A Randomized Pilot Study of Perioperative Nivolumab and Paricalcitol to Target the Microenvironment in Resectable Epithelial Subtype Pancreatic Cancer

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Study Products: Paricalcitol [Trade Name: Zemplar]
Nivolumab [Trade Name: Opdivo]

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Study Summary

Title	A Randomized Pilot Study of Perioperative Nivolumab and Paricalcitol to Target the Microenvironment in Resectable Epithelial subtype Pancreatic Cancer
Short Title	Perioperative Nivolumab and Paricalcitol in Resectable Epithelial Pancreatic Cancer
IND	139493
IRB Number	827788
Protocol Number	UPCC 22217
Phase	Pilot
Methodology	Open-label Randomized Pilot/Pharmacodynamic/Genomic
Study Duration	18 Months
Study Center	Abramson Cancer Center at University of Pennsylvania)

Objectives	**Primary Objective** To determine the effect of neoadjuvant targeting of the immune microenvironment with checkpoint blockade and chemotherapy with or without vitamin D in subjects with resectable epithelial-subtype pancreatic cancer through an assessment of (a) tumor fibrosis, (b) the degree and type of tumor-infiltrating lymphocytes, (c) expression of vitamin D-regulated genes, and (d) circulating cytokine profiles, and (e) stromal imaging features using DCE- and DW-MRI. **Secondary Objectives** 1. To describe the effect of gemcitabine/cisplatin/nab-paclitaxel/nivolumab with or without vitamin D on tumor response to neoadjuvant chemotherapy in the primary tumor in epithelial subtype patients 2. To determine the safety of this perioperative approach by defining the adverse effects in both arms of the study 3. To determine the feasibility of this perioperative approach
Number of Subjects	20 randomized

Diagnosis and Main Inclusion/Exclusion Criteria	**Inclusion Criteria**: 1. Subjects must have previously untreated apparently resectable adenocarcinoma of the pancreas at registration. 2. A tumor biopsy must be obtained before the initiation of treatment for characterization of the tumor subtype (epithelial vs quasi-mesenchymal (QM) – unless the patient has usable baseline tissue obtained previously. [Note that patients who meet these inclusion criteria, and have tissue sent for analysis may have treatment initiated with chemotherapy while tissue analysis is completed.] 3. Subjects must be age 18 years or older. 4. Standard laboratory criteria for hematologic, biochemical, and urinary indices. 5. Subjects must have an ECOG performance status of 0-2. 6. Subjects must be able to sign a written informed consent document. **Exclusion Criteria:** 1. Subjects who are currently pregnant, planning to become pregnant, or breast-feeding. 2. Subjects who, in the opinion of the physician, would not be clinically appropriate for receipt of the therapy regimen associated with participation 3. Subjects with serious autoimmune disease, organ transplant, need for immunosuppression, or other contraindication to immunotherapy

Study Products, Dose, Route, Regimen	**Product:** Paricalcitol **Dose:** 50 micrograms **Route:** IV **Regimen:** (in subjects randomized to paricalcitol arm) IV days 1, 8, and 15 of each chemotherapy cycle and weekly up to surgery **Product:** Nivolumab **Dose:** 360 mg **Route:** IV **Regimen:** Day 1 of each chemotherapy cycle
Duration of administration	Chemotherapy with gemcitabine/nab-paclitaxel/cisplatin may be given before the tissue analysis to define pancreatic cancer subtype is available, and randomization will take place only in the epithelial-subtype population. Registered patients with QM-subtype disease will be excluded from further treatment on study and treated as per local standards. For those randomized, evaluable patients for response should have received a minimum of one full 21-day cycle of nivolumab/gemcitabine/cisplatin/abraxane +/- paricalcitol (unless curtailed for toxicity). Those receiving paricalcitol will continue weekly up until surgery. The last dose of paricalcitol may be given up to one day before surgery. Post-operatively, (beginning approximately 4-8 weeks after surgery) all randomized subjects will be treated with gemcitabine/nab-paclitaxel/cisplatin/nivolumab with or without paricalcitol for 6 21-day cycles

Statistical Methodology	Subjects with established epithelial-subtype pancreatic cancer will be randomized to receive or not receive IV paricalcitol weekly along with chemotherapy/nivolumab pre-operatively. All eligible subjects will receive gemcitabine, cisplatin, nab-paclitaxel, and nivolumab preoperatively. All subjects will also receive 6 additional cycles of the same therapy post-operatively. This trial is directed to establishing feasibility of the approach, and has the primary endpoint of detecting changes in tumor morphology, the tumor microenvironment, and immune cell biology, and MRI markers of tumor stroma in subjects treated with vitamin D as compared to controls. The primary benchmarks will be qualitative.

1.0 Objectives and Endpoints

1.1 Primary Objective

To determine the effect of neoadjuvant targeting of the immune microenvironment with checkpoint blockade and chemotherapy with or without vitamin D in subjects with epithelial-subtype resectable pancreatic cancer through an assessment of (a) tumor fibrosis, (b) profiling of circulating lymphocytes and tumor-infiltrating lymphocytes, (c) expression of vitamin D-regulated genes, and (d) circulating cytokine profiles , and (e) stromal imaging features using DCE- and DW-MRI.

1.2 Primary Endpoints

1. Tumor fibrosis score by immunohistochemistry
2. Number and subtype of tumor-infiltrating lymphocytes by immunohistochemistry, T-cell clonality in tumor and blood by T-cell receptor sequencing, and characterization of T-cell neoantigen responses *in vitro*
3. Gene expression profile of tumor and lymphocytes by RNA-Seq and, if feasible, ATAC-Seq
4. Cytokine expression profile by 30-plex Luminex panel
5. Parametric maps of K^{trans} (the rate constant of transferring unit volume of contrast agent across capillaries to interstitial space, min^{-1}), k_{ep} (the rate constant between extracellular space and capillaries, min^{-1}), τ_i (the intracellular water life time, sec), V_p (vascular fraction) and V_e (extracellular and extravascular volume fraction, %, $V_e = K^{trans}/k_{ep}$) will be obtained from modeling of the DCE-MR images. Parameter map of the apparent diffusion coefficient (ADC) of water will be derived from DW-MR images of the tumor.

1.3 Secondary Objectives

1. To describe the effect of gemcitabine/cisplatin/nab-paclitaxel/nivolumab with or without vitamin D on tumor response to neoadjuvant chemotherapy in the primary tumor in epithelial-subtype resectable pancreatic cancer
2. To determine the safety of this perioperative approach by defining the adverse effects in each arm of the study
3. To determine the feasibility of this perioperative approach

1.4 Secondary Endpoints

1. Objective response rate (ORR) by RECIST 1.1 criteria
2. Progression-free survival (PFS), disease-free survival (DFS) and overall survival (OS) by Kaplan-Meier methods
3. Toxicity rates using CTCAE v. 5

4. Feasibility, defined as the proportion of subjects who receive any neoadjuvant therapy who proceed to surgery
5. Proportion of R0 surgical resections

2.0 Background

2.1 Systemic Therapy for Pancreatic Cancer

Pancreatic cancer is one of the most lethal malignancies of the gastrointestinal tract, with a 5-year survival of less than 8%. In the United States, an estimated total of 56,770 pancreatic cancers will occur in 2019, with 45,750 estimated deaths among these subjects, making it the third leading cause of cancer related mortality [1]. The majority of patients with pancreatic adenocarcinoma have evidence of metastatic disease at presentation, and they have an expected median survival of only about 12 months despite the recent success of new chemotherapy regimens FOLFIRINOX and gemcitabine with nab-paclitaxel [2,3]. Single agent therapy with 5-flurouracil (5-FU) or gemcitabine achieves response rates of about 10%, and survival less than 6 months [4,5]. In Phase III trials, the response rates with FOLFIRINOX and gemcitabine/nab-paclitaxel were 32% and 23%, respectively. These improvements in systemic therapy for metastatic disease have led to ongoing studies of FOLFIRINOX and gemcitabine/nab-paclitaxel for earlier stage disease, and FOLFIRINOX has demonstrated superiority over gemcitabine for the adjuvant indication [6].

