 231.12 cell/mm2, p=0.03). Finally, neoadjuvant treatment was associated with decreased density of CD15+ granulocytes with immunosuppressive ARG1 expression (median CD15+Arg1+ 35.92 v.s. 61.95 cell/mm2, p=0.01). Overall, these results indicate that treatment with FOLFIRINOX is associated with changes in the composition of the pancreatic cancer immune microenvironment, with altered distributions of T lymphocytes, shifted macrophage polarization and reduced granulocytic immunosuppressive activity.

TGF-Beta and PDAC

Given the disappointing results of PD-1 inhibitor in PDAC, there is a crucial need to test a novel approach to prime the pancreatic TIME prior to introducing PD-1 blockade. We have identified the TGFβ pathway, and specifically NIS793, as an agent that could potentially augment the immune response to pancreatic cancer and by doing so, improve patient outcomes. TGFβ plays an important regulatory role in the inflamed and neoplastic pancreas (41, 42). In acinar and pre-neoplastic epithelial cells, TGFβ signals through nuclear translocation of SMAD2/4/5 and induces an anti-proliferation signal (42). PanIN lesions and early-stage pancreatic ductal adenocarcinoma (PDAC) are sensitive to TGFβ, and blockade of TGFβ signaling in epithelial cells leads to rapid outgrowth and disease progression (43-45). However, loss of SMAD4 is a frequent event in PDAC and renders these tumors insensitive to the growth inhibitory effects of TGFβ (46-48) (6-8). At the same time, TGFβ signaling in pancreatic stellate cells leads to upregulation of SMA, differentiation of myofibroblasts, and enhanced deposition of extracellular matrix (ECM), contributing to fibrosis (43, 49). TGFβ signaling in CD4 T cells can convert them to Foxp3-expressing regulatory T cells (Tregs) which protects against tumor-promoting inflammation in early stages of disease but inhibit CD8 T cell function in established tumors (50). TGFβ signaling in CD8 T cells attenuates their proliferation and cytokine production (51). In mouse models of pancreatitis, TGFβ can ameliorate inflammation, demonstrating the important role of this cytokine in immune homeostasis of the pancreas. In

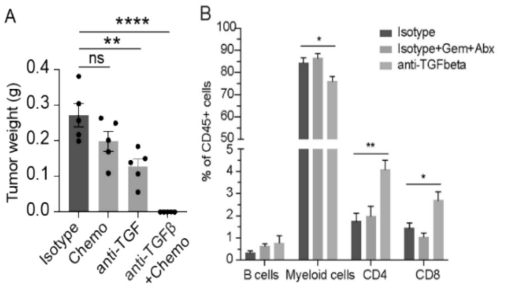

Figure 2: Anti-TGFβ+chemo is effective in poorly immunogenic 6694c2 orthotopic tumors. A) Tumor weights of mice treated starting on day 2. B) Tumors were digested and analyzed by flow cytometry.

models of colorectal and other fibrotic cancers, TGFβ blockade alters the stromal compartment to allow for influx of activated CD8 T cells and, in combination with PD-1 or PD-L1 blockade, immune-mediated tumor regression (52, 53). Mouse models of pancreatic cancer have been less responsive to single agent TGFβ blockade, however the stromal modulating properties of TGFβ blockade may synergize in appropriately designed combination strategies (54, 55), including combination with radiation therapy and PD-L1 blockade (56).

Blockade of TGFβ as a monotherapy has relatively little efficacy in pancreatic cancer (54, 55); however, we hypothesized that TGFβ blockade would be effective in combination with standard of care chemotherapy. We recently tested this hypothesis using an orthotopic model of murine PDAC that contains relatively few T cell infiltrates and has shown no response to anti-PD1/anti-CTLA4 therapy. We used a TGFβ blocking antibody (NIS793) in combination with gemcitabine and n(ab)-paclitaxel and showed that while TGFβ blockade monotherapy induced a slight reduction in tumor size, the combination treated mice were all cured. TGFβ blockade alone induced a significant increase in intratumoral CD8 T cells, consistent with a hypothesis that TGFβ restricts accumulation of CD8 T cells in tumors (Figure 2). Histological evaluation using Masson's trichrome staining revealed a reduction in ECM deposition in both chemotherapy alone and single-agent TGFβ blockade groups. When therapy was initiated at day 2 post-inoculation, all mice were apparently tumor-free. To evaluate the effects of combination therapy, we started treatments at day 4, when tumors are more established, and the combination would ideally be less effective. Indeed, this treatment delay did allow tumor outgrowth in all groups, although notably both TGFβ blockade and combination treatment significantly extended mouse survival. Use of the Novartis clinical grade reagent NIS793 was also effective at decreasing PDAC tumor size and increasing survival.

We have shown that a TGFB1/2 blocking antibody NIS793 blocks SMAD2 signaling in pancreatic cancer cells, depletes aSMA+ fibroblasts from orthotopic 6694c2 tumors, and reduces tumor burden in combination with either gemcitabine/n(ab)paclitaxel or FOLFIRINOX in mice (Figure 3) (57).

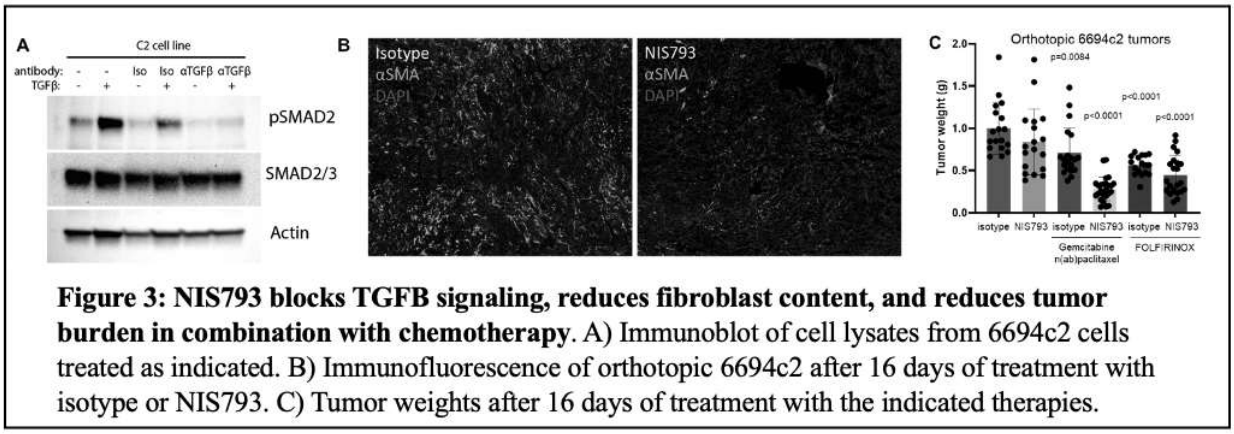

Figure 3: NIS793 blocks TGFB signaling, reduces fibroblast content, and reduces tumor burden in combination with chemotherapy. A) Immunoblot of cell lysates from 6694c2 cells treated as indicated. B) Immunofluorescence of orthotopic 6694c2 after 16 days of treatment with isotype or NIS793. C) Tumor weights after 16 days of treatment with the indicated therapies.

We profiled primary pancreatic tumors from mice treated with NIS793 +/- chemotherapy by single cell transcriptional profiling after bead enrichment for fibroblasts. Sub clustering on fibroblasts revealed a cycling population and several flavors of myCAFs and iCAFs, as well as a CXCL1/2/5+Saa3+ population that uniquely appeared in tumors treated with NIS793 + FOLFIRINOX. (Figure 4).

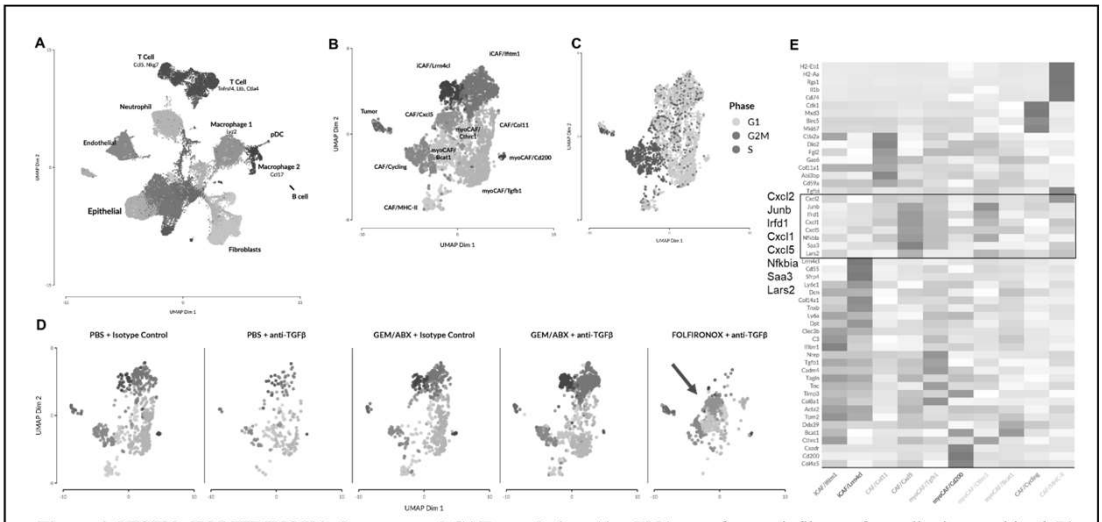

Figure 4: NIS793+FOLFIRINOX induces a novel CAF population. A) scRNA seq of tumor infiltrates from all mice combined. B) Subclustering of fibroblasts. C) Cell cycle gene signature overlaid on fibroblast uMAP. D) Separation of fibroblasts by treatment regimen. E) Top cluster defining genes among fibroblasts.

To assess the effects of combination NIS793 treatment on tumor cells, we evaluated the transcriptional profiles of subclustered tumor cells and found that NIS793 strongly skews tumor

cells in vivo to a classical cell state. This skewing was further exemplified by expression of the classical lineage marker Tff2 (Figure 5). Based on these data, we hypothesize that TGFB blockade with NIS793, a novel clinical grade anti-TGFB1/2 antibody, disrupts a critical trophic tumor cell-CAF signaling network to polarize tumor cells to a classical lineage and sensitize to chemotherapy.

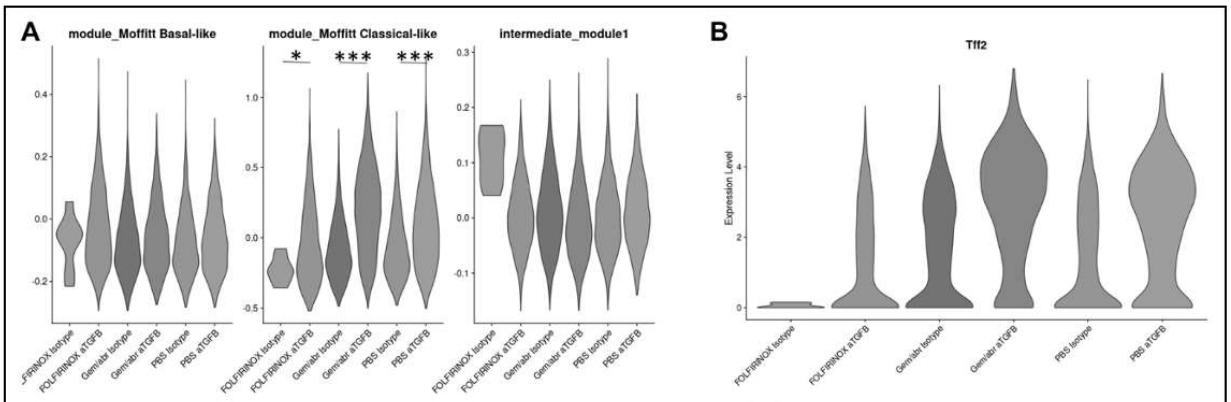

Figure 5: NIS793 induces a classical phenotype in PDAC tumor cells. A) Basal, classical, and intermediate signatures in tumor cells from orthotopic 6694c2 tumors treated with NIS793 +/- chemotherapy. B) Expression of the classical marker Tff2.

Radiomics of PDAC

We have previously shown that quantitative imaging features of PDAC associate with the delivery of, response to, and outcome after gemcitabine-based therapy and radiation (58). These findings were further validated in retrospective datasets and prospective trial, focusing on a reproducible and visually apparent imaging feature prior to treatment termed the delta classification (59, 60). These studies demonstrate that patients with high delta PDAC demonstrate less stroma, more immunosuppressive elements in the TME, poorer responses to cytotoxic therapies, and worse survival outcomes, compared to those with low delta PDAC. Furthermore, we have identified a metric of response on conventional contrast-enhanced computed tomography (CT) scans that focuses on how the interface of the tumor changes during cytotoxic therapies. This interface response associated with pathological response to neoadjuvant therapy and survival outcomes of patients with resectable, borderline resectable, locally advanced, and metastatic PDAC in retrospective and prospective studies (59, 61). Here, we propose correlating these two imaging features of PDAC on CT scans with our immune-related measurements and the clinical outcomes in the two arms, hypothesizing that patients with high delta tumors and poor interface responses will exhibit differential responses to the experimental therapy, compared to low delta tumors.

2.2 IND Agent NIS793 (TGF-beta inhibitor)

NIS793 is a recombinant, human anti TGFβ, IgG2 monoclonal antibody. Based on the mechanistic and preclinical data above, we hypothesize that combination of NIS793 and standard of care FOLFIRINOX could improve outcomes for patients with resectable or borderline resectable pancreatic cancer.

NIS793 specifically antagonized TGFβ1 and TGFβ2 and to a lesser extent, TGFβ3. Inhibition of TGFβ in the tumor microenvironment has multiple benefits (62) that are particularly relevant to pancreatic cancer. The pancreatic tumor microenvironment is notoriously immunosuppressive with a strong desmoplastic reaction. TGFβ signaling is a mediator of epithelial-mesenchymal transition, extracellular matrix regulation, and potent immunosuppression (62). Inhibition of these pathways are hypothesized to alter the pancreatic tumor microenvironment and increase pathological and clinical responses to therapy. In murine models, specific inhibition of TGFβ1 and TGFβ2, without TGFβ3, was sufficient to augment immunological effects of vaccine and PD-1 checkpoint inhibition (63). In addition, in our murine model of pancreatic cancer described above, NIS793 demonstrated synergy with FOLFIRINOX chemotherapy.

Multiple strategies have been developed to achieve TGFβ inhibition, including anti-sense oligonucleotides, neutralizing antibodies or soluble receptors, and inhibitors of intracellular signaling(62). Several agents have been evaluated in clinical trials including fresolimumab, a pan-TGFβ humanized antibody; LY3022859, an IgG1 monoclonal antibody targeting TGFβRII; and galunisertib (LY2157299), a small molecule inhibitor of TGFβRI. However, there is no approved TGFβ inhibitor for the treatment of pancreatic cancer.

NIS793 is currently under investigation in two prospective combination studies and has thus far had an acceptable toxicity profile. As of 18-May-2021, a total of 129 patients have been treated with NIS793 alone or in combination with other agents.

The first trial is evaluating NIS793 alone or in combination with spartalizumab (anti PD-1 antibody) in adult patients with solid malignancies. The trial closed to enrollment due to limited

efficacy on interim analysis. There were no dose limiting toxicities attributed to NIS793 in this trial. The second trial is a phase II randomized, open label, parallel arm study of NIS793 (with and without spartalizumab) in combination with SOC chemotherapy gemcitabine/nab-paclitaxel, and SOC alone in first-line metastatic pancreatic ductal adenocarcinoma (mPDAC). As of 26-Mar-2021, nine patients have been enrolled and treated in safety run-in part with NIS793 2100 mg Q2W and spartalizumab 400 mg Q4W in combination with gemcitabine 1000 mg/m2 Days 1, 8 and 15 and nab-paclitaxel 125 mg/m2 Days 1, 8 and 15. Out of nine patients, one patient (11.1%) experienced a DLT grade 3 colitis.

For complete information regarding dosing, pharmacokinetics, pharmacodynamics and updated safety information please refer to the most updated Investigator's Brochure. NIS793 has not been combined with FOLFIRINOX or radiation in clinical trials thus far.

2.3 *Modified FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)*

mFOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan) will be administered as neoadjuvant chemotherapy for resectable or borderline resectable disease per institutional standards. mFOLFIRINOX is a chemotherapy regimen comprised of 5-flurouracil, leucovorin, oxaliplatin and irinotecan. Dosing of these medications is as follows: *Fluorouracil 2400 mg/m2, Leucovorin 400 mg/m2, Irinotecan 150 mg/m2, Oxaliplatin 85 mg/m2.* mFOLFIRINOX has been extensively studied and characterized for the treatment of pancreatic and other cancers. It is a preferred regimen for the neoadjuvant treatment of resectable or borderline resectable pancreatic cancer per NCCN guidelines(14-16). For metastatic pancreatic cancer and for adjuvant therapy, it is a category 1 recommended regimen by NCCN guidelines, and it is also a preferred regimen for locally advanced disease.

For a comprehensive list of side effects and toxicities, please refer to the FDA label for the individual agents.

2.4 Rationale

Surgical resection continues to be the only hope for cure from pancreatic cancer, however, only 10-15% of patients present with resectable disease and those with negative surgical margins tend to have a favorable prognosis (64). Therefore, employing strategies to increase the proportion of resectable or borderline resectable pancreatic cancer patients who are able to undergo surgery with negative margins is of great importance.

Immune checkpoint blockade, including PD-1/PD-L1 and/or CTLA-4 inhibition, has yielded disappointing results in advanced pancreatic cancer (65, 66), and our experience in the neoadjuvant setting also suggests limited activity of PD-1 inhibition(67). Thus, there is a crucial need to test novel immunomodulatory approaches to altering the pancreatic tumor microenvironment and improving clinical outcomes.

In this trial, we will evaluate the effect of adding NIS793 to standard of care neoadjuvant mFOLFIRINOX, with or without radiation. mFOLFIRINOX is routinely administered at our institution as neoadjuvant treatment for resectable or borderline resectable pancreatic cancer. We anticipate that the immunomodulatory effects of TGFβ blockade (Section 1.1) will synergize with the pro-inflammatory, anti-tumor effects of mFOLFIRINOX (Section 1.1) in the tumor microenvironment. We hypothesize that this synergy will lead to improved major pathological response rate, the primary outcome of our study, as well as progression-free and overall survival.

NIS793 is being evaluated in the metastatic setting and as of 18-May-2021, there have been no dose limiting toxicities in 120 patients that received treatment as single agent or in combination with PD-1 inhibition. This supports the safety profile of this agent and the incorporation of NIS793 in the neoadjuvant setting, in combination with standard therapy.

The utilization of this regimen in the neoadjuvant setting will also allow for extensive correlative studies that will contribute to our understanding of the pancreatic TIME and inform future translational and clinical studies.

2.5 Correlative Studies Background

Neoadjuvant trials are exceptionally positioned to explore the biological and immunological effects of systemic cancer therapies. In this trial, we will collect biospecimens to elucidate the effect of combination immunotherapeutic agents with FOLFIRINOX on pancreatic cancer, the pancreatic cancer microenvironment, and systemic changes that are reflected in peripheral blood. These specimens will include pancreatic cancer tissue from the surgical resection or biopsy taken during attempted resection; peripheral blood, plasma and additional specimens.

To determine the additive effect of NIS793 beyond FOLFIRINOX, we plan to perform several correlative studies. Based on the preclinical data presented above, we hypothesize that NIS793 will lead to increased CD8 T-cell infiltration into the pancreatic tumor microenvironment, with expansion of tumor-associated T-cells in the tumor and peripheral blood. To test this hypothesis, we will enumerate CD8+ and CD8+CD45RO+ cells within and around the tumor and characterize the distributions of T-cells relative to intratumoral stroma. We will also sequence the unique T-cell receptors that are found in the tumor and peripheral blood, and compare clonal overlap.

We also hypothesize that the distribution of fibroblasts will be altered with NIS793 treatment. The role of TGF-beta in stroma formation suggests that alterations of the stromal compartment would be expected as well. These will be assayed by using scRNA-seq and more focused targeted immunofluorescence panels. We will further characterize tumor cell transcriptional state via transcriptional profiling and multiplex immunofluorescent panels.

We also hypothesize that there are unanticipated changes that will occur in the microenvironment with NIS793 treatment, that could provide further insight into the drivers of histological and / or clinical outcome. We are therefore planning to take an unbiased approach and leverage single cell and bulk RNA sequencing to describe the cellular composition and the transcriptomic landscape of pancreatic cancer treated with NIS793. We will also compare the cellular composition and transcriptomic landscape of tumors treated with NIS793 vs those in the control arm. Furthermore given likely heterogeneity to response to therapy we will compared tumors treated with NIS793 based on the level of histologic response to therapy.

Finally, for our radiomics investigations, we plan to measure the baseline and post-neoadjuvant CT scans of patients as previously described (58-61). We will compare the delta classification with the measures of immune infiltration and peripheral blood assays, hypothesizing that the high delta tumors will exhibit more immunosuppression than the low delta tumors based on these assays. We also hypothesize that the interface response on CT will further stratify patients based on these immune-related endpoints. Clinical outcomes will be correlated with the CT-based radiomic features and Kaplan Meier curves will be constructed, along with appropriate univariable and multivariable analyses.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

In order to be eligible for participation in this trial, the subject must:

3.1.1 The clinical, radiographic, and pathologic evidence support a diagnosis of pancreatic adenocarcinoma, with histology confirmatory for adenocarcinoma.

3.1.2 Subjects must be determined to meet the criteria for resectable or borderline resectable pancreatic cancer based on the M.D. Anderson Cancer Center (MDACC) and Alliance Intergroup Criteria classification at initial diagnosis (Table 1). Patients with locally advanced or metastatic disease are not eligible for this trial.

Table 1. Criteria for resectability of pancreatic cancer

Vessel	**Resectable**	**Borderline resectable**	**Locally advanced (Not Eligible)**
SMA	No extension; normal fat plane between the tumor and the artery	Interface between tumor and vessel measuring less than 180º of the circumference of the vessel wall	Encased (>180°)
Celiac axis	No extension	Interface between tumor and vessel measuring less than 180º of	Encased and no technical option for reconstruction usually

Vessel	Resectable	Borderline resectable	Locally advanced (Not Eligible)
		the circumference of the vessel wall	because of extension to the celiac axis/ splenic/left gastric junction or the celiac origin
Common hepatic artery		Reconstructable§, short-segment interface between tumor and vessel of any degree	
SMV/PV	Patent	Interface between tumor and vessel measuring 180º or greater of the circumference of the vessel wall, and/or reconstructable§ occlusion	Occluded and no technical option for reconstruction

Referenced from: Varadhachary et al., 2006(6) and Katz et al, 2013 (8). SMA, superior mesenteric artery; SMV/PV, superior mesenteric vein/portal vein.

§ Normal vein or artery proximal and distal to the site of suggested tumor-vessel involvement suitable for vascular reconstruction

3.1.3 In subjects requiring biliary decompression, biliary stent or drainage using percutaneous transhepatic cholangiogram (PTC) are allowed.

3.1.4 Participants must be ≥18 years of age at the time of enrollment.

3.1.5 Participants must have an ECOG performance status 0-1 (see Appendix A).

3.1.6 Participants must have adequate organ and marrow function as defined as:

- Absolute neutrophil count ≥1,500/mcL
- Platelets ≥100,000/mcL
- Total bilirubin ≤1.5 × institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- Creatinine ≤1.5 × institutional upper limit of normal

OR

- Creatinine clearance	≥60 mL/min/1.73 m^2 for participants with creatinine levels above 1.5 × upper limit of normal. Creatinine clearance can be calculated per institutional standard.

3.1.7 Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity for the course of the study through 9 months after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

3.1.8 Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 6 months after the last dose of study therapy.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

3.2.1 Has locally advanced or metastatic disease as determined by CT scan or MRI.

3.2.2 Tumors with histologic features in addition to an adenocarcinoma component are excluded. Variant histologies include but are not limited to adenosquamous, squamous, neuroendocrine, undifferentiated with osteoclast like giant cells, acinar, hepatoid, medullary carcinomas.

3.2.3 Has either had any prior chemotherapy or targeted small molecule therapy, or

immunotherapy or radiation therapy for pancreatic cancer.

Note: If subject received major surgery for reason other than pancreatic cancer they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.2.4 Has a known prior or current synchronous malignancy, except:

- Malignancy that was treated with curative intent and for which there has been no known active disease for >5 years prior to enrollment
- Curatively treated non-melanoma skin cancer, cervical cancer in situ or prostatic intraepithelial neoplasia, without evidence of prostate cancer.

3.2.5 Significant history of uncontrolled cardiac disease defined as uncontrolled hypertension (defined by a systolic BP >=160 mm Hg and/or diastolic BP >= 100mm Hg), unstable angina, myocardial infarction within the last 4 months, or uncontrolled congestive heart failure. Subjects with a history of cardiac disease should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, participants should be class 2B or better.

3.2.6 Has a medical history or current diagnosis of myocarditis.

3.2.7 Has a left ventricular ejection fraction <50%, cardiac valvulopathy > grade 2, or elevated cardiac enzymes (troponin I) elevation > 2x ULN.

3.2.8 Has a condition/s that are considered to have a high risk of clinically significant GI bleed or any other condition associated with or history of significant bleeding.