In the approximately 20% of subjects with resectable pancreatic cancer, relapse rates after curative-intent surgery range from 75-85% with historical standards of adjuvant therapy, either gemcitabine or 5-FU chemotherapy with or without the addition of 5-FU-based chemoradiotherapy [7,8]. The ESPAC-4 trial demonstrated activity with the addition of capecitabine to gemcitabine in the adjuvant setting, with improvement in 5-year survival from 16.3% to 28.8% [9]. More recently, adjuvant modified FOLFIRINOX (mFOLFIRINOX) has become the standard of care in the adjuvant setting for patients fit enough for the regimen, with improvements in median overall survival to 55.4 months compared to 35.0 months with gemcitabine [6]. The multinational phase III APACT trial presented preliminary results at ASCO in 2019 and did not meet its primary endpoint, with no improvement in disease-free survival (DFS) by central radiology review compared to gemcitabine monotherapy. Investigator-assessed DFS was significantly improved with GA compared gemcitabine (median 16.2 vs. 13.7 months), and there was a strong trend towards overall survival favoring GA although data was still immature [10].

Additional studies of adjuvant gemcitabine/nab-paclitaxel and FOLFIRINOX are ongoing, but in this study we pilot inclusion of the addition of cisplatin to gemcitabine/abraxane. This combination has been associated with high response rates, with 2 complete responses and 15 partial responses (68% overall response rate) in 25 patients with metastatic PDAC treated in a phase IB/II trial [11].

2.2 Neoadjuvant Therapy of Pancreatic Cancer

The neoadjuvant setting provides an ideal framework to combine clinical results and advanced tissue biomarkers to address key questions for targeted cancer therapy. Despite the advances afforded by targeted therapies in selected solid tumors, in pancreatic as in other epithelial cancers progress been modest in the past ten years. One advance in other tumors has been in the application of systemic therapy and radiation therapy in advance of, instead of after surgery. The advantages of this neoadjuvant approach are many, and include: earlier systemic therapy of what is usually disseminated (i.e. not local) disease; better tolerability of chemotherapy and of chemoradiation than in the post-operative setting, allowing more subjects to receive the full doses and duration of therapy; smaller radiation fields when the tissue planes have not been disrupted by surgery; and shrinkage of the primary tumor to facilitate surgical resection. Importantly, this has generally resulted in no loss of subjects who would benefit from surgery, i.e., no progression during this phase to render a potentially operable subject inoperable. Neoadjuvant therapy is now widely used in locoregionally-advanced cancers of lung, breast, gastrointestinal, head and neck, urological, and gynecological origin.

Because of the limited activity of single-agent 5-FU or gemcitabine, neoadjuvant therapy in pancreatic cancer has historically been reserved for subjects with borderline resectable or unresectable locally-advanced disease, with a goal of conversion to resectable disease. Subjects presenting with initially resectable disease generally proceed to upfront surgery to avoid the risk of disease progression during neoadjuvant therapy, despite the recognition that many subjects have occult metastatic disease that manifests soon after surgery. The activity of FOLFIRINOX and gemcitabine/nab-paclitaxel is changing this paradigm, with several ongoing studies of both regimens in the neoadjuvant setting for borderline or initially unresectable disease. The use of FOLFIRINOX with chemoradiotherapy resulted in surgical resection in 32 of 48 patients with borderline pancreatic cancer treated with neoadjuvant therapy, with 31 patients having an R0 resection with clean surgical margins [12]. Increasingly, neoadjuvant therapy has become standard at some centers even in patients with resectable disease, as evidenced by the rapid complete accrual of the SWOG 1505 trial randomizing patients with resectable disease to perioperative gemcitabine/nab-paclitaxel or FOLFIRINOX. We believe that neoadjuvant therapy represents a unique setting for novel therapeutic approaches in pancreatic cancer, combining unmet need with the rare opportunity for clinicopathologic correlative studies.

Our previous study of gemcitabine/abraxane and paricalcitol (25µg three times weekly) in 14 subjects resulted in several findings of interest: (a) excellent tolerability with no significant adverse effects from the paricalcitol; (b) Expected changes in expression of vitamin D-regulated genes; (c) a prominent lymphocytic infiltrate, but with cells that were not activated [O'Dwyer PJ, unpublished]. Continued development of this regimen requires continued exploration of dose and schedule of paricalcitol, as well as an effort to activate the infiltrating T cell population. The current trial will address aspects of both of these goals.

2.3 Microenvironment in Pancreatic Cancer

The tumor microenvironment represents a barrier to the successful treatment of pancreatic cancer [13]. Our studies in tumor samples from subjects with resected pancreatic cancer have focused on a group of multi-potent cells in the pancreatic tumor environment [14]. These pancreatic stellate cells (PSCs) are neuroendocrine, nestin-positive, lipid-accumulating cells whose homologues in the liver are the principal repository of Vitamin A esters. When activated, lipid droplets are lost and via trans-differentiation they become the key cell type responsible for driving the severe desmoplasia that characterizes pancreatic ductal adenocarcinoma (PDA). We harvested these cells from pancreatic cancer cell suspensions, and identified the vitamin D receptor (VDR) as a master genomic regulator of PSC activation and function. *In vitro* we found that VDR activation reduces expression in PSCs of genes implicated in activation, inflammation, and extracellular matrix production, as well as restoring lipid droplet integrity. *In vivo*, the VDR ligand calcipotriol enhances the anti-tumor effects of gemcitabine by increasing intratumoral concentration 5-fold, reducing tumor volume to near baseline and lowering metastases by more than 65% [14]. These findings prompted us to test the therapeutic potential of VDR activation in the clinic. We recently completed accrual of a randomized pilot study of paricalcitol combined with gemcitabine and nab-paclitaxel in the neoadjuvant setting, and initial results appear promising [O'Dwyer, unpublished data]. Our preclinical experience suggests that this activity may be due in part to a microenvironment that is more hospitable to tumor-infiltrating lymphocytes (TILs). We hypothesize that the addition of immune checkpoint blockade using a programmed death ligand 1 (PD-1) inhibitor will further improve the efficacy of VDR activation.

2.4 Clinical Experience with Gemcitabine/cisplatin/nab-paclitaxel in Pancreatic Cancer

After the FDA approval of gemcitabine for metastatic pancreatic cancer in 1996, numerous attempts were made to improve upon either gemcitabine or 5-FU with combination therapy. A series of phase III trials using gemcitabine along with oxaliplatin, bevacizumab, or cetuximab [15-17] failed to improve upon single-agent gemcitabine, despite promising phase II results. Several studies suggest that taxanes are active in pancreatic cancer, but a randomized trial of gemcitabine with paclitaxel was never pursued (probably on the basis that the differences seen in Phase II trials were insufficiently persuasive). The development of a novel taxane conjugate with albumin, nab-paclitaxel, with established activity in breast cancer, prompted a Phase II trial of gemcitabine/nab-paclitaxel by Von Hoff [18]. The Phase I/II data were highly promising, with response rates of the order of 40%, tolerable toxicity, and a one-year survival of about 48% [18]. A phase III trial of gemcitabine versus gemcitabine/nab-paclitaxel confirmed the survival benefit associated with this approach [3]. The development of a more intensive, but toxic regimen (FOLFIRINOX) in no way diminishes the enthusiasm for this chemotherapy backbone, given the activity in Phase II trials that appears comparable [18,19]. Additionally, FOLFIRINOX has proven to be a more difficult chemotherapy backbone upon which to layer additional agents. This was recently evidenced by two randomized phase II studies using chemotherapy with or without the hyaluronidase PEGPH20 in patients with untreated metastatic PDAC. The addition of PEGPH20 to gemcitabine/nab-paclitaxel improved PFS and ORR while the addition of PEGPH20 to FOLIFIRNOX resulted in markedly worse overall survival and early study termination [20, 21].