3.2.9 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Patients receiving physiological replacement doses of corticosteroids (10mg of prednisone or equivalent) are allowed.

3.2.10 Has known active, uncontrolled HIV (high viral load), Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

a. Patients who have been vaccinated for hepatitis B and do not have a history of infection are eligible.

3.2.11 Has received a live vaccine within 30 days prior to the first dose of trial treatment. COVID-19 vaccination or booster is permitted any time prior to enrollment or during treatment on trial, in a manner consistent with individual institutional guidelines.

3.2.12 Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

3.2.13 Has an active serious infection requiring systemic therapy.

3.2.14 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.2.15 Subject is unable or unwilling to participate in a study related procedure.

3.2.16 Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4 REGISTRATION And Randomization PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

The eligibility checklist(s) and all pages of the consent form(s) will be emailed to the ODQ at qact@dfci.harvard.edu. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and/or randomization will be sent to the study coordinator(s) from the registering site, treating investigator and registering person immediately following the registration and/or randomization.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 GENERAL GUIDELINES FOR OTHER INVESTIGATIVE SITES

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. All sites should contact the Project Manager to verify dose level availabilities. The required forms can be found in **Section 4.4.**

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and e-mailed to the Project Manager:

- Signed participant consent form
- HIPAA authorization form
- Eligibility checklist
- Screening provider note including medical/surgical history, ECOG performance status, vital signs, and physical exam findings
- Pathology report confirming pancreatic cancer (adenocarcinoma, squamous, or adenosquamous histologies)
- Laboratory reports including:
    - CBC with differential
    - Chemistry panel
    - Pregnancy test (if applicable)
    - Cardiac enzymes

- Screening imaging report (CT and/or MRI scans)
- Screening EKG
- Screening echocardiogram

To complete the registration process, the Project Manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The registering party will email the participant study number and assigned arm or dose treatment level to the participating site.

NOTE: Registration can only be conducted during the regular business hours of 8:30 AM to 4:30 PM Eastern Standard Time Monday through Friday, holidays excluded. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Project Manager.

5 TREATMENT PLAN

5.1. Treatment Regimen

The defined trial treatment to be used in this trial is outlined below in Table 2. Patients will be randomized 2:1 to Arms A and B, the combination of mFOLFIRINOX with NIS793 and mFOLFIRINOX, respectively. Arm A will accrue 30 patients and arm B will accrue a total of 15 patients. Treatment with NIS793 will not be blinded.

Table 2. Trial treatment

Regimen Description					
Arm	Fluorouracil (mg/m^2 IV on days 1 over 46 hours of a 14-day cycle)	Leucovorin (mg/m^2 IV on days 1 of a 14-day cycle)	Irinotecan (mg/m^2 IV on days 1 of a 14-day cycle)	Oxaliplatin (mg/m^2 IV on days 1 of a 14-day cycle)	NIS793 (mg/m^2 IV on days 1 of a 14-day cycle)
A	*2400 mg/m2*	*400 mg/m2*	*150 mg/m2*	*85 mg/m2*	*2100mg*
B	*2400 mg/m2*	*400 mg/m2*	*150 mg/m2*	*85 mg/m2.*	

Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2. Pre-Treatment Criteria

Cycle 1, Day 1, and Subsequent Cycles:

- History and physical exam with vital signs, body weight, and height (obtained within 2 weeks (14 days)).

Laboratories will be collected as follows:

- Hematological profile: CBC with differential on day 1 of each cycle
- Complete metabolic profile: Electrolytes, BUN, creatinine, liver function tests (albumin, total protein, AST, ALT, alkaline phosphatase, total bilirubin), and magnesium on day 1 of each cycle
- Tumor marker profile: CA 19-9 and CEA on day 1 of each cycle
- ANC must be ≥1500 for eligibility and Cycle 1 Day 1. Subsequent ANC must be ≥1000.

*For all laboratory measures a window of up to 3 days prior to treatment day is acceptable.
*Baseline laboratory values obtained on Day 1 Cycle 1, with the exception of ANC as noted above, will not affect the patient's eligibility to participate in the study after the patient has undergone successful screening and randomization.
*Results must be available prior to the administration of study drug.

Imaging studies will be performed as follows:

- Chest/Abdomen/Pelvis CT scan or Chest CT scan and Abdomen/Pelvis MRI must be performed within 28 days of the date of registration. In case of CT abdomen/pelvis is used as the radiographic modality it should be protocoled specifically for evaluation of pancreas i.e. Pancreas protocol CT.

5.3 Agent Administration

5.3.1 IND Agent: NIS793

NIS793 will be administered at a fixed dose of 2100mg via IV infusion every 14 days +3/-1 days, before administration of FOLFIRINOX.

NIS793 will be supplied in a vial as liquid concentrate for infusion. At the appropriate time, infuse the volume of the infusion bag with a maximum administration time of 60 minutes. Shorter infusion times can be applied with a minimum infusion time of 30 minutes. The selection of infusion speed within that requirement is the responsibility of the project-responsible clinician and needs to comply with the specs given by the pump. Infusion must take place in a facility with appropriate resuscitation equipment available at the bedside, and a physician readily available during the period of drug administration.

Per sponsor, Baxter: Long primary flush tubing with 0.2 micron filter extension set add-on (PVC-containing) (for volumes ≤150 ml) 2R8537 + 1C8363 are acceptable to be used. In addition, needles with a length of 2” or longer are recommended as a standard dimension, which was also used in Technical Research and Development (TRD) compatibility studies with NIS793. Shorter needles may be used as long as correct dosing is assured. In terms of needle diameter, gauge numbers equal to or larger than 21G are recommended, so 22 or 23G needles are fine as well.

Participants should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever, and vital signs monitored more frequently if clinically indicated, during and for at least 2 hours after the first two NIS793 infusions. No pre-medications are to be administered during the observation window. The same may apply for the subsequent NIS793 infusions if medically indicated. Participants should notify study personnel if symptoms of infusion reaction occur after any NIS793 infusion. Further instructions for the preparation and dispensation of NIS793 are described in the study pharmacy manual.

Management and dose modifications associated with the administration of NI793 are outlined in Section 6.

Other Agent(s)

5.3.2 mFOLFIRINOX

All participants on both arms will receive mFOLFIRINOX, consisting of 5-Fluorouracil (5-FU), Oxaliplatin, Irinotecan, and Leucovorin. These drugs are commercially available. A central line will be placed for these infusions.

Given that mFOLFIRINOX is standard of care, study treatment will be continued as per institutional standard of care.

No pre-medications for mFOLFIRINOX are to be administered during the NIS793 observation window.

The FOLFIRINOX regimen will be administered intravenously. Treatment will be every 14 days +3/-1 days at physician discretion (unless a further delay is mandated by toxicity criteria). There will be eight cycles of FOLFIRINOX, with each cycle being 14 days in length. Treatment will be administered on an *outpatient* basis. Participants enrolled on Arm A will be treated with mFOLFIRINOX chemotherapy as per institutional standards with NIS793 at 2100mg IV every 2 weeks. Participants enrolled on Arm B will be treated with mFOLFIRINOX chemotherapy alone as per institutional standards.

Dosing schedules and modifications: all commercially supplied drugs will follow the manufacturer-provided labeling with respect to its storage and stability, preparation, handling, and administration. Decisions regarding dose modifications, and delays will be made for each patient at the discretion of the attending physician. All other treatments, including chemotherapy pre-medications, will be determined at the discretion of the attending physician.

All treatments, anti-emetics, and supportive medications should follow institutional guidelines. Subcutaneous growth factor support will be administered between 0 and 72 hours after

discontinuation of continuous infusion of 5-FU in all patients receiving FOLFIRINOX after each cycle. Participants may self-administer at home or have the injection administered in clinic.

5.3.3 Restaging during/after FOLFIRINOX +/- NIS793

Participants will be restaged after four cycles of therapy (interim scans) and following the completion of induction mFOLFIRINOX (after eight cycles of therapy). Restaging scans can be performed after mFOLFIRINOX C4 and C8 pump disconnect (at the earliest) but must be completed prior to C5 and prior to RT administration, if the latter is required. The post-C4 scan review visit can be combined with the C5D1 visit pre-infusion. The post-C8 scan review can be combined with the pre-RT visit if RT is required. Up to one week's delay between cycles for restaging is allowed. Participants who do not demonstrate progression on either restaging scan will undergo RT and/or surgery depending on treatment arm.

5.3.4 Radiation

Patients with borderline resectable pancreatic adenocarcinoma will receive radiation therapy 2-4 weeks after receiving last dose of chemotherapy as part of this trial. This section outlines the general guidelines for radiation planning and target volumes. These may be modified as part of each module.

5.3.4.1 Simulation

All patients must undergo CT simulation in the supine position with a customized immobilization device.

- Patients will be positioned supine in an Alpha Cradle or equivalent immobilization device that will be custom-made for each patient.
- Administration of IV and oral contrast is required for target and normal tissue delineation unless patient has a contrast allergy refractory to premedication or at the discretion of the treating physician. A pretreatment renal scan to assess kidney differential will be performed prior to initiation of treatment as clinically appropriate.
- MRI simulation may be performed in the treatment position and later fused to the CT simulation scan to assist in target volume delineation, or if IV contrast cannot be used, but this is not required.

5.3.4.2 Treatment planning

- Only ≥6 MV photons are permitted

- Particle therapy is not permitted.
- Target Volumes:
- Gross Tumor Volume (GTV):
- The GTV will be created in the same manner irrespective of form of radiation therapy delivered.
- The GTV will include the primary pancreatic tumor and any grossly involved locoregional lymph nodes.
- The diagnostic CT, respiratory-correlated 4D-CT scan, pancreas protocol CT, MRI, and/or the FDG-PET/CT scan (when available) should be reviewed to facilitate accurate delineation of the GTV.
- Clinical Target Volume (CTV):
- For pancreatic head, body, or tail tumors, the celiac and superior mesenteric arteries (SMA) should be contoured starting from the origin of the aorta.
- A tumor-vessel interface (TVI) may be created for cases in which the tumor is in direct contact with a segment of portal vein, superior mesenteric vein, superior mesenteric artery, and/or celiac artery. This contour should include the entire circumference of the blood vessel(s) in contact with tumor as visualized on the CT and/or MRI.
- Elective regional nodal irradiation (porta hepatis, celiac, pancreaticoduodenal, superior mesenteric artery) otherwise may be performed, but is generally not encouraged unless the treating physician thinks it is needed to cover gross tumor or grossly involved lymph nodes.
- Generally, the CTV should be a combination of the celiac artery contour, the SMA contour, and the TVI contour (if applicable) and is expanded at least 1-2 cm around the combined structures of GTV, and regional nodes. Smaller margins are preferred for the CTV expansion if possible. After appropriate expansion to PTV, the area will receive the prescription dose for conventional radiation therapy.
- Planning Target Volume (PTV):
- For conventional radiation therapy, the PTV is expanded from the CTV using a 3-5 mm uniform expansion.
- The physician should review the expansions to confirm the targets are covered throughout the respiratory cycle on the 4D CT scan.
- Techniques of radiation delivery that are acceptable include 3D conformal, intensity modulated radiation therapy, and volumetric modulated arc therapy (or similar) using photon (or conventional x-ray) radiation.
- Organs at Risk (OARs):
    - The spinal cord, bilateral kidneys, liver, stomach, duodenum, and other small bowel should be contoured carefully.
    - Radiation dose to OARs must be minimized.
    - Conventional radiation therapy constraints

- Greater than 95% of the PTV should receive the prescription dose.
- Quality assurance: All treatment plans should be reviewed by the radiation oncology collaborators (Dr. Koay and Dr. Mancias) to confirm proper target coverage and dose constraints are met. This should happen within one week of beginning radiation therapy +/- 3 days.

Description	Planning System Name	Constraints
PTV	PTV	PTV covered by Rx dose > 95%
OAR		**Constraints**
Duodenum	Duodenum	Dmax < 40 Gy
Bowel	Bowel	Dmax < 35 Gy
Stomach	Stomach	Dmax <40 Gy
Liver	Liver	Mean < 20 Gy
Combined Kidneys	Kidneys	Each with V10 < 33%
Spinal Cord	Spinal_Cord	Dmax < 35 Gy
Spleen	Spleen	Mean less than 6 Gy

5.3.4.3 Treatment

5.3.4.3.1 Treatment Interruptions

- Per Protocol: All treatments occur within the number of total fractions plus 2 calendar weeks.
- Variation Acceptable: All treatments occur within 16 to 21 calendar days of the original radiation schedule.
- Deviation Unacceptable: All treatments take 22 or more calendar days to complete, beyond the original radiation schedule.
- Questions regarding the radiotherapy section of this protocol, including treatment interruptions, should be directed to: Dr. Eugene Koay or Dr. Joseph Mancias.

5.3.5 Chemotherapy during radiation

All patients receiving radiation will receive concurrent chemotherapy with either Capecitabine or 5-FU as a continuous infusion (CI). The choice between capecitabine or 5-FU CI will be at the discretion of the treating physician and dose calculation per institutional standard. The recommended dose of capecitabine is 1650 mg/m2 taken on the days of the radiation. It is recommended that 5-FU will be dosed Monday through Friday at 225mg/m2 for the duration of the radiation. No specified timing of radiation treatment in relation to the chemotherapy is required.

5.3.6 Surgery

Surgical resection of the primary tumor and regional lymph nodes in the absence of disease progression 2-8 weeks following completion of neoadjuvant chemotherapy and/or radiation.

5.3.6.1 Surgical Quality Assurance

General considerations

Pancreaticoduodenectomy should occur within 2-8 weeks after the completion of neoadjuvant therapy. Staging laparoscopy may be performed at the time of planned laparotomy but is not required. Either standard or pylorus-preserving pancreaticoduodenectomy may be performed. Both laparoscopic and/or robotic pancreaticoduodenectomy are allowed. Surgical drains and enteral tubes (e.g. gastrostomy and/or jejunostomy tubes) may be placed at the discretion of the operating surgeon.

The operation should be performed in accordance with techniques espoused in the first edition of Operative Standards for Cancer Surgery, published by the American College of Surgeons and the Alliance for Clinical Trials in Oncology (68).

Specific considerations

Exploration of the peritoneal cavity should include evaluation for radiographically occult macroscopic peritoneal or hepatic metastases. Lymph node sampling or frozen section lymph node biopsy is not required or recommended as part of the intraoperative assessment for extra-pancreatic disease, and is at the discretion of the surgeon.

A standard lymphadenectomy should be performed routinely, to include lymph node stations 8a, 12a2, 12p2, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, 17b. Other lymph node stations dissected should be detailed if performed in the operative report.

The retroperitoneal dissection along the medial edge of the uncinate process and the right lateral border of the superior mesenteric artery is believed to be an important oncologic part of the operation. All soft tissue to the right of the superior mesenteric artery (SMA) should be removed. This requires exposure and dissection along the right lateral border of the SMA.

Vascular resection and/or reconstruction of the superior mesenteric vein, portal vein, SMA/portal vein confluence, or hepatic artery will be performed at the discretion of the operating surgeon. In general, vascular resection should be performed when necessary to achieve an R0 resection. The operating surgeon or a vascular/transplant surgeon consult can perform this reconstruction. The technical details of the operation should be delineated in the operative report.

Intraoperative Frozen Section Assessment of Surgical Margins

Frozen section evaluation of the pancreatic parenchymal and hepatic (or bile) duct margins should be performed. In the event of a positive frozen section margin at either of these loci, further resection in an effort to achieve microscopically negative margins should be performed if possible. However, the extent of additional parenchymal resection should be left to the discretion of the operating surgeon.

The superior mesenteric arterial (SMA) margin should be evaluated on permanent section only.

Specimen Orientation for Surgical Pathology

The surgeon should ensure that the specimen is oriented for the surgical pathologist. Any segment of resected vascular structure (e.g. superior mesenteric or portal vein) should be identified and marked. Relevant margins evaluated by intraoperative frozen section (i.e. the hepatic (bile) duct, and pancreatic parenchymal) should be identified. The SMA margin (the soft tissue immediately adjacent to the SMA) should be separately inked using the principles outlined in the 7th edition AJCC staging system for exocrine pancreatic cancer. Note: The SMA margin cannot be identified accurately after the specimen has been fixed in formalin or after the specimen has been dissected for histopathologic analysis.

Aborting Surgery

The planned resection should be aborted if the operating surgeon identifies:

1. Metastatic disease in distant organs (e.g., liver). Presumed disease should be biopsied and confirmed as metastatic cancer on frozen section.
2. Localized cancer that is nonetheless, in the opinion of the operating surgeon, unsafe to resect. In such cases, the specific reasons for aborting the operation should be enumerated in the operative report.

In case of aborting surgery a tissue biopsy of the primary pancreatic tumor should be performed for correlative science as long as it is deemed safe by the primary surgeon.

Operative Note Dictation and Editing: Resection Classification

The attending surgeon should dictate the operative note. The operative report should contain:

1. A section detailing the operative findings with respect to the extent of disease and the primary tumor anatomy.
2. A statement as to whether or not the surgeon believes there is residual macroscopic tumor following completion of the resection.

The surgeon should integrate the operative findings with the microscopic surgical margins reported on the final pathology report in order to assign a resection classification prefix of R0, R1, or R2 (defined below). Whenever possible, this prefix should be added to the final operative note before finalizing the document or be documented in the first post-operative clinic visit note. An example of the final procedure description for a patient who underwent macroscopically complete tumor removal with a positive SMA margin on permanent section final pathology is: "R1 pylorus-preserving pancreaticoduodenectomy." The definitions for the resection classification that should be utilized in operative notes include:

- R0 – macroscopically complete tumor removal with negative microscopic surgical margins (bile duct, pancreatic parenchyma, and SMA margins)
- R1 – macroscopically complete tumor removal with any positive microscopic surgical margin (bile duct, pancreatic parenchyma, or SMA margins)

- R2 – macroscopically incomplete tumor removal with known or suspected residual gross disease

Surgical Pathology

A local pathologist experienced in the diagnosis of pancreatic adenocarcinoma should carry out pathological examination of the resected pancreatic tumor specimen.

Three primary margins (bile duct, pancreatic neck, and SMA) should be identified and inked by the surgeon and/or pathologist. Any segment of resected vascular structure (e.g. superior mesenteric or portal vein) should be identified and marked. The SMA margin (that tissue immediately adjacent to the SMA) should be separately inked according to the procedures and recommendations of the American Joint Commission on Cancer (AJCC) 7th edition staging system and the College of American Pathologists guidelines for reporting of resected exocrine pancreatic cancer (2012). The distance between the closest tumor cell and the inked SMA margin (the "SMA margin distance") should be reported.

The tumor should be thoroughly sampled: At least 2 sections per cm should be submitted if there is grossly identifiable and histologically confirmed tumor. The entire tumor bed should be submitted if no viable tumor is identified in initial sections.

The AJCC 8th edition staging may be used for clinical reporting, but is not necessary for the trial purposes.

Frozen Section Assessment of Margins

Section assessment of bile duct and pancreatic neck margins should be performed by the local pathologist in all cases as requested by the surgeon.

Permanent Section Assessments and Final Pathology Report

The pathology report should contain all of the elements outlined in the College of American Pathologists guidelines for reporting of resected exocrine pancreatic cancer (2012). In particular, there should be specific comment on:

1. Histologic diagnosis with comment on the cell of origin (pancreatic vs. bile duct vs. ampulla)
2. Degree of differentiation (well, moderate, poor)
3. Total number of lymph nodes examined
4. Number of positive nodes
5. Final margins status for the bile duct, pancreatic parenchymal, and SMA margin
6. Distance (in mm) from the tumor to the inked SMA margin
7. Extent of tumor infiltration (if present) of the blood vessel wall for any resected major blood vessels including the maximum histologic depth of invasion (e.g., adventitia, media).

Treatment effect score will be determined using the following system:

- Treatment Effect Score I - 0% residual tumor cells in the specimen (pCR)
- Treatment Effect Score II - 1 to <5% residual tumor cells in the specimen
- Treatment Effect Score III - ≥5% residual tumor cells in the specimen

5.3.6.2 Definitions of Variations in Surgical Performance

The following will be considered minor surgical variations:

- Failure to perform a frozen section of bile duct or pancreatic neck margins at the time of surgery.
- Documentation of an incomplete dissection of uncinate off the SMA.
- Documentation of a lymphadenectomy less extensive than that described above.

5.3.6.3 Surgical Quality Control

For all patients who undergo surgery during protocol treatment (including resection or not), the study chair and surgical co-chair will review the preoperative CT scan, the operative note, the surgical pathology report, and the adverse events associated with surgery (30 days postoperative) within 60 days of surgery. This requires that the study team complete the adverse event case report form (AE CRF) without delinquency.

Specific attention will be paid to deviations as listed above, as well as adverse events that occur in association with surgery. Operative reports and outcomes which, in the opinion of the study chair and surgical co-chair, raise potential patient safety concerns will be discussed and reviewed. Two operations which lead to such a discussion may lead to a surgeon being restricted from enrolling future patients.

5.4 Post-operative therapy

Post-operative chemotherapy for up to 2 months is allowed after recovery from surgery based on the primary treating physicians discretion.

5.5 General Concomitant Medication and Supportive Care Guidelines

In general, concomitant medications and therapies deemed necessary for the supportive care (such as anti-emetics, anti-diarrheal) and safety of the participant are allowed. This includes growth factor support for prevention of neutropenia. Myeloid growth factors will be used prophylactically, and all patients should receive pegfilgrastim or approved biosimilar 6mg SC x1, 0 to 72 hours after disconnecting from CI 5-FU as clinically indicated per institutional standard of care.

The participant must be asked to notify the investigational team about any new medications they take after the start of the study treatment. In the event that an Adverse Event occurs, the investigational team must record any concomitant medications related to this event on the appropriate Case Report Forms.

Acute allergic reactions will be treated per institutional standards. In the event of anaphylactic reaction, this includes any therapy necessary to restore normal cardiopulmonary status.

There is no known effect of NIS793 on the cytochrome P450 system, but the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative

therapies. The PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for *8 cycles (each consisting of 14 days as noted above*), followed by Radiation (if applicable) and Surgery, or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.7 Duration of Follow Up

Participants will be followed until (1) initiation of a new regimen of anti-neoplastic therapy, (2) first disease progression event after removal from protocol therapy, or (3) until death. Tumor

assessments should continue to be performed every 12 weeks on these participants until first disease progression event, new regimen of anti-neoplastic therapy, or until death, whichever occurs first.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- At the discretion of the investigator

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following section. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.). All adverse events experienced by participants will be collected form the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience

toxicity at the off-study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 FOLFIRINOX therapy dose adjustments

Since fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) are FDA approved drugs for the treatment of metastatic pancreatic cancer, subjects who experience toxicity related to FOLFIRINOX will be dose modified according to institutional standards of care at the treating investigator's discretion. Toxicities will be graded using the NCI-CTCAE Version 5.0.

If needed, dose adjustments can be reviewed with:
Harshabad Singh, M.B.B.S (Harshabad_singh@dfci.harvard.edu) or Kimberly Perez, M.D. (Kimberly_perez@dfci.harvard.edu).

6.2 NIS793 therapy dose adjustments

- No dose reductions for NIS793 are allowed. In the event of treatment-related toxicity that is deemed by the investigators to be related to NIS793, NIS793 will be held until toxicity improves to Grade 1 or resolves.
- If toxicity is not attributed to chemotherapy, chemotherapy can continue per treating provider discretion. If attribution of toxicity is unclear, all treatment should be held and restarted until toxicity improves to grade 1 or resolves. In this circumstance discussion with the overall trial PI regarding restarting treatment should take place.
- If the investigator considers it to be in the participant's best interest to resume systemic chemotherapy before the toxicity has resolved to Grade 1, this may be permitted without accompanying NIS793 following documented discussion with the study PI.
- If NIS793 is held for 2 consecutive cycles it will be permanently discontinued. NIS793 would be permanently discontinued for first occurrence of certain specific toxicities detailed below. All dose interruptions or discontinuations must be based on the worst toxicity graded according to CTCAE v5.0.
- Consider early referral to specialists with expertise in the diagnosis and management of

immune related adverse events to thoroughly investigate events of uncertain etiology.

- Events not included in the study protocol should be managed as per institutional preference.

Infusion reaction or hypersensitivity reaction	**Management/Next Dose for *NIS793***
≤ Grade 1	Decrease infusion rate until recovery from symptoms.
Grade 2	Stop infusion immediately, and keep line open. Follow institutional guidelines for the management and follow up with infusion reaction. Restart infusion at 50% of previous rate under continuous observation period ensure that there is a minimum observation period of one hour prior to restarting the infusion. If the AE recurs at the reinitiated slow rate of infusion, when despite oral premedication, then permanently discontinues that a treatment.
Grade 3 or 4	Discontinue infusion immediately, and discontinue study treatment. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g. blood pressure, pulse, respiration and temperature) every 15 minutes until resolution.
Cytokine Release Syndrome (CRS)	**Management/Next Dose for *NIS793***
Grade 2	See instructions for grade two infusion reaction above.
Grade 3 or 4	Discontinue study treatment. Follow up CRS as per institutional guidelines.

Ocular (uveitis, eye pain, blurred vision)	**Management/Next Dose for *NIS793***
≤ Grade 1	Continue study treatment without dose modification. Ophthalmology consultation.
Grade 2	Hold NIS793. Urgent ophthalmology consultation. Upon resolution to ≤ Grade 1 may consider resuming treatment without dose reduction after discussion with study PI and in consultation with ophthalmology.
Grade 3 or 4	Discontinue study treatment. Urgent ophthalmology consultation.