Nab-paclitaxel (nab-paclitaxel) is a cremophor-free formulation of nanoparticle paclitaxel stabilized with human serum albumin (130 nm particles). The drug achieves enhanced tumor penetration through gp60 albumin receptor-mediated endothelial transcytosis, which enables transit across the vessel endothelium, and makes the active paclitaxel available to the tumor. Combination therapy with gemcitabine has been shown to result in increased intratumoral levels of gemcitabine [22] as well as marked reduction in collagen deposition and tumor fibroblasts [23]. In the phase III trial of gemcitabine/nab-paclitaxel, the objective response rate by independent review was 23% in the combination arm, with a total of 48% of subjects with disease control (stable disease at 16 weeks or response) [3]. Median survival was 8.5 months, which was significantly improved compared to 6.7 months in the gemcitabine arm. The therapy was generally well tolerated, with some increased toxicity compared to single-agent gemcitabine, predominantly neuropathy attributable to nab-paclitaxel and increased myelosuppression. Based on this tolerability as well as the effects on the microenvironment, we selected it as the backbone chemotherapy regimen.

The activity of platinum seen in the FOLFIRINOX regimen for pancreatic cancer led to the development of a phase Ib/II trial adding cisplatin to gemcitabine and nab-paclitaxel for newly diagnosed metastatic pancreatic cancer [11]. This trial established that gemcitabine/cisplatin/nab-paclitaxel is tolerable using a cisplatin dose of 25mg/m2 with gemcitabine 1000mg/m2 and nab-paclitaxel 125mg/m2 on days 1 and 8 of a 21-day treatment cycle. Efficacy was highly promising, with response rates of 68% (2 complete responses and 15 partial responses in 25 patients) and only 3 of 25 patients experiencing initial progression. The main increased toxicity was thrombocytopenia, with 40% of patients experiencing grade 4 thrombocytopenia. A more recent iteration of this chemotherapy combination in advanced biliary cancer used slightly lower doses of chemotherapy (800mg/m2 of gemcitabine and 100mg/m2 of nab-paclitaxel) and showed lower rates of dose interruption or grade 4 toxicity [24]. Because of concerns about surgical delays due to toxicity in this potentially curable population, the lower dose regimen used in biliary cancers was selected.

2.5 Paricalcitol

In this trial, we will perform an analysis of the effects of VDR activation in stellate cells in the initial therapy of pancreatic cancer, as manifested by fibrosis in the resected specimen. We have selected paricalcitol based on its broad use over a decade in the management of calcium and vitamin D homeostasis in subjects undergoing renal dialysis. Paricalcitol is chemically designated as 19-nor-1α,3β,25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene, and is a non-metabolized vitamin D analogue that has little hypercalcemic activity. As such, it is the ideal compound to effect the desired transcriptional change in the stellate cells. In addition to well-established effects on bone mineral homeostasis, there is increasing recognition that vitamin D may play a role in renal and cardiovascular function, as well as T cell function in some circumstances. Randomized clinical trials showed a positive effect of paricalcitol in subjects with chronic renal disease on mineral metabolism, on cardiovascular outcome, and on markers of kidney damage [25]. This positive effect on survival is observed not alone in subjects with elevated intact parathyroid hormone (iPTH), but even in those with low levels of this hormone [26].

The recommended starting dose of IV paricalcitol is 0.04-0.1 µg/kg (or about 3-7µg per dose) up to three times weekly, but total weekly doses of 15 to 30 µg are reported in the literature in subjects with CKD without safety concerns [27-29]. For oral paricalcitol, starting doses range from 1-2 µg/day for daily dosing or 2-4 µg/day for thrice weekly dosing, with the effect on PTH dependent on the total weekly dose [30,31]. Bioavailability of paricalcitol capsules ranges from 72-86%. In healthy volunteers, the half-life of paricalcitol is significantly shorter than in subjects with CKD (IV: 5-7 hours vs. 14-15 hours; PO: 4-6 hours vs. 17-20 hours), and dosing data is limited in individuals with normal renal function, with the exception of several oncology trials. A trial in combination with paclitaxel in breast cancer subjects gave up to 7µg per day PO for 12 weeks [32], while a trial in subjects with myelodysplastic syndrome reached doses of up to 56 µg PO per day [33]. In a population of prostate cancer subjects (mean age 74) thrice weekly IV paricalcitol was administered at doses up to 25µg, with no dose-limiting toxicity [34]. The authors suggested, in the discussion, that higher doses be explored. In concentration ranges achievable in humans, a dose-dependent effect on PBMC activity [35] and radiosensitivity [36] has been demonstrated, and we aimed to achieve doses near the maximum of tolerability.

We selected the thrice weekly 25µg IV dose in our initial trial with gemcitabine/nab-paclitaxel/paricalcitol. Subjects were randomized to receive or not receive paricalcitol with 1 cycle of preoperative chemotherapy, and then all subjects received thrice weekly paricalcitol with an additional 3 postoperative cycles of chemotherapy. While the toxicity attributable to paricalcitol was minimal at this dose, with a single instance of asymptomatic grade 2 hypercalcemia in one of 15 subjects, thrice weekly IV dosing was logistically difficult for some subjects. As noted above, toxicity, primarily hypercalcemia, is dependent on the total weekly dose. Based on our finding of tolerability at a total dose of 75 µg weekly, as well as prior evidence of tolerance of up to 56µg per day orally [33] , this study will examine IV dosing at 50 µg once weekly. We hypothesize that this dosing will achieve the same effects as our prior thrice weekly dosing with a more practical schedule. A detailed population pharmacokinetic analysis including over 600 subjects showed mean plasma clearance of 1.75l/h, and stable phosphorus and calcium levels in the first 30 days of treatment [37]. This analysis lends support to both the dose and schedule chosen here as well as to the schedule of weekly electrolyte monitoring.

Pancreatic Cancer subtypes exhibit differential effects in response to paricalcitol.

Transcriptional profiling has defined pancreatic ductal adenocarcinoma (PDAC) into distinct subtypes with the majority being classical epithelial (E) or quasi-mesenchymal (QM) [38-40]. Despite clear differences in clinical behavior, growing evidence indicates these subtypes exist on a continuum with features of both subtypes present and suggestive of interconverting cell states [41-43]. We investigated the impact of different therapies being evaluated in PDAC on the phenotypic spectrum of the E/QM state. We demonstrate that FOLFIRINOX combination chemotherapy induces a common shift of both E and QM PDAC towards a more mesenchymal state in cell lines and patient tumors. Vitamin D, another drug under clinical investigation in PDAC, instead augments baseline E and QM states of PDAC cell lines, resulting in transcriptional and functional changes that increase metastatic propensity in QM PDAC, but decrease dissemination in E PDAC in vivo mouse models. These data highlight the critical need for molecular subtyping of PDAC tumors to guide current and future clinical trials and we demonstrate the feasibility of an RNA-in situ hybridization (RNA-ISH) assay for this purpose.