Cardiovascular EKG QTc-interval prolonged; hypertension	**Management/Next Dose for *NIS793***
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline (hypertension, QTc) or <30msec difference from baseline (QTc) within ≤ 7 days, may resume study treatment without dose modification after discussion with study PI. Baseline EKG refers to the EKG(s) collected at screening.
Grade 4	Discontinue study treatment.

Valvulopathy	**Management/Next Dose for *NIS793***
Grade 2	Hold study treatment. Repeat echocardiogram and assess cardiac function. Once resolved to grade <=1 or baseline, consider re-administration of treatment, if benefit outweights the potential risk
Grade 3 or higher	Discontinue study treatment.

Elevated cardiac enzymes (Trop I, pro NT BNP)	**Management/Next Dose for *NIS793***
Grade 1	Continue study treatment. Consider appropriate cardiac imaging and referral to specialist.
Grade 2	Hold study treatment. Consider appropriate cardiac imaging and referral to specialist. Upon resolution to ≤ Grade 1 or baseline, may resume study treatment without dose modification after discussion with study PI.
Grade 3 or higher other cardiac disorders related to study treatment.	Discontinue study drug

Other cardiovascular disorders	**Management/Next Dose for *NIS793***

Other cardiovascular disorders	**Management/Next Dose for *NIS793***
Grade 2 (Except myocarditis)	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may resume study treatment without dose modification after discussion with study PI. Baseline EKG refers to the EKG(s) collected at screening.
Grade 2 myocarditis	Discontinue study treatment.
Grade 3 or higher other cardiac disorders related to study treatment.	

AST and/or ALT elevation	**Management/Next Dose for *NIS793***
Grade 2 AST and/or ALT	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification.
Grade 2 transaminitis with bilirubin >1.5 x ULN (unless Gilbert's syndrome)	Discontinue study treatment.
Grade 3 AST and/or ALT	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification after discussion with study PI. Otherwise, discontinue study treatment.
Grade 4 AST and/or ALT	Discontinue study treatment.

Isolated total bilirubin elevation	**Management/Next Dose for *NIS793***
Grade 2	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may continue study treatment without dose modification.
Grade 3	Hold study treatment.

Isolated total bilirubin elevation	**Management/Next Dose for *NIS793***
	Upon resolution to ≤ Grade 1 or baseline, may consider resuming study treatment without dose modification after discussion with study PI. Otherwise, discontinue study treatment.
Grade 4	See footnote**. Otherwise, discontinue study treatment.
** If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then delay study treatment until resolved ≤ Grade 1, and resume study treatment at the discretion of the Investigator.	

Renal Serum creatinine	**Management/Next Dose for *NIS793***
Grade 2	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification after discussion with study PI.
Grade 3 or 4	Discontinue study treatment.

Musculoskeletal	**Management/Next Dose for *NIS793***
Grade 2 or 3	Hold study treatment. Consider resuming study treatment without dose modification upon resolution to ≤ Grade 1 with appropriate management.
Grade 4	Discontinue study treatment. In some cases, resuming study treatment may be considered after discussion with the study PI and consultation with a rheumatologist.

Dermatology (rash)	**Management/Next Dose for *NIS793***
≤ Grade 1	Continue study treatment without dose modification. Topical steroids, antihistamines, topical emollients
Grade 2	Consider holding study treatment. Topical or oral steroids, antihistamines. If study treatment is held and resolution to ≤ Grade 1,

Dermatology (rash)	**Management/Next Dose for *NIS793***
	resume study treatment without dose modification.
Grade 3 or 4	Hold study treatment. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming study treatment after discussion with the study PI.
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue study treatment.

Neutropenia	**Management/Next Dose for *NIS793***
Grade 3 or 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification, after discussion with the study PI.

Febrile neutropenia	**Management/Next Dose for *NIS793***
Grade 3 or 4	Hold study treatment. Upon resolution of fever and improvement of neutropenia to ≤ Grade 2 or baseline, resume study treatment without dose modification, after discussion with the study PI.

Thrombocytopenia	**Management/Next Dose for *NIS793***
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline, resume study treatment without dose modification. For Grade 3 associated with major bleeding, discontinue study treatment.
Grade 4	Discontinue study treatment.

Anemia	**Management/Next Dose for *NIS793***

Anemia	**Management/Next Dose for *NIS793***
Grade 3 or 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification.

Lymphopenia	**Management/Next Dose for *NIS793***
Any grade	Treatment-related lymphopenia does not require study treatment hold or discontinuation.

Other laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	**Management/Next Dose for *NIS793***
Grade 3 or 4	Hold study treatment. Upon resolution to ≤ Grade 1, resume study treatment without dose modification. Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and corrected after appropriate management within 72 hours of their onset do not require discontinuation. In the case of Grade 4 electrolyte imbalances associated with clinical sequelae, or not resolved to ≤ Grade 1 within 72 hours despite appropriate management, discontinue study treatment.

Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	**Management/Next Dose for *NIS793***
Grade 2	Consider study treatment hold, at Investigator discretion. Upon resolution to ≤ Grade 1, resume study treatment without dose modification.

Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	**Management/Next Dose for *NIS793***
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, resuming study treatment must be discussed with the study PI.
Grade 4	Discontinue study treatment.

6.3 Radiation Dose Adjustments

Radiation therapy will be held for Grade 3 or 4 nausea that is not well controlled with anti-emetic support, until nausea resolves to Grade 2 or less. It will then be resumed to complete the remaining radiation therapy course after multi-disciplinary discussion and at the discretion of the treating physicians.

6.4 Capecitabine Dose Adjustments

Capecitabine dose modifications are at the discretion of the treating physician following the guidelines outlined in the package insert. Toxicity due to capecitabine administration may be managed by symptomatic treatment, dose interruptions and adjustment of capecitabine dose. Once the dose has been reduced it should not be increased at a later time.

6.4 5-Fluorouracil continuous infusion (CI) Dose Adjustments

5-FU CI dose modifications are at the discretion of the treating physician following the guidelines outlined in the package insert. Toxicity due to infusional 5-FU administration may be managed by symptomatic treatment, dose interruptions and adjustment of infusional 5-FU dose.

Once the dose has been reduced it should not be increased at a later time.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List(s) for NIS793

Less Common (less than 5 in 100)

- Allergic reaction
- Cytokine release syndrome
- Cardiac toxicity such as valvulopathy
- Skin rash
- Bleeding or bruising
- Lowering of blood counts
- Decreased kidney function
- Eye pain, visual disturbances, and color perception changes
- Liver test abnormalities
- Bone pain
- Fatigue
- Specific skin issues including keratoacanthomas and squamous cell carcinoma

7.1.2 Adverse Event List(s) for mFOLFIRINOX (Fluorouracil, leucovorin, oxaliplatin, irinotecan)

7.1.2.1 5-Fluorouracil:

Very Common (more than 1 in 10 patients)

- Sickness
- Vomiting
- Mouth sores
- Diarrhea
- Abdominal pain
- Tiredness
- Swelling and redness of the skin
- Fever

Less Common (less than 5 in 100)

- Itching, peeling, and/or pain of the skin of the hands and feet (hand-foot syndrome)
- Diminished appetite
- Loss of hair
- Dizziness
- Cardiac disorders such as angina
- Heart attack and change of heart rhythm
- Confusion
- Disorientation
- Emotional instability
- Watering of the eyes due to excessive tear production
- Abnormal drowsiness
- Weakness
- The lowering of blood cells
- Bleeding or bruising

7.1.2.2 Leucovorin:

Less Common (less than 5 in 100 patients)

- Allergic reaction
- Rash
- Itching
- Facial flushing

- Nausea
- Vomiting

7.1.2.3 Irinotecan:

Very Common (more than 1 in 10 patients)

- A decrease in blood counts (red blood cells, white blood cells, and platelets)
- Anorexia
- Mild Diarrhea
- Mild fatigue
- Sores in the mouth and throat (mucositis)
- Cardiovascular events such as a fast or irregular heartbeat
- Hair loss
- Abnormal liver test values
- Decreased kidney function
- Nausea and vomiting
- Constipation
- Pain

Less Common (less than 5 in 100 patients)

- Severe Diarrhea
- Hemorrhage which may require a blood transfusion
- Moderate fatigue
- Infection

Rare but Serious

- A serious decrease in blood counts that could result in infection, sepsis, a need for blood transfusion, a need for platelet replenishment
- Liver failure that may lead to death
- Kidney failure that may lead to death or the need for dialysis
- Heart attack
- Stroke

- Hypertension

7.1.2.3 Oxaliplatin:

Very Common (more than 1 in 10 patients)

- Peripheral sensory neuropathy, especially in the case of cold exposure, and an unusual feeling of numbness of the mouth and throat that may cause difficulty in swallowing, and can be made worse by cold water or drinks
- This neuropathy can cause the following:
    - Acute reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. This is a sensation of pain when you are exposed to cold, either by touch, or by eating/drinking something cold. Do not eat or drink anything that is colder than room temperature for five days after you receive each dose of oxaliplatin.
    - Decrease in feeling or funny feeling in the hands, feet and mouth or throat that can interfere with daily activities (writing, buttoning, swallowing, and walking). This may worsen over time.
- Jaw spasm
- Abnormal tongue sensation
- Difficulty speaking
- Eye pain
- Feeling of chest pressure
- Fatigue
- Nausea
- Vomiting
- Diarrhea

Less Common (less than 5 in 100 patients)

- Mouth sores
- Hair loss
- Temporary loss of hearing

- Disturbances of kidney function
- Reduced reflexes
- Skin rash
- Fever
- Fainting
- Fibrosis of the lung
- Severe allergic reaction and mild to moderate swelling and redness at the injection site
- An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% of patients that is characterized by a feeling of tightness or tingling in the throat.
- The lowering of blood cell counts
- Bleeding or bruising
- Increase in the value of liver enzymes

7.1.3 Adverse Event List for Capecitabine

Very Common (more than 1 in 10 patients)

- Edema
- Fatigue
- Palmar-plantar erythrodysesthesia (hand-and-foot syndrome)
- Dermatitis.
- Diarrhea
- Nausea, vomiting
- Abdominal pain
- Stomatitis
- Decreased appetite
- Lowering of white blood cell counts
- Anemia
- Thrombocytopenia
- Increase in Bilirubin
- Elevation of liver tests
- Paresthesia

- Eye irritation
- Dyspnea

Less Common (less than 5 in 100 patients)

- Venous thrombosis
- Chest pain
- Headache
- Lethargy
- Dizziness
- Insomnia
- Mood alteration, depression.
- Nail disorder
- Rash
- Skin discoloration
- Alopecia
- Erythema.
- Dehydration
- Gastrointestinal motility disorders
- Oral discomfort
- Taste perversion
- Dyspepsia
- Gastrointestinal hemorrhage
- Ileus
- Neuromuscular & skeletal: Back pain, weakness, neuropathy, myalgia, arthralgia,limb pain
- Abnormal vision
- Conjunctivitis
- Cough

7.1.4 Events expected after radiation

Very likely (80-90%)

- Fatigue (which generally goes away after the radiation therapy is completed)
- Temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms

Less likely (30%)

- Nausea, vomiting (during therapy) – more common if stomach or gastrointestinal track irradiated
- Skin irritation, redness, itchiness, discomfort

Less likely, but serious (<5%)

- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (< 5% permanent changes)
- Radiation-induced liver disease (RILD) (<1%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver
- Non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~5%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.
- Diabetes (<1%)
- Cancer caused by radiation (<0.1%)

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For expedited reporting purposes only:

- AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

Attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the PI.

7.3.2 Investigators **must** report to the PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.					

7.3.4 Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, all AEs are to be captured and reported to the sponsor-investigator.

7.4 Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and other agents administered in this study can be found in Section 7.1.

8.1 NIS793

8.1.1 Description

NIS793 is a fully human anti-TGFβ IgG2 mAb that belongs to the IgG2/λ isotype subclass and binds TGFβ1 and TGFβ2 with high affinity and, to a lesser extent, TGFβ3. It is expressed in a Chinese hamster ovary cell line (CHO-C8TD) and consists of two heavy chains and two light chains. The theoretical average molecular mass of NIS793 based on the amino acid composition as deduced from the DNA sequence without post-translational modification is 143,519 Daltons. The drug substance is a slightly to strongly opalescent, colorless to slightly yellowish aqueous solution.

Following administration of NIS793 via a 30 minute intravenous infusion, approximately dose-proportional increase in NIS793 exposure (i.e. Cycle 1 Cmax and AUClast) was observed from 0.3 mg/kg to 30 mg/kg. Moderate accumulation (approximately up to 2.0-fold) of NIS793 was observed based on ratio of AUClast and Cmax on cycle 3 versus cycle 1. PK variability was low to moderate as illustrated by between subject variability [coefficient of variation % (CV%)] (e.g. 12.9 to 73.3 % for Cmax).

Population PK analysis on the concentration data from the dose escalation phase of the study

CNIS793X2101 was used to describe the pharmacokinetic characteristics of NIS793 including the impact of weight as a covariate on clearance and volume of distribution. The analysis suggested that the pharmacokinetics of NIS793 can be well described using a two compartment model with first order elimination from the central compartment. This is consistent with the observation that NIS793 PK appears dose proportional and time-independent based on the non-compartmental analyses. Based on preliminary population PK analysis, the estimated terminal half-life is approximately 18 days (95% confidence interval: 9 to 30 day), the systemic clearance is 9 mL/h with inter-individual variability of 31% and the volume of distribution at steady state is 5.1 L, consistent with the values for conventional monoclonal antibody. There was no significant difference in PK observed among various tumor types. Although body weight (BW) is a covariate on clearance in the population PK model with the estimated exponent of 0.55 (CV%=40%) from the power model, the predicted exposure and trough concentration at steady state between weight-based and fixed dosing regimens were comparable across different BW categories. This analysis supports the use of fixed or flat dosing on a mg basis irrespective of patient body weight as weight-based dosing does not decrease inter-individual variability. Model-based simulations indicated that a dose of 2100 mg would match exposure observed at 30 mg/kg.

Renal elimination is relatively unimportant for mAbs as their large size limits the extent of their glomerular filtration. The majority of mAb elimination occurs via intracellular catabolism. Therefore, no specific studies were conducted to study NIS793 excretion or elimination.

No specific drug–drug interactions studies were conducted for NIS793. NIS793 is a mAb, not metabolized by Cytochrome P450 (CYP450) enzymes, or transported by P-glycoprotein (Pgp) or related ABC membrane transporters.

8.1.2 Form

NIS793 liquid concentrate for solution for infusion is provided in glass vials with rubber stoppers which are sealed with a flip-off caps. Each 10 mL glass vial contains 700mg/7mL of NIS793 liquid concentrate. A 7% overfill is provided to allow a complete withdrawal of the entire dose. The formulation does not contain a preservative as it is to be used for single-dose administration

only. In the future, 15 mL glass vials containing 1050 mg/mL NIS liquid concentrate may be used.

8.1.3 Storage and Stability

Refrigerated between 2°C to 8°C (36 to 46°F). Do not freeze. Protected from light

8.1.4 Compatibility

This study will use 700mg/7mL NIS793 liquid concentrate. There is a new 1050mg/10.5mL formulation which may be used in the future. Detailed information on the reconstitution of the dosage form is available in the 'Pharmacy Manual'.

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

NIS793 is an investigational agent and will be supplied free-of-charge from Novartis.

8.1.7 Preparation

Refer to 'Pharmacy Manual'.

8.1.8 Administration

At the appropriate time, infuse the volume of the infusion bag with an administration time of 40 - 60 minutes (+/- 10 minutes). Infusion time can be no shorter than 30 minutes and infusion times

greater than 60 minutes need to have the reason for extension clearly documented. The selection of infusion speed within that requirement is the responsibility of the project-responsible clinician and needs to comply with the specs given by the pump.

8.1.9 Ordering

NIS793 will be provided by Novartis.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 Destruction and Return

Unused drug remaining after all patients have completed treatment will be retained per protocol or for a maximum of 30 days unless agreement is made with the research pharmacies. Expired medications will be destroyed per protocol or held for a maximum of 30 days from date of expiration for Investigator disposition. At the end of the 30 days, any remaining expired drug will be destroyed per each research pharmacy's institutional policy in accordance with INV-100.

8.2 Oxaliplatin

Refer to the package insert for comprehensive pharmacologic and safety information.

8.2.1 Description

Please refer to the package insert for complete product information.

Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including

monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter- and intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.

8.2.2 Form

Oxaliplatin is an antineoplastic agent with the molecular formula C8H14N2O4Pt and the chemical name of cis-[(1 R,2 R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)- O,O'] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane(DACH) and with an oxalate ligand as a leaving group. The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone.

8.2.3 Storage and Stability

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze and protect from light (keep in original outer carton).

8.2.4 Compatibility

Oxaliplatin is compatible with D5W.

8.2.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.6 Availability

Oxaliplatin is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free, aqueous solution at a concentration of 5 mg/mL. Water for Injection, USP is present as an inactive ingredient.

8.2.7 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 sodium chloride 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 black precipitant.

8.2.8 Administration

An appropriate amount of drug will be prepared in 5% dextrose in water (D5W) and administered as a 120 minutes intravenous infusion.

8.2.9 Ordering

Oxaliplatin will be commercially obtained.

8.2.10 Accountability

Drug accountability will be completed per institutional standard.

8.2.11 Destruction and return

Drug destruction and return will be completed per institutional standard.

8.3 Irinotecan Study Agent Information

Sites must refer to the package insert for detailed pharmacologic and safety information.

8.3.1 Description

Please refer to the package insert for complete product information.

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis

when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

8.3.2 Form

Irinotecan is available in three single-dose sizes:
2 mL-fill vial containing 40 mg irinotecan hydrochloride
5 mL-fill vial containing 100 mg irinotecan hydrochloride
15 mL-fill vial containing 300 mg irinotecan hydrochloride

8.3.3 Storage and stability

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until the time of use.

8.3.4 Compatibility

Irinotecan is compatible with D5W.

8.3.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.3.6 Availability

Inspect vial contents for particulate matter and discoloration and repeat inspection when drug product is withdrawn from vial into syringe.

Irinotecan 20 mg/mL is intended for single use only and any unused portion should be discarded.

8.3.7 Preparation

Irinotecan must be diluted prior to infusion. Irinotecan should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration

range of 0.12 mg/mL to 2.8 mg/mL. Other drugs should not be added to the infusion solution.

The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing irinotecan and admixtures of Irinotecan may result in precipitation of the drug and should be avoided.

The irinotecan solution should be used immediately after reconstitution as it contains no antibacterial preservative. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 4 hours if kept at room temperature. If reconstitution and dilution are performed under strict aseptic conditions (e.g., on Laminar Air Flow bench), irinotecan solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if refrigerated (2° to 8°C, 36° to 46°F).

8.3.8 Administration

Administer irinotecan as an intravenous infusion per institutional standards.

8.3.9 Ordering

Irinotecan is commercially available.

8.3.10 Accountability

Drug accountability will be completed per institutional standard.

8.3.11 Destruction and return

Drug destruction and return will be completed per institutional standard.

8.4 5-Fluorouracil

Sites must refer to the package insert for detailed pharmacologic and safety information.

8.4.1 Description

Please refer to the package insert for complete product information.

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create
a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and which take up fluorouracil at a more rapid rate.

8.4.2 Form

Fluorouracil injection, an antineoplastic antimetabolite, is a sterile, nonpyrogenic injectable solution for intravenous administration. Each 10 mL contains 500 mg fluorouracil; pH is adjusted to approximately 9.2 with sodium hydroxide.

8.4.3 Storage and stability

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until the time of use.

8.4.4 Compatibility

5-FU is compatible with D5W.

8.4.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the

chemotherapeutic agent in a self-contained and protective environment.

8.4.6 Availability

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

8.4.7 Preparation

Fluorouracil Injection should be administered only intravenously**.**

8.4.8 Administration

Fluorouracil Injection should be administered only intravenously, using care to avoid extravasation. No dilution is required.

8.4.9 Ordering

5-fluorouracil is commercially available.

8.4.10 Accountability

Drug accountability will be completed per institutional standard.

8.4.11 Destruction and return

Drug destruction and return will be completed per institutional standard.

8.5 Leucovorin

Sites must refer to the package insert for detailed pharmacologic and safety information.

8.5.1 Description

Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)-l-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of “one-

carbon" moieties. l-Leucovorin (l-5-formyltetrahydrofolate) is rapidly metabolized (via 5, 10-methenyltetrahydrofolate then 5, 10-methylenetetrahydrofolate) to l,5-methyltetrahydrofolate. l,5-Methyltetrahydrofolate can in turn be metabolized via other pathways back to 5,10-methylenetetrahydrofolate, which is converted to 5-methyltetrahydrofolate by an irreversible, enzyme catalyzed reduction using the cofactors FADH2 and NADPH.

Administration of leucovorin can enhance the therapeutic and toxic effects of fl uoropyrimidines used in cancer therapy, such as 5-fluorouracil. Concurrent administration of leucovorin does not appear to alter the plasma pharmacokinetics of 5-fluorouracil. 5-Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication).

8.5.2 Form

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists. Also known as folinic acid, Citrovorum factor, or 5-formyl-5,6,7,8-tetrahydrofolic acid, this compound has the chemical designation of Calcium N-[p-[[[(6RS)-2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl]methyl]amino]benzoyl]-L-glutamate (1:1).

8.5.3 Storage and stability

Leucovorin Calcium Injection USP, 10 mg/mL, is supplied in sterile, single use vials as follows:
NDC 55390-009-01 500 mg individually-boxed.
Store in refrigerator 2° to 8°C (36° to 46°F). Protect from light. Discard unused portion. Retain in carton until time of use.

Leucovorin Calcium for Injection is supplied in sterile, single use vials as follows:
NDC 55390-051-10 50 mg boxed vial, packs of 10.
NDC 55390-052-10 100 mg boxed vial, packs of 10.
NDC 55390-053-01 200 mg boxed vial.
NDC 55390-054-01 350 mg boxed vial.
Store at 20°C to 25°C (68° to 77° F). [See USP Controlled Room Temperature.] Protect from

light. Retain in carton until time of use.

8.5.4 Compatibility

Leucovorin is compatible with D5W.

8.5.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.5.6 Availability

Leucovorin Calcium Injection USP, 10 mg/mL, is supplied in sterile, single use vials as follows:
NDC 55390-009-01 500 mg individually-boxed.

Leucovorin Calcium for Injection is supplied in sterile, single use vials as follows:
NDC 55390-051-10 50 mg boxed vial, packs of 10.
NDC 55390-052-10 100 mg boxed vial, packs of 10.
NDC 55390-053-01 200 mg boxed vial.
NDC 55390-054-01 350 mg boxed vial.

8.5.7 Preparation

Each 50, 100, and 200 mg vial of Leucovorin Calcium for Injection when reconstituted with 5, 10, and 20 mL, respectively, of sterile diluent yields a leucovorin concentration of 10 mg per mL. Each 350 mg vial of Leucovorin Calcium for Injection when reconstituted with 17.5 mL of sterile diluent yields a leucovorin concentration of 20 mg per mL. Leucovorin Calcium for Injection contains no preservative.
Reconstitute the lyophilized vial products with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), or Sterile Water for Injection, USP. When reconstituted with Bacteriostatic Water for injection, USP, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, USP, use immediately and discard any unused portion.

8.5.8 Administration

Leucovorin should be administered only intravenously, using care to avoid extravasation. Leucovorin will be prepared in 5% dextrose in water (D5W) and may be administered as a 120 minute intravenous infusion concurrently with oxaliplatin.

8.5.9 Ordering

Leucovorin is commercially available.

8.5.10 Accountability

Drug accountability will be completed per institutional standard.

8.5.11 Destruction and return

Drug destruction and return will be completed per institutional standard.

8.6 Capecitabine

Sites must refer to the package insert for detailed pharmacologic and safety information.

8.6.1 Description

Capecitabine is classified as an antineoplastic agent, antimetabolite (pyrimidine analog). Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesserdegree, RNA synthesis. Fluorouracil appears to be phase specific for the G1 and S phases of the cell cycle.

8.6.2 Form

Commercially available in 150 mg and 500 mg tablets for oral administration.

8.6.3 Storage and stability

Store at room temperature of 25°C with excursions between 15°C and 30°C permitted.

8.6.4 Compatibility

Capecitabine is an oral medication and tablets should be swallowed with 6-8 oz. of water. The medication is to be taken within 30 minutes of meals.

8.6.5 Handling

Not applicable

8.6.6 Availability

Commercially available in 150 mg and 500 mg tablets for oral administration

8.6.7 Preparation

Not applicable

8.6.8 Administration

Usually administered in 2 divided doses taken 12 hours apart. Doses should be taken with water within 30 minutes after a meal (Because current safety and efficacy data are based upon administration with food, it is recommended that capecitabinebe administered with food. In all clinical trials, patients are instructed to take with water within 30 minutes after a meal). Tablets are to be taken whole, not crushed, chewed or dissolved. Missed or vomited doses are not to be made up.

8.6.9 Ordering

Capecitabine is commercially available.

8.6.10 Accountability

Drug accountability will be completed per institutional standard. Participants will be provided with dosing instructions and a sufficient supply of capecitabine for dosing on days of radiation.