In pursuing the activity of vitamin D analogues further in pancreatic cancer models, it was observed that anti-proliferative and antimetastatic effects were observed in certain models, but that in some cell types, a more invasive phenotype was generated [Ting, manuscript in press]. Further analysis of these models by our co-Investigator David Ting showed differences in pre-treatment gene expression, such that the vitamin D-sensitive cells could all be classified as having an epithelial profile, while that of the more invasive cells, was quasi-mesenchymal, a cell type that already possesses these more metastatic features, in that that they overlap with the epithelial-mesenchymal transition (EMT) phenotype. This may further suggest some plasticity between the populations, nonetheless numerous analyses support an impact of these profiles on the biological behavior of pancreatic cancers. While these responses of the QM tumors are an increase of an already existing propensity, such that in metastatic disease the contribution may be less important, it was agreed by the investigators that we should amend the eligible population in the perioperative setting to eliminate those classified as QM. This cautious approach required that the analyses in Dr Ting's laboratory be transferred and operationalized in a CLIA-compliant environment, and this has now been achieved in the Pathology Department in MGH, where all the samples will be analyzed under the supervision of Dr John Iafrate. It is for this reason that the protocol has been delayed in its implementation, and is amended. As discussed under Study Design, below, the revised procedures will permit all patients to begin standard neo-adjuvant chemotherapy, so as not to delay that. When the results of the classification are available, the epithelial subtype patients (60%) will be randomized to receive paricalcitol or not while the QM patients will not be eligible for further study therapy.

2.7 Immune Checkpoint Blockade in Pancreatic Cancer

Pancreatic adenocarcinoma has traditionally been considered a non-immunogenic tumor, with a paucity of tumor-infiltrating T-effector lymphocytes that characterize tumors targeted successfully with immune checkpoint blockade. The biology underlying the immunosuppressive microenvironment is complex, and is well described in multiple recent reviews [44-48]. Preclinical models and pathologic correlates demonstrate a densely fibrotic desmoplastic stroma surrounding the tumor with a variety of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). These suppressive myeloid cells interact with T-cells, promoting polarization towards a microenvironment rich in $CD4^+$ T-cells with a Th2 phenotype and $CD25^{high}Foxp3^+$ Tregs. MDSCs also induce expression of PD-L1 in $CD8^+$ T-cells via a MAPK-dependent mechanism [45]. Despite this PD-L1 response, single agent checkpoint blockade with either CTLA-4 or PD-1 antibodies has been ineffective in pancreatic cancer, with no objective responses in clinical trials [49, 50]. One strategy to overcome this lack of efficacy has been combination immunochemotherapy to induce antigen release. In early results from a phase I trial of nab-paclitaxel, and nivolumab with or without gemcitabine, 2 of 11 subjects with prior chemotherapy had a partial response to nab-paclitaxel and nivolumab without gemcitabine [51]. Additionally, 3 of 6 treatment-naïve subjects had a partial response to the triplet regimen, while the remaining 3 subjects had stable disease at 12 weeks. The regimen was well tolerated with only the toxicity expected of nab-paclitaxel and gemcitabine.

Our prior study with neoadjuvant gemcitabine/nab-paclitaxel/paricalcitol demonstrated "normalization" of the $CD8^+$ T-cell infiltration in the tumor microenvironment [O'Dwyer PJ, unpublished]. In untreated subjects, $CD8^+$ T-cell densities were markedly lower than in the surrounding tissue, while those treated with neoadjuvant therapy had equivalent $CD8^+$ T-cell infiltrates in the tumor and the surrounding tissue. Comparison of subjects who did and did not receive paricalcitol with their neoadjuvant therapy is ongoing, but our preclinical work suggests VDR-dependent augmentation of the T-cell response via CXCL12 inhibition [14]. We hypothesize therefore that that neoadjuvant therapy with gemcitabine/cisplatin/nab-paclitaxel/paricalcitol in combination with nivolumab will generate a more robust immune response and induce immunosurveillance by $CD8^+$ effector T-cells.

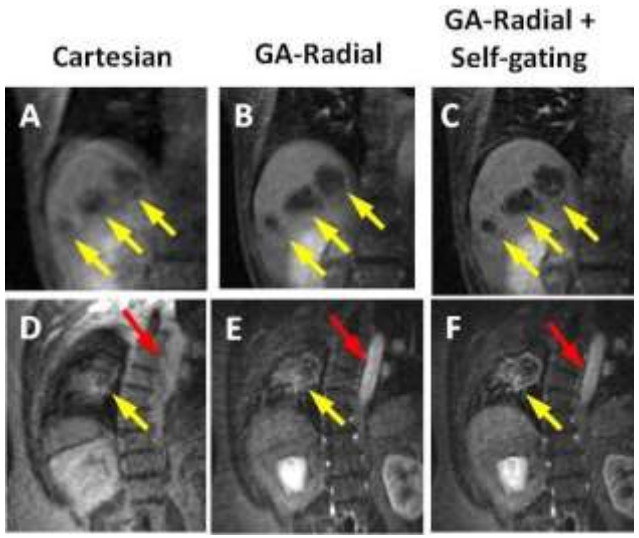


Figure 1 In standard Cartesian images (left column), liver metastatic lesions (yellow arrows in A) and lung lesion (yellow arrow in D) are blurred due to respiration motion. Lesion boundaries and structures are better defined in images obtained by golden angle radial acquisition (GA-radial in middle column) and by GA-radial + respiration self-gating (right

2.8 Dynamic contrast enhanced MRI (DCE-MRI) and Diffusion-weighted trace MRI (DW-MRI)

DCE-MRI and DW-MRI are quantitative MRI techniques which are sensitive to changes of tumor microenvironment and can be used to evaluate responses to stroma-directed drugs. For example, DW-MRI is sensitive to changes of water diffusion induced by changes of cellularity and extracellular matrix components. Preclinical studies have shown that the aberrant accumulation of extracellular hyaluronan (HA), a matrix component, results in high interstitial fluid pressure of the tumor that restricts vessel permeability and perfusion [52, 53], the reversal of which is detected by DCE-MRI [54]. Although DCE- and DW-MRI techniques have been applied in the clinic setting to assess antiangiogenic and chemotherapy [55-60], their utility has not been examined carefully for stroma-directed therapy of PDA patients. A preliminary study in 6 patients has shown that DCE-MRI appeared promising in detect changes induced by the stroma-directed drug, PEGPH20, a PEGylated recombinant human hyaluronidase that degrades HA in PDA and we have shown similar DCE-MRI changes in mouse PDAC models using both PEGPH20 and vitamin D [52, 61-62].

Located in the upper abdomen, the pancreatic tumor is prone to respiratory motion-induced blurring & ghosting and susceptibility-related anatomic distortions in DCE- and DW-MR images. In the past, we have addressed these issues by designing motion-resistant image acquisition methods as well as several post-processing methods.

We have shown (Figure 1) these methods are effective to suppress motion in DCE-MRI of breast, liver and lung cancer in patients while maintaining special and temporal resolution of the images [63-66]. To minimize the motion artifacts in DW-MRI, the echo planar imaging (EPI) alone or in combination with respiration-gating during image acquisition will be applied.

In parallel to the proposed human trial, we are conducting a co-trial in mice supported by NCI (U24-CA-231858), and we have previously shown that K^{trans} (derived from DCE-MRI) is sensitive and robust in detecting the early response to the stroma-directed drug as well as combined treatment (stromal drug plus chemotherapy) [67].