8.6.11 Destruction and return

Drug destruction and return will be completed per institutional standard.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The following planned exploratory correlative studies are required at all participating sites.Please refer to study-specific Correlative Lab Manual for complete details.

RNA and DNA sequencing data will be shared with collaborating investigators for correlative science research. Original sequencing data will be shared with collaborators, but all samples will be de-identified and labeled with anonymized coding. In addition, all original data will be uploaded to the appropriate NCBI archive (i.e. GEO, dbGAP, SRA) as directed by grant funding and publication rules.

In addition to the tumor and blood samples, data collected will include known tumor histopathology features including site the tumor was obtained from, tumor type, grade, TMN staging, receptor status, and molecular features (using our Oncopanel, FISH and IHC analysis, and/or future clinical genotyping platforms), as well as patient age and any known mutational status. Mutational data collection will be incorporated in correlative sample analysis. Tissue obtained per the Correlative Lab Manual may be cultured in vitro in order to derive primary tumor and non-tumor cell lines to be used for subsequent biomarker, genotyping and preclinical drug evaluation studies by the study investigators.

Peripheral blood will be collected for each patient at multiple time points: prior to initiation of and during systemic therapy, prior to surgery, and every 6 months during the 2 years post-surgery. A surgical resection specimen after completion of neoadjuvant treatment on each arm – or a biopsy if surgery is not completed – will be collected for clinical and correlative study purposes.

9.1 Pathologic Biomarker Studies

This section includes all tissue samples obtained before treatment (preferably by Core needle biopsy – CNB; alternatively through Fine needle aspirate – FNA) and the post-treatment resection specimen (RS).

We hypothesize that anti-TGFβ therapy with FOLFIRINOX will lead to changes in multiple immune and stromal cells in PDAC, presenting a favorable substrate for T cell priming.

9.1.1 Single cell RNA-sequencing

Resected tumors from control and NIS793 treated patients will be cut into 1mm chucks and stored immediately in tissue freezing media. These frozen specimens will be later digested to single cell suspension. We will prepare single cell TCR and transcriptome libraries using 5'beads from 10x Genomics. We will analyze transcriptional shifts in all cells, including CD8 T cell subsets and fibroblasts and compare evolution of tumor and microenvironment in patients treated with NIS793 with mFOLFIRINOX compared to mFOLFIRINOX alone. For TCR clonotype analysis, we will amplify TCR libraries using the 10x Genomics platform. This will enable identification of paired alpha/beta TCR sequences with high recovery to allow for tracking of clonal expansion and matching of individual clonotypes between tumor and blood and across time points. Theses analyses will be performed in the Dougan Lab at Dana-Farber Cancer Institute.

Please refer to the protocol laboratory manual for specific handling and shipping instructions.

9.1.2 Multispectral flow cytometry on tumor infiltrates

We will validate cell frequencies and major cell surface phenotypes by multi-spectral flow cytometry including but not limited to the following markers: CD45, CD115, CD14, CD15, CD16, CX3CR1, CXCR2, CCR2, HLA-DR, CD4, CD25, Foxp3, CD8, CD38, PD-1, Ki67, CD45RO, CD45RA.

Multispectral flow cytometry will be performed to capture granulocytes and other immune cells and provide accurate frequencies for major cell populations. Granulocytes can sequence poorly in single cell transcriptomics; therefore, granulocyte subsets and phenotyping will also be performed using multispectral flow cytometry. Additional granulocyte and other immune cell markers may be added to the immunofluorescence platform, if deemed of interest.

This analysis will be performed in the Dougan Lab at Dana-Farber Cancer Institute.

Please refer to the protocol laboratory manual for specific handling and shipping instructions.

9.1.3 Multi-color immunofluorescence

Recent methods have allowed multiple antigens to be detected in standard FFPE slides with use of multi-color immunofluorescence. We will employ either the Ventana Roche or the Perkin Elmer multi-IF staining platform with multispectral imaging (Vectra 3 Perkin Elmer) with spectral demixing for multiple immune, tumor and fibroblast markers including but not limited to CD3, CD4, CD8, CD80, CD163, CD68, ICOS, CTLA-4, Ki67, PD-1, FoxP3, Lag3, IDO1, Tim-3, and TIGIT. This analysis will be performed in the Wolpin/Nowak laboratories at Dana-Farber Cancer Institute.

Please refer to the protocol laboratory manual for specific handling and shipping instructions.

9.2 Blood based Correlative Studies

This section includes all blood samples collected for correlative studies.

Please refer to the protocol laboratory manual for specific collection and handling instructions with regards to: (a) amount and type of specimen collected, number. (b) number, size and type of tubes or cryovials used for collection; and (c) processing instructions.

9.2.1 Peripheral immune cell profiling

Immune cell response will be monitored in the peripheral blood using multispectral flow cytometry using a similar panel to the one used for primary tumor analysis. The goal would be correlate changes in peripheral immune compartment to those seen in the primary tumor.

This analysis will be performed in the Dougan Lab at Dana-Farber Cancer Institute.

9.2.2 Peripheral T-cell receptor clonotyping

We will track the evolution of T-cell clones with treatment using sorted CD3+ T-cells from the peripheral blood followed by single cell T-cell receptor sequencing at various timepoints during

the treatment course. This will allow us to match expanded T-cell clones in the peripheral blood to those which are also present and expanded in the primary tumor. We will also freeze peripheral blood mononuclear cells (PBMCs) for later in vitro analyses as needed.

This analysis will be performed in the Dougan Lab at Dana-Farber Cancer Institute.

9.2.3 Serum cytokine analysis

We will evaluate the concentration of serum cytokines and chemokines using a multiplex panel including but not limited to the following analytes: 6CKine, BCA-1, CTACK, EGF, ENA-78, Eotaxin, Eotaxin-2, Eotaxin-3, FGF-2, Flt3L, Fractalkine, G-CSF, GM-CSF, GROα, I-309, IFNα2, IFNγ, IL-1α, IL-1β, IL-1RA, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-16, IL-17A, IL-17E/IL-25, IL-17F, IL-18, IL-20, IL-21, IL-22, IL-23, IL-27, IL-28A, IL-33, IP-10, LIF, MCP-1, MCP-2, MCP-3, MCP-4, M-CSF, MDC, MIG, MIP-1α, MIP-1β, MIP-1δ, PDGF-AA, PDGF-AB/BB, RANTES, sCD40L, SCF, SDF-1α+β, TARC, TGFα, TNFα, TNFβ, TPO, TRAIL, TSLP, VEGF-A.

Serum will also be stored frozen for later in vitro analysis as needed.

This analysis will be performed in the Dougan Lab at Dana-Farber Cancer Institute.

9.2.4 Circulating tumor DNA/Cell free DNA:

Circulating tumor DNA (ctDNA) is a sensitive molecular assay for tumor detection and evolution with therapy. We will use a sensitive quantitative circulating tumor DNA assay to assess early response or resistance to therapy. Early identification of tumor resistance to neoadjuvant therapy can allow later development of adaptive trials involving switching of chemotherapy backbone based on early response or resistance characterization. In addition, we will correlate single cell RNA profiles for tumors which demonstrate resistance vs. response to neoadjuvant therapy.

This analysis will be performed in the Dougan and Aguirre Labs at Dana-Farber Cancer Institute.

9.2.5 Radiomics studies:

The baseline delta classification is based on the difference in iodine contrast measured in Hounsfield Units at the observed tumor/pancreas interface on the baseline (pre-treatment) CT scan, as previously described (60). The interface response is based on the change in the interface morphology, comparing the baseline and post-neoadjuvant therapy CT scan (61). These CT scans will be de-identified prior to analysis and linked to the patient through a unique identifier in the database for the study. The CT scans will be analyzed in the lab of Dr. Eugene Koay at MD Anderson Cancer Center and the radiomic measurements will be stored in the database for the study for subsequent correlations as proposed.

10 STUDY CALENDAR

Baseline evaluations (vital signs, physical exam, ECOG performance status) are to be conducted within 2 weeks prior to start of protocol therapy. Informed consent, tumor assessment by imaging, laboratory evaluation, echocardiogram, and EKG must be done ≤4 weeks prior to the start of therapy. If the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

	Screening*	**Day 1 of each cycle of chemotherapy****	**RT*****	**Surgery ********	**Off Tx*********	**Post Tx Follow-up**********	**EDC Timepoints**
FOLFIRINOX[A,B]		X					
NIS793[C,D]		X					
Fluorouracil[E]			X				
Informed Consent	X						N/A
Tests & Observations							
Medical History	X						N/A
Concurrent Medications[a]	X						N/A
Physical Exam[b], Vital Signs[c]	X	X	X	X	X	X	N/A
Height	X						N/A
ECOG Performance Status	X	X	X	X	X	X	Prior to registration, Day 1 of every cycle, prior to radiation, surgery, Off treatment
Adverse Event Assessment [†]		X	X	X	X	X	All visits
Laboratory Studies							
CBC, Differential, Platelets [d,f]	X	X	X	X	X	X	N/A
Serum Chemistry[e,f]	X	X	X	X	X	X	N/A
HIV, Hepatitis B/C serologies	X						
Pregnancy Test	X	X[r]					N/A
CA 19-9, CEA[g]	X	X	X	X	X	X	N/A
EKG[h]	X	X					N/A
Troponin I, NT proBNP[i]	X	X					N/A
Echocardiogram or MUGA or cardiac CT/MRI[j]	X						Prior to registration. Thereafter only if clinically indicated &/or if cardiac enzymes are elevated
Tumor Measurements[k]	X		X	X		X	Prior to registration, every 8 weeks on chemotherapy, prior to radiation, prior to surgery
Pathology Review[l, m]				X			
Optional tumor biopsy[n]	X				X		Prior to registration at baseline and at time of progression.
Archival tumor sample[o]	X						Prior to registration at baseline.
Research blood[p]	X	X	X	X[q]	X	X	Prior to registration, Day 1 of all chemotherapy, Prior to radiation, prior to surgery, off treatment

A: Fluorouracil 2400mg/m^2 IV on days 1 over 46 hours; Leucovorin 400mg/m2 on day 1; Irinotecan 150mg/m2 IV on day 1; Oxaliplatin 85mg/m2 IV on day 1 of a 14 day cycle (+3/-1 days) for patients randomized to Arm A and B (See section 5.1).

B: Subcutaneous growth factor support will be administered between 0 and 72 hours after discontinuation of continuous infusion of 5-FU in all patients receiving FOLFIRINOX after each cycle. Participants may self-administer at home or have the injection administered in clinic.

C: NIS793 2100mg IV on day 1 of a 14-day cycle (+3/-1 days) for patients randomized to Arm A (See section 5.3)

D: The first five patients randomized to NIS793 (Arm A) will be part of a safety lead-in. Study will pause until the last patient accrued for safety lead-in has completed two full treatment cycles (i.e., 28 days). Participants must have received at least 75% of their assigned doses of FOLFIRINOX and NIS793 to be considered evaluable for this safety analysis, unless dosing was held or reduced due to toxicity. If one or more of the first five participants enrolled does not meet this parameter for a reason other than toxicity (e.g. rapid disease progression and subsequent removal), Arm A will continue to accrue as many participants as needed to have five evaluable participants for safety assessment.

E: Capecitabine twice daily on days of radiation OR Fluorouracil by continuous infusion on days of radiation. Doses to be determined by institutional standards and physician discretion but the recommended doses are 5FU 225mg/m2/day continuous infusion Monday-Friday, Capecitabine 1650mg/m2/day po.

* Screening evaluation (vital signs, physical exam, ECOG performance status) are to be conducted within 2 weeks of starting protocol therapy. Informed consent, tumor assessment by imaging, laboratory evaluation, echocardiogram, and EKG must be done </= 4 weeks prior to start of therapy.

** Drug dosages to be modified due to changes in body weight or body surface area (BSA) based on institutional criteria. If no such criteria exist recalculate doses when there is a greater than 10% change in weight or BSA.

*** RT only delivered for patients with borderline resectable PDAC. Radiation planning visit should occur at the time of Cycle 7 of treatment. Assessments should be done approximately weekly, and at least once for every five fractions of radiation.

**** Surgical assessments should be done once within 14 days prior to the operation.

***** End of treatment appointment to be performed within 4 weeks of the last study treatment event. Performed prior to the initiation of any non-study related cancer therapies.

****** Post treatment follow up should be at least once every 12 weeks (+/- 28 days) until first disease progression event, new regimen of anti-neoplastic therapy, or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

[a] If new medications or changes are prescribed while patient is receiving treatment on study, these medications should be recorded.

[b] A complete physical examination will be performed at baseline, prior to radiation and prior to surgery. A limited physical exam will be completed prior to therapy on Day 1 of the 8 cycles of chemotherapy +/- NIS793, and weekly during chemotherapy and radiation.