2.9 Dose Selection for gemcitabine/nab-paclitaxel/cisplatin with nivolumab and paricalcitol

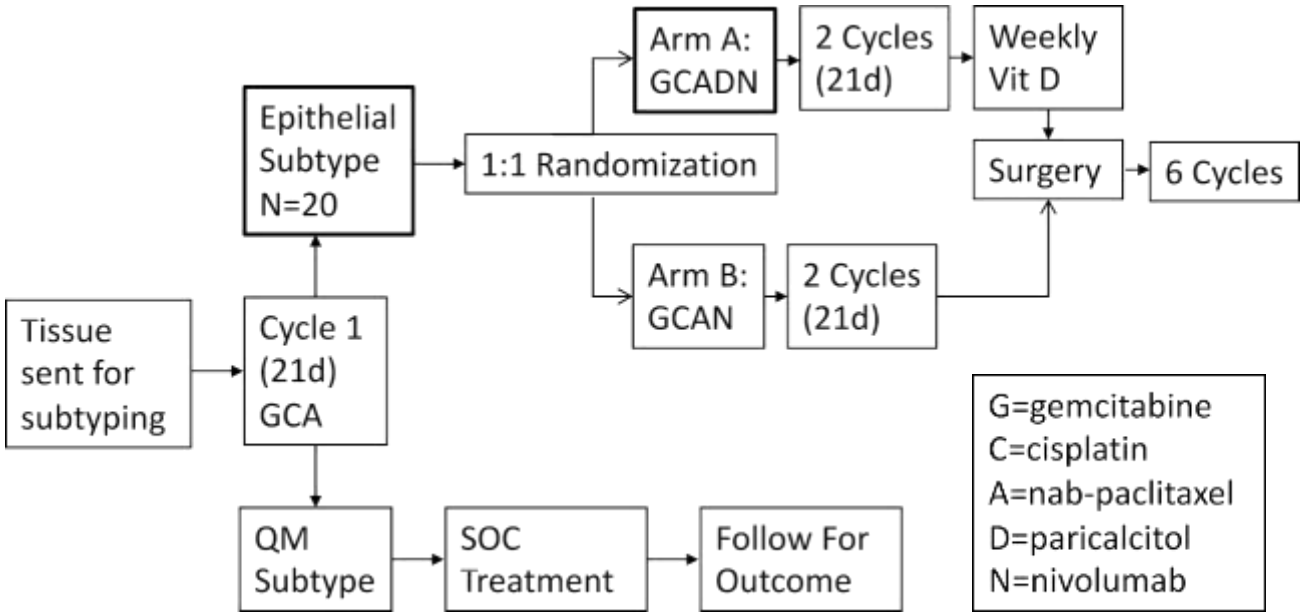
The safety of gemcitabine/nab-paclitaxel/cisplatin with nivolumab and paricalcitol has been demonstrated in an ongoing trial in patients with metastatic pancreatic cancer [Von Hoff et al, unpublished data]. As detailed above, the chemotherapy backbone of gemcitabine/cisplatin/nab-paclitaxel was chosen based on highly promising efficacy results as well as safety concerns with using an untested FOLFIRINOX combination. The lower dose regimen of gemcitabine/cisplatin/nab-paclitaxel established in biliary cancers was selected to minimize dose delays or interruptions in this curative-intent population. The weekly paricalcitol dose was chosen based on safety demonstrated at doses at or above 50mcg daily and the logistical difficulties experienced by some patients in our prior trial using a three-times weekly administration schedule. Lastly, the nivolumab doses of 360mg every 3 weeks was selected to coincide with the start of each chemotherapy cycle, and this dose has been validated in phase III studies with 21-day chemotherapy regimens [52].

3.0 Study Design

We propose a small feasibility trial, piloting the pre-treatment chemotherapy with nivolumab and 1:1 randomization to receive or not receive weekly intravenous paricalcitol. The feasibility of the approach will be assessed in the completion of the preoperative therapy; success will be defined by at least 90% of the subjects who receive any preoperative therapy on study subsequently undergoing pancreatic resection. The trial was originally designed to provide one cycle of pre-operative therapy: the need to obtain sub-classification data on the eligible patients, a process that will take some time (generally 7-14 days) has led us to build flexibility into the trial. The diagnosis of pancreatic cancer carries with it some urgency to start treatment, on the part of both physician and patient. Accordingly, initiation of chemotherapy is permitted as soon as tissue for analysis has been obtained and shipped. While the patient will be registered on the trial at that time, only those with the epithelial subtype will be randomized.

The primary endpoint of interest will be in the effects on tumor (e.g. compared with previous tumors we have examined is there evidence of a difference in fibrosis, both qualitatively and by immunohistochemistry, or in the appearance or proportion of the tumor cells, or infiltrating lymphocytes). We also propose an extensive immunological and inflammatory assessment at intervals. This trial is pilot in nature, and therefore, hypothesis-generating with descriptive endpoints.

Figure 1: Treatment Schema



4.0 Study Population

4.1 Target population

This trial will seek to enroll 20 treatment naïve subjects with apparently resectable adenocarcinoma of the pancreas with the epithelial subtype who have a planned standard of care resection surgery scheduled (or in scheduling).

An estimated 14 patients (40% of all PDAC patients) will have the quasimesenchymal subtype and will be not be randomized.

It is recognized that a few subjects thought to have apparently resectable adenocarcinoma of the pancreas, and for whom surgery is indicated, may turn out not to have an adenocarcinoma. The subjects should be identified with the tissue biopsy analysis and will be replaced.

4.2 Inclusion Criteria

1. Previously untreated, apparently resectable (defined in section 4.5) adenocarcinoma of the pancreas at registration. Histologic confirmation of adenocarcinoma must be obtained before chemotherapy is initiated.
2. A tumor biopsy must be obtained before the initiation of treatment for characterization of the tumor subtype (epithelial vs quasi-mesenchymal (QM) – unless the patient has usable baseline tissue obtained previously. [Note that patients who meet these inclusion criteria, and have tissue sent for analysis may have treatment initiated with chemotherapy while tissue analysis is completed.]
3. Age greater than or equal to 18 years
4. ECOG performance status of 0-2.
5. Standard laboratory criteria for hematologic, biochemical, and urinary indices within a range that, in the opinion of the physician, clinically supports enrollment of the subject on the trial.
    a. Note: subjects must have: Creatinine $\leq$ 1.5 xULN AND eGFR $\geq$50 by Cockroft-Gault equation, Neutrophils >1.5x10^9/L, total bilirubin $\leq$ 1.5 xULN (3 x ULN if due to biliary obstruction), AST $\leq$3 x ULN (5 x ULN if due to biliary obstruction), ALT $\leq$3 x ULN (5 x ULN if due to biliary obstruction), and Platelets >100,000/mm^3
6. Ability to provide written informed consent
7. Willing and eligible to undergo paired MRI examinations

4.3 Exclusion Criteria

1. Subjects with hypercalcemia (blood levels greater than 11.5 mg/dL). In subjects with creatinine clearance 50-60mL/min, blood calcium levels must be 9.5 mg/dL or lower.
2. Subjects who are currently pregnant, planning to become pregnant, or breast-feeding.
    a. *Females participants of child-bearing potential are required to use an effective contraception method (see Appendix A) or abstain from intercourse during treatment and for at least 5 months following the last dose*
    b. *Males participants with partners of child-bearing potential are required to use an effective contraception method (see Appendix A) or abstain from intercourse during treatment and for at least 7 months following the last dose*
3. Subjects who, in the opinion of the physician, would not be clinically appropriate for receipt of the therapy regimen associated with participation
4. Subjects with contraindications to immune checkpoint therapy, as follows:

a. Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity
b. Prior organ allograft or allogeneic bone marrow transplantation
c. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication
d. Active autoimmune disease, except for vitiligo, type 1 diabetes mellitus, asthma, atopic dermatitis, or endocrinopathies manageable by hormone replacement; other autoimmune conditions may be allowable at the discretion of the principal investigator
e. Condition requiring systemic treatment with either corticosteroids
    - Systemic steroids at physiologic doses (equivalent to dose of oral prednisone 10 mg) are permitted. Steroids as anti-emetics for chemotherapy are strongly discouraged (see section 5.1.3)
    - Intranasal, inhaled, topical, intra-articular, and ocular corticosteroids with minimal systemic absorption are permitted.

4.4 Withdrawal, Removal, and Replacement of Subjects

Subjects may withdraw from the study at any time at their own request in which case investigators will seek permission from such subjects for investigators to continue to contact them every 6 months for follow-up; however, subjects may choose to withdraw completely from all procedures and follow-up. Subjects may also be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, and request the subject to return for a final visit and follow-up regarding any unresolved AEs. If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

An individual subject will not receive any further study drug if any of the following occur in the subject in question:

- Progressive Disease
- Complete Withdrawal of consent from the study (no further data collection permitted)
- Withdrawal of consent from further treatment with study drug (data collection as per study schedule permitted)
- Lost to Follow up
- An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing including but not limited to hypersensitivity to any of the therapeutic agents
- Pregnancy or intent to become pregnant
- Subject Non-Compliance that, in the opinion of the investigator warrants withdrawal (e.g., refusal to adhere to the scheduled visits)

- Initiation of another anti-cancer therapy (excluding surgery or palliative radiotherapy), including another investigational agent

4.4.1 Replacement of subjects

Subjects who at the time of resection who do not have a diagnosis of adenocarcinoma will be replaced for the total accrual goal, but where possible samples of primary tumor will be obtained for the endpoints of the study. In addition, subjects who may have previously unrecognized criteria for unresectability will be replaced for the total accrual goal. Subjects who receive fewer than two doses of chemotherapy for toxicity in the preoperative period will be discontinued from participation and continue per clinical care to surgery. These enrollment slots will then be replaced. Subjects who are determined to be not appropriate for post-operative adjuvant therapy or receive alternative adjuvant therapy will not be replaced in the sample size.

4.5 Resectability

The primary objective of this trial is surgical tissue analysis for all randomized patients to ascertain the effects of vitamin D plus chemoimmunotherapy. Extension of neoadjuvant therapy beyond 3 cycles and/or the addition of chemoradiation is not permitted on trial. Resectability for this study is thus defined as a tumor that a surgeon and/or multidisciplinary tumor board believes can be completely resected prior to treatment and without any need for response to neoadjuvant therapy. We will secondarily analyze the proportion of cases that were defined as resectable and the proportion defined as borderline by NCCN guidelines, but the determination of the surgeon is paramount. Patients requiring vein reconstruction or other vascular procedures for complete tumor removal are permitted to enroll at the discretion of their surgeon.

5.0 Treatment Plan

5.1 Chemotherapy

5.1.1 Initial Chemotherapy while Awaiting Molecular Subtype

All subjects will receive one cycle of the gemcitabine/cisplatin/nab-paclitaxel regimen while awaiting tissue subtyping. Gemcitabine/cisplatin/nab-paclitaxel will be administered on Days 1 and 8 of a 21-day cycle. If tissue subtyping is delayed, a second chemotherapy cycle may be administered while awaiting results.

5.1.2 Tissue Subtyping

FFPE biopsy tissue, either archival or via a fresh biopsy (EUS core biopsy preferred), will be analyzed to determine pancreatic cancer subtype as follows:

For detection of Epithelial (E) and Quasimesenchymal (QM) marker mRNA expression, RNA in situ hybridization (RNA-ISH) will be performed on FFPE slides. FFPE slides will be fresh cut, dried overnight at room temperature and shipped on wet ice or stored at -20 degrees C followed by shipping on ice to the testing laboratory at the Massachusetts General Hospital Cancer Center.

Slides will be stained by RNA-ISH using RNAscope 2.5 Duplex technology with the automation platform (Catalogue No. 322440 on the Bond RX automated immunohistochemistry and RNA-ISH staining system using BDZ 6.0 software (Leica Biosystemd, Buffalo Grove, Ill). The antigen retrieval, probe hybridization and signal amplification methods will be performed per automated ACD protocol on the BondRX device. The panel for E markers include CDH1, EPCAM, KRT5, KRT7, KRT8 and KRT19 and the panel for QM markers include CDH2, SERPINE1 and FN1 as previously described (Mahadevan K et al. Modern Pathology 2019). As a complementary assay, RNA-ISH for GATA6 will also be performed as described (Aung KL et al. Clinical Cancer Research 2018).

Slides will be digitally imaged using a Leica Aperio CS-O slide scanning microscope at 40x magnification. To determine the amount of epithelial (E) versus quasi-mesenchymal (QM) expression, images will be reviewed and scored by a gastrointestinal anatomic pathologist using the criteria of:

Epithelial predominant: Intensity of epithelial transcripts equivalent or greater than normal ductal epithelium [AND] Mesenchymal negative: No mesenchymal transcripts

Quasimesenchymal Epithelial loss: Intensity of epithelial transcripts weaker than normal ductal epithelium [OR] Mesenchymal gain: Gain of mesenchymal transcripts in more than five tumor cells/ HPF

For GATA6 analysis the following scoring will be done:

Score 0, absent to rare discernable dots under 40x objective lens

Score 1, few discernable dots at 20x

Score 2, dots (4–9/cell) resolved at 10x

Score 3, dots (more than 10 dots/cell) or clusters resolved at 5x

E = Score 2-3

QM = Score 0-1

The gastrointestinal anatomic pathologist will evaluate both RNA-ISH markers and determine the E and QM predominance of the tumor.

Patients who are determined to have the quasimesenchymal subtype OR whose tissue is deemed insufficient for assignment of a subtype will not be eligible for further study treatment.

5.1.3 Randomization

Patients with the epithelial subtype will be randomized 1:1 to receive or not receive paricalcitol. All patients randomized will also receive gemcitabine/cisplatin/nab-paclitaxel plus nivolumab as detailed below. Patients with the QM subtype will be ineligible for further treatment on study.

For randomization, a randomly ordered list of numbers 1-20 will be generated using the random number generator available at www.randomizer.org and eligible subjects will be assigned the next available number on this list. Subjects receiving an odd number will be assigned to arm A and subjects receiving an even number will be assigned to arm B. This list will be maintained by the study coordinator at Penn and will not be revealed to other study personnel. This will result in a single block randomization. Neither patient nor investigator will be blinded to treatment once assigned by randomization.

5.1.3 Pre-operative Chemotherapy

All patients will receive a total of 3 pre-operative therapy cycles prior to surgical resection. Once the subtype is determined, patients with the epithelial subtype will begin treatment with chemotherapy plus nivolumab and, in patients randomized to arm A, paricalcitol. Patients who received one cycle of chemotherapy while awaiting subtyping will thus receive two cycles with nivolumab +/- paricalcitol while those who receive two chemotherapy cycles while awaiting subtyping will receive one cycle with nivolumab +/- paricalcitol.

5.1.1.1 Post-operative chemotherapy

After recovery from surgery, subjects will receive 6 adjuvant cycles of the same therapy received pre-operatively.

*Subjects for whom it would not be clinically appropriate to receive this adjuvant therapy will not go on to receive the treatment specified herein. Clinical appropriateness for adjuvant therapy will be determined by the treating physician. Subjects who are determined to be not appropriate for adjuvant therapy or in whom an alternative adjuvant therapy is administered will not be replaced in the sample size.

5.1.2 Paricalcitol

Subjects on Arm A will receive paricalcitol IV 50 µg weekly. Paricalcitol will be administered on Day 1, 8, and 15 of each chemotherapy cycle and continued weekly up until surgical resection. If surgery is delayed, subjects will continue to receive paricalcitol weekly up until the day before surgery. Subjects on Arm A will have calcium/phosphorus monitored to detect calcium or phosphorous changes that would require dose modification. Please see Section 6.1.2 for complete details on dose modifications. Subjects in Arm A will receive paricalcitol post-operatively for 6 cycles on days 1, 8, and 15 of each 21-day cycle.

Subjects on Arm B will not receive paricalcitol pre- or post-operatively.

5.1.3 Nivolumab

Subjects will receive nivolumab at a fixed dose of 360mg on day 1 of each 21-day cycle. When given concurrently with chemotherapy, nivolumab should be administered prior to the chemotherapy.