[c] Vital sign assessments include measurements of heart rate, systolic and diastolic blood pressures, respiratory rate, temperature, and weight.

[d] Hematology includes: hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent and absolute differential count. Results must be available prior to the administration of study drug. ANC must be ≥1500 for eligibility and Cycle 1 Day 1. Subsequent ANC must be ≥1000.

[e] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

[f] Labs completed prior to registration may be used for day 1 of cycle 1 if obtained ≤ 7 days prior to treatment (except pregnancy test, CA 19-9, cea). Labs (hematology and serum chemistry) to be drawn every 2 weeks during chemotherapy, weekly during radiation, prior to surgery (+/-2 weeks), and 2 weeks with the post-operative assessment.

[g] Ca19-9 and CEA to be checked during screening, day 1 of all cycles of chemotherapy, prior to chemotherapy and radiation (+/-2 weeks), prior to surgery (+/- 2 weeks), and at post-treatment follow up.

[h] EKG will be performed at screening for all patients. Thereafter EKG is required on day 1 of each cycle of chemotherapy for *patients receiving NIS793*. QTc to be calculated using Bazzett's formula.

[i] Cardiac specific enzyme Troponin I and NT-proBNP will be checked on screening for all

patient and thereafter will be checked on C3D1 and day 1 of every third cycle during treatment duration or as clinically indicated, and at EOT visit for the patients randomized to the NIS793 arm.

[j] Echocardiogram or other cardiac imaging such as MUGA or CT or MRI should be done in *patients receiving NIS793* prior to cycle 1. Thereafter it is repeated only if clinically indicated &/or if cardiac enzymes are elevated: ≥ 2x ULN (if normal at screening) or ≥ 2x baseline (if baseline value was elevated).

[k] Tumor assessments should consist of 1) CT chest/abdomen/pelvis and/or MRI of the abdomen/pelvis, and 2) any other imaging studies (CT neck, plain films, etc.) as clinically indicated by the treating physician. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then she should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study). In case of CT abdomen/pelvis is used as the radiographic modality it should be protocoled specifically for evaluation of pancreas i.e. Pancreas protocol CT. Tumor assessments will be +/- 4 weeks prior to C1D1, every 8 weeks during chemotherapy (+/- 2 weeks), then once (+/- 2 weeks) prior to start of radiation, and once (+/- 2 weeks) prior to surgical date, then and once every 12 weeks (+/- 28 days) after surgery. Additional scans are permitted as clinically indicated.

[l] In cases where surgery is aborted due to intra-operative identification of unresectable or metastatic disease a tissue biopsy of the primary pancreatic tumor should be performed as long as deemed safe by the primary surgeon.

[m] Patients with imaging evidence of disease progression precluding surgery at restaging imaging will be offered an optional percutaneous or endoscopic biopsy of primary pancreatic tumor.

[n] Patients will be consented for an optional tissue biopsy of the primary pancreatic tumor during initial consenting process.

[o] Archive tissue biopsy from diagnostic specimen would be obtained.

[p] Research blood collection. See lab manual.

[q] Research blood to be collected within 14 days prior to the operation.

[r] In female subjects of child-bearing potential as defined in the eligibility criteria, pregnancy test must be performed within 24 hours prior to the initial administration of study drug, then every 4 weeks ± 1 week.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every *8* weeks. In addition to a baseline scan, confirmatory scans should also be obtained *8* weeks following initial documentation of objective response.

Response will be evaluated during surgical resection and on histopathology. Major pathologic response will be defined as less than 5% viable tumor cells left in the pancreatic resection specimen.

Progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be

considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-

cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize

each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease

on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine). The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days

total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor

evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target

lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression

status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**

CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign

this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7 Response Review

Not applicable

11.2 Antitumor Effect – Hematologic Tumors

Not applicable

11.3 Other Response Parameters

Not applicable

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The DF/HCC Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The Board is chaired by a medical oncologist from outside of DF/HCC and its membership composed of internal and external institutional representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Sponsor-Investigator, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; all adverse events and serious adverse events reported across all sites by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint is the rate of major pathological response (MPR) defined as <5% residual tumor cells visible in the pancreatic resection specimen. The major pathological response rate will be analyzed among all patients who start protocol therapy, including those not resected due to early progression, death or off study.

Major pathologic response (MPR) is based on the CAP grading system for response to neoadjuvant therapy in pancreatic adenocarcinoma (69) and includes both grade 0 (pathologic complete response) and grade 1 (single or small groups of cells) responses. MPR is defined specifically as <5% residual cells (70) and is attempted to allow easier cross comparison between studies by using an objective number as opposed to subjective assessment of the amount of residual cells remaining in the tumor. MPR has been correlated with outcomes and is strongly associated with improved long term outcomes in patients with resected pancreatic adenocarcinoma(70, 71).

Eligible patients with newly diagnosed resectable or borderline resectable pancreatic adenocarcinoma will be randomly assigned in a 2:1 allocation ratio to one of the two interventions: NIS793 and FOLFIRINOX chemotherapy for 8 cycles (Arm A, Experimental arm) followed by surgery, or FOLFIRINOX for 8 cycles (Arm B, Control arm) followed by surgery. The experimental (Arm A) and control arms (Arm B) will accrue 30 and 15 patients respectively. The first five patients randomized to NIS793 (Arm A) will be part of a safety lead-in. Study will pause until the last patient accrued for safety lead-in has completed two full treatment cycles (i.e., 28 days). Participants must have received at least 75% of their assigned doses of FOLFIRINOX and NIS793 to be considered evaluable for this safety analysis, unless dosing was held or reduced due to toxicity. If one or more of the first five participants enrolled does not meet this parameter for a reason other than toxicity (e.g. rapid disease progression and subsequent removal), Arm A will continue to accrue as many participants as needed to have five evaluable participants for safety assessment. Patients with borderline resectable pancreatic adenocarcinoma will receive chemoradiation after completion of systemic chemotherapy prior to surgery. As per the standard of care, the time interval between completion of neoadjuvant chemotherapy and radiation will be 2-4 weeks for patients with borderline resectable pancreatic adenocarcinoma and the interval between completion of neoadjuvant treatment and surgery for all patients will between 2-8 weeks.

We will compare experimental arm to the control arm to see if it has improved the major pathological response rate (MPR). The experimental treatment will be claimed to be successful if

Pr(p.e > p.c + 0.05 |data) > θ_t, where p.e and p.c are the MPR for the experimental arm and control arm, respectively, and θ_t is the threshold value. We assume the prior distributions p.e ~ Beta(0.3, 0.7) and p.c~Beta (0.13,0.87), which reflect that the expected MPR being 30% in experimental arm and 13% in control arm.

We set the threshold, θ_t = 0.74, so that the type I error is controlled to be less than 20%. That is, if the experimental arm has the same MPR as the control arm with response rate of 0.13, the probability of claiming its success is less than or equal to 20%. The results are presented in Table 1. In this setting, we have 67.7% power to claim the success of an experimental arm with MPR being 30%. That is, when MPR being 30% in the experimental arm, the probability of claiming its success is 67.7%. Table 1 shows the operating characteristics for the design.

Table 1. Operating characteristics for MPR being 0.13 in control arm and MPR varying from 0.08 to 0.40 in experiment arm. The maximum sample size for experimental and control arms are N=30 and 15, respectively.

MPR in experimental arm	Percentage of claiming success
0.08	0.064
0.13	0.162
0.26	0.563
0.30	0.677
0.35	0.795
0.40	0.884

13.2 Sample Size, Accrual Rate and Study Duration

Based on the DFCI and MDACC experience, the accrual duration is projected to be 36 months to enroll a total of 45 patients who receive protocol therapy. Patients will be followed actively for 5 years or until disease progression or initiation of an alternative anti-cancer therapy and thereafter

for survival.

13.3 Randomization and Stratification Factors

Treatment assignment will be between the two arms will be stratified by the extent of disease:

- Resectable
- Borderline resectable

The biostatistics collaborator will generate and provide two separate randomization lists, with each list corresponding to one disease subtype, to be used for treatment assignment during the trial.

13.4 Interim Monitoring Plan

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor protocol progress and patient safety according to their standard schedule twice a year. Since all patients will receive standard of care therapy no formal plan will be implemented for interim analysis of primary and secondary endpoints. Additional safety monitoring plan is detailed in Section 13.7.1.

13.5 Analysis of Primary Endpoints

Patients' demographic and clinical characteristics will be summarized using descriptive statistics. Specifically, categorical covariates will be summarized by frequencies and percentages and their associations between groups will be assessed using the Chi Square test or Fisher's exact test. Continuous covariates will be summarized by means, standard deviations, medians and ranges, and the difference between groups will be assessed using the t-test or Wilcoxon rank sum test.

We will estimate the MPR for each arm. Due to the small sample size, we will estimate the MPR with its 95% exact confidence interval (CI). Among 30 patients treated in experimental arm, assuming 9 out of 30 patients have achieved primary endpoint, the 95% CI of MPR will be (0.15, 0.49). Additionally, generalized linear regression models will be explored to evaluate the

associations between the endpoint of MPR and covariates of interest.

13.6 Analysis of Secondary Endpoints

- Progression free survival time is defined as the time period from the date of randomization to the date of disease progression, recurrence after surgery or death from any cause whichever occurs first.
- The overall survival time is defined as the time duration from randomization till death or last follow-up if the patient is alive.

The distributions of overall survival and progression free survival will be estimated using the Kaplan-Meier method. Comparisons of these time-to-event endpoints by important covariate subgroups will be made using the log-rank tests. Cox proportional hazards regression models will be explored to evaluate the associations between the time-to-event endpoints and covariates of interest.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the first dose of protocol therapy.

For patient safety, a Bayesian toxicity monitoring rule will be implemented for the dose limiting toxicity (DLT) events that are at least possibly related to the investigational agent in the opinion of the investigators and occur within 28 days from the end of the drug administration according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. DLT events will include:

- Grade 3 or higher non-hematologic toxicity except:
  - Grade 3 fatigue
  - Grade 3 diarrhea or vomiting that lasts less than 72 hours
- Grade 4 or higher hematologic toxicity and:
  - Febrile neutropenia
  - Grade 4 neutropenia lasting longer than 7 days

Let p.tox be the toxicity probability at least possibly related to the investigational agent in the opinion of the investigators with a prior distribution of Beta(0.33, 0.67), then if Pr [p.tox > 0.33] >0.7, we will terminate the experimental arm early. Patients within the safety lead in cohort of the first 5 patients will be monitored for DLT at least possibly related to investigational agent. Based on these assumptions and monitoring conditions, we will early stop the study if we observe [# patients experiencing toxicity] / [#patients being treated] >=3/5 DLTs in the safety lead in cohort. The operating characteristics are shown in Table 2.

Table 2. Operating characteristics for toxicity monitoring

True toxicity probability	Early stopping probability	Average s ample size
0.1	0.010	29.8
0.2	0.093	28.0
0.3	0.354	23.4
0.4	0.710	16.7
0.5	0.931	11.0

The toxicity boundaries and operating characteristics were generated using web-based applications available at https://trialdesign.org.

Safety data analysis: Toxicity severity and grade data will be summarized with descriptive statistics overall and by treatment arms.

13.7.2 Evaluation of the Primary Efficacy Endpoint

Major pathologic response will be analyzed according to modified intent-to-treat, excluding patients determined to be ineligible at randomization or who withdraw consent prior to starting any protocol therapy.

14 PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

DF/HCC Protocol #: *22-314*

APPENDIX B

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

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1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1. Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Policies and Operations.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1. External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document..

The general responsibilities for each External Site may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions..
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.
- Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.

- Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable..
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1. Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Protocol revisions:** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.

- **Protocol closures and temporary holds:** External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.2. Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In

these cases, the approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.3. IRB Re-Approval

Verification of IRB re-approval for the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received for the External Site on or before the anniversary of the previous approval date.

3.4. DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5. Participant Registration and Randomization

To register a participant, the following documents should be completed by the External Site and faxed or e-mailed to the Coordinating Center:

- Copy of required laboratory tests including: CBC with differential, Chemistry panel, Pregnancy test (if applicable), and Cardiac enzymes
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the External Site and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.6. Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

3.7. Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8. Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web based training for all eCRF users.

3.4.1. Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

If study forms are not submitted on schedule, the External Sites will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

3.9. Protocol Reporting Requirements

Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4. MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1. Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

External Sites will be required to participate in monthly Coordinating Center initiated teleconferences. “Newsletters” highlighting overall protocol progress and important announcements will be distributed regularly.

External Sites will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification.

4.2. Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3. Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

Participating institutions will be expected to meet the minimum annual accrual requirement of 3 patients per site.

5. AUDITING: QUALITY ASSURANCE

5.1. DF/HCC Internal Audits

All External Sites are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

5.2. Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.3. Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the IRB as applicable.

5.4. External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.