Table 1: Treatment Plan

Agent	**Dose**	**Route**	**Frequency** **(within a 21-day cycle)**
Nab-paclitaxel	100mg/m^2	IV infusion per institutional guidelines and the Package Insert	Day 1, 8
Cisplatin	25mg/m^2	IV infusion per institutional guidelines and the Package Insert	Day 1, 8
Gemcitabine	800mg/m^2	IV infusion per institutional guidelines and the Package Insert	Day 1, 8

Nivolumab	360mg	IV infusion per institutional guidelines and the Package Insert	Day 1
Paricalcitol (Arm A only)	50 µg IV	IV bolus	Days 1, 8, 15 Weekly prior to surgery

NOTE: Nivolumab should be given prior to chemotherapy.

Surgery will occur (schedules permitting) within 1-4 weeks of the end of preoperative therapy. The maximum window from the last dose of chemotherapy to surgery should not exceed 6 weeks.

The 6 cycles of post-operative adjuvant gemcitabine/cisplatin/nab-paclitaxel/nivolumab with or without paricalcitol will begin 4-12 weeks after surgery as determined by the physician.

5.1.3 Premedication for Chemotherapy

Subjects should receive an anti-emetic regimen that does not include a corticosteroid (usually a 5-HT3 agent of choice such as ondansetron or granisetron plus aprepitant or fosaprepitant) prior to administration of chemotherapy to decrease the incidence and severity of chemotherapy-associated nausea and vomiting. Olanzapine 10mg daily should also be given prior to chemotherapy and for 3 days after each dose of chemotherapy. Exceptions to the corticosteroid restriction should be discussed with the principal investigator, and steroid administration should follow completion of nivolumab when scheduled concurrently. Standard of care drugs such as lorazepam may also be used if clinically indicated.

5.1.4 Duration of Treatment

3 pre-operative cycles, followed by standard of care resection and recovery, then 6 cycles of post-operative therapy —approximately 8-9 months depending on scheduling of resection and recovery before post-operative cycles.

Patients who discontinue one or two chemotherapeutic agents or nivolumab or paricalcitol for toxicity may continue on study therapy. Patients who discontinue all three chemotherapy agents are not permitted to continue therapy with nivolumab and/or paricalcitol alone.

6.0 Dosing Delays/Dose Modifications

Toxicity will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The main toxicities reported with the combination gemcitabine/nab-paclitaxel are neutropenia, nausea/vomiting, reversible elevations of liver enzymes, and neuropathy. The main toxicity reported with vitamin D preparations is hypercalcemia, which will be monitored by serial laboratory testing. Toxicities with nivolumab are uncommon but potentially serious, and include a variety of autoimmune phenomena, including adrenal insufficiency, colitis, pneumonitis, hypophysitis, rash, type I diabetes mellitus, and encephalitis.

Laboratory abnormalities on the day of treatment for second and subsequent courses will be considered in treatment decisions. Values that deviate from eligibility criteria for the study may cause a delay of up to three weeks for recovery to occur. If the abnormalities have not resolved by then, the subject should ordinarily be taken off study. Exceptions to this may be made after discussion with the Principal Investigator and formal approval by the IRB/CTSRMC. Regular meetings of the investigators will take place to ensure that tolerability at later time points is maintained, and changes in dosing strategies that may be needed as a consequence of any possible cumulative toxicity (not currently known to occur) will be accomplished by amendment as needed.

6.1 Dose Modifications

Dose modification should be based upon the worst grade of toxicity experienced.

6.1.1 Dose Modifications for Gemcitabine, Cisplatin and Nab-paclitaxel Toxicity

Subjects who experience toxicity related to gemcitabine/cisplatin/nab-paclitaxel should have their dose modified according to dose reduction/discontinuation recommendations utilized by Shroff et al [12].

per the US package inserts for gemcitabine/nab-paclitaxel for hematological and non-hematological toxicity as described in Table 2, 3 and 4.

These dose adjustments are for AEs deemed related to the study medications. If, in the opinion of the treating Investigator, a toxicity is thought to be unrelated to study medications and resolves to a “Continue” or below lowest grade in the table below, no dose adjustments for the study medications are necessary.

For any toxicity (regardless of grade) that, despite optimal supportive care, is felt by the treating Investigator to present a risk to the patient safety, additional dose reduction, treatment delay, or treatment discontinuation is permitted at the discretion of the treating Investigator. Dose re-escalation will be permitted with approval of the Sponsor/Investigator*:*

Table 2: Dose Level Reductions

Dose Level	Nab-Paclitaxel (mg/m2)	Cisplatin	Gemcitabine (mg/m2)
Full Dose	100	25	800
1st dose reduction	75	25	600
2nd dose reduction	50	25	600
3rd dose reduction	50	20	600
4th dose reduction	Discontinue	Discontinue	Discontinue

Table 3: **Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas**

Cycle Day	ANC (cells/mm3)		Platelet count (cells/mm3)	nab-paclitaxel/ cisplatin/gemcitabine
Day 1	<1500	OR	<100,000	Delay doses until recovery
Day 8	500 to <1000	OR	50,000 to <75,000	Reduce 1 dose level
	<500	OR	<50, 000	Withhold doses

Table 4: **Dose Modifications for Other Adverse Drug Reactions**

Adverse Drug Reaction	Cisplatin	Nab-Paclitaxel	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level		
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level		No dose reduction

Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists		
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level		
Hepatic Toxicity[a]: SGOT (AST) < 10 x ULN and Bilirubin > 1.5 to ≤ 5 x ULN	Withhold[a]	Withhold[a]	Withhold[a]
Hepatic Toxicity[a]: SGOT (AST) > 10 x ULN or Bilirubin > 5 x ULN	Withhold[a]	Withhold[a]	Withhold[a]
Creatinine Elevation: Grade 2	Withhold until improves to ≤ Grade 1	Continue	Continue
Creatinine Elevation: Grade 3 or 4	Withhold until improves to ≤ Grade 1		

[a] The need for further dose adjustments in subsequent cycles and doses should be based on individual tolerance. If bilirubin is >1.5 x ULN and <3 x ULN for reasons unrelated to study therapy (e.g. biliary obstruction), treatment with gemcitabine and cisplatin are permitted at full doses. Nab-paclitaxel should be held if bilirubin ≥ 1.5 ULN

Permanently discontinue gemcitabine for any of the following:

- Hypersensitivity
- unexplained dyspnea or other evidence of severe pulmonary toxicity
- severe hepatic toxicity, hemolytic-uremic syndrome, capillary leak syndrome
- Posterior Reversible Encephalopathy Syndrome (PRES)

Permanently discontinue Abraxane (Nab-Paclitaxel) for any of the following:

- Severe Hypersensitivity

Permanently discontinue cisplatin for any of the following:

- Severe Hypersensitivity
- Hearing loss or tinnitus grade 3
- Optic neuritis, papilledema, cerebral blindness

For any toxicity (regardless of grade) that, despite optimal supportive care, is felt by the treating Investigator to present a risk to the patient safety, additional dose reduction, treatment delay, or treatment discontinuation is permitted at the discretion of the treating Investigator. Dose re-escalation will be permitted with approval of the Principal Investigator.

6.1.1.1 Additional Recommendations for Fever/Infection

Because of significant risk of non-neutropenic sepsis, at the first occurrence of fever > 38.5 degrees Celsius, regardless of the neutrophil count, either ciprofloxacin (500mg orally twice a day) or amoxicillin/clavulanate (Augmentin, 875-125mg orally twice a day) should be instituted. The clinical team will follow the standard of care plan for blood count evaluation, and clinical assessment for infection, and/or the need for hospitalization.

Febrile subjects will have their treatment interrupted until recovery (temperature below 100F for >3 days), and will be managed according to standard practice for this disorder. Upon resolution of this condition, nab-paclitaxel, cisplatin and gemcitabine therapy can resume.

6.1.1.2 G-CSF

The use of growth factors to support neutrophil counts is permissible after cycle 1 if neutropenia requires a dose reduction. G-CSF may also be considered for therapeutic administration in the event of febrile neutropenia as noted above, according to institutional practice.

6.1.1.3 Supportive Care

All supportive measures consistent with optimal standard of care will be given throughout treatment. The use of corticosteroids for supportive care is discouraged.

6.1.2 Dose Modifications and Dose Delays for Nivolumab

Subjects who experience toxicity related to nivolumab will be managed in accordance with guidelines in the management algorithms provided in the nivolumab investigator brochure and in **Appendix B**. These dose adjustments are for AEs deemed related to the study medications. If, in the opinion of the treating Investigator, a toxicity is thought to be unrelated to study medications and resolves to lowest grade, no dose adjustments for the study medications are necessary.

Subjects with drug-related endocrinopathies controlled with hormone replacement may resume treatment. Corticosteroids are frequently indicated for grade 3 or greater toxicities, and are necessary at times for lower grade toxicities. Guidance for their use and dosing is available in the Appendix B.

Any dose delay of nivolumab lasting longer than 6 weeks will result in discontinuation of nivolumab, unless approved to continue by the sponsor-investigator.

6.1.3 Dose Modifications for Paricalcitol

Doses of paricalcitol will be modified for hypercalcemia as follows:

Serum calcium	Interpretation	Paricalcitol Dose
8.9 – 10.3	Normal	50µg IV
10.3-11.5	Mild elevation/ Grade 1	40µg IV
11.6-12.5	Grade 2	Hold and resume at 30µg IV when Ca 11.5 or less
12.6-13.5	Grade 3	Hold and resume at 15µg IV when Ca 11.5 or less
> 13.5	Grade 4	Hold and resume at 15µg IV when Ca 11.5 or less

*If grade 3 or 4 toxicity recurs at the lowest dose (15µg IV), paricalcitol should be discontinued

Modifications to paricalcitol dosing for other reasons will only be made:
1. To avoid immediate, apparent hazard to the subject, or
2. With prospective approval from the IRB if the PI or sub-investigator believes it is in the best interest of the subject.

7.0 Study Procedures

Study procedures are further detailed in section 16.0 (Schedule of Events).

7.1 Tumor Analysis, Correlative Studies

Tumor. After the standard of care resection surgery, tumor tissue will be dissected and processed as per standard hospital policy in the pathology department. Details about correlative testing may be found in the laboratory manual. Tissue remaining after clinical allocation for diagnostic purposes will be portioned and prepared as follows:

(i) One rapidly frozen aliquot for subsequent whole genome sequencing, CGH, expression profiling, and metabolomics, as may become possible in the course of the study.

(ii) One or more FFPE blocks for IHC-based research by Dr E. Furth;

(iii) One FFPE block for expression studies out of paraffin in case the fresh tissues studies fail.

Blood. Blood samples (see Section 16.0, Schedule of Events) will be shipped to the Human Immunology Core for PBMC isolation and plasma storage.

7.2 Assessment of Laboratory Measures and Disease Progression

CBC with differential will be assessed at screening, on days 1 and 8 of each treatment cycle, and at the end of treatment visit.

Serum pregnancy will be assessed, for women of childbearing potential at screening and within 24 hours, prior to cycles 1, 3, 4, 6 and 8, and at the end of treatment visit. Non-childbearing potential is defined as: Surgically sterile (e.g., hysterectomy with or without oophorectomy; fallopian tube ligation; endometrial ablation) or at least 5 years post-menopause (e.g., 6 years post last menstrual period), or menopause documented in the history by follicle-stimulating hormone (FSH) testing.

Serum chemistry labs will be assessed at screening, on days 1, and 8 of each treatment cycle, and at the end of treatment visit. In Arm A, serum calcium/phosphate will be checked weekly for cycles 2 (only if given with paricalcitol) and 3 and prior to surgery, on days 1 and 8 of adjuvant treatment cycles, and at the end of treatment visit. We will not be performing twice weekly labs as we have established safety in this population with thrice weekly 25µg IV dose in our initial trial with gemcitabine/nab-paclitaxel/paricalcitol. There was a single instance of asymptomatic grade 2 hypercalcemia in one of 15 subjects.

Serum TSH will be assessed at screening, prior to every even-numbered cycle, and at the end of treatment visit. CA 19-9 and iPTH will be assessed at screening, the first day of each treatment cycle, and at the end of treatment visit. A 25-OH vitamin D level will be checked at screening.

Additional research labs (50mL for PBMC isolation and plasma storage) will be taken on day 1 of cycles 1, 2, 3, and 4, on day 8 of the cycle where nivolumab is started (usually cycle 2 day 8), and at the end of treatment visit as described in the table of events.

*For all laboratory measures a window of +/- 3 days is acceptable.

CT/MRI of the abdomen will be performed for disease assessment at screening, prior to surgery, after surgery prior to resumption of therapy, 2-6 weeks after the completion of adjuvant therapy, and then at a frequency to be determined by standard of care. Baseline chest and pelvic imaging are encouraged but not required if not felt to be standard of care by the treating investigator. PET-CT is an acceptable substitute for CT/MRI if determined to be the standard of care by the treating physician.

7.3 Duration of Follow-Up

For this protocol, all subjects, including those who discontinue protocol therapy, will be followed through review of the medical record for recurrence and survival for up to 5 years from their end of study visit (every 6 months for the first year, then annually).

7.4 DCE- and DW-MRI

Two DCE- and DW-MRI studies will be performed on a 1.5T Siemens Avanto scanner using the abdominal/spine phase-array coil at baseline (D-28 to 0) and after the completion of 3 cycles of neoadjuvant therapy.

The MRI protocol includes: 1) high resolution anatomical images to measure the tumor size; 2) DCE/DW-MRI to evaluate tumor microenvironment and changes in response to stroma-directed (PEGPH20) alone and in combination with a standard of care.

Anatomical MRI: A 3-plane localizer will be followed by axial T1 and T2 images. An axial volume will be prescribed covering the entire pancreas, which will also cover a portion of the descending aorta for the measurement of the AIF. This prescription volume will remain the same for the native T1 mapping, the actual flip angle calculation, the DCE- and DW- MRI.

DCE-MRI: A 3D golden-angle radial acquisition combined with post-processing including respiration self-gating and KWIC filtering will be applied. This protocol has been proved to have excellent motion-compensation and optimal image quality in the previous DCE studies of lung and liver cancer (13-16).

Following the selection of the lesion and aorta by co-investigator and experienced radiologist (Mark Rosen, M.D.), the tumor and aorta signal intensities will be converted to Gd concentration and fit to the commonly used pharmacokinetic (PK) model including the Toft's and Shutter-speed models to estimate parameters including K^{trans} (the rate constant of transferring unit volume of contrast agent across capillaries to interstitial space, min^{-1}), k_{ep} (the rate constant between extracellular space and capillaries, min^{-1}), τ_i (the intracellular water life time, sec), V_p (vascular fraction) and V_e (extracellular and extravascular volume fraction). Distribution of K^{trans} values by histograms will be used to assess tumor heterogeneity and its change upon treatment.

DW-MRI: We will utilize respiratory-gated single-shot EPI for diffusion imaging, the current standard for the pancreas due to its robustness to motion. The total imaging volume and axial FOV will be matched to that of the DCE-MRI acquisition. Other sequence parameters include: b-values = 0, 100, 500 and 1000, BW = 2000Hz/pixel, TR = 4 sec, total scan time ~ 5 min. To anticipate a small degree of motion-blurring or anatomic distortion may occur in the standard single-shot DW-EPI, we will compare it with respiratory-gated DW-EPI in the repeatability study. This will allow us to decide if the gating helps reduce these artifacts and thus should be used in DW-MRI of PDA.

Using MIPAV program, regions of interest (ROIs) will be defined by the radiologist on DW-MR images. ADC will be calculated pixel-wise via linear least-squares fitting to the logarithmically-transformed, and the mean values will be extracted. Image signal-to-noise-ratio will be quantified from ROIs drawn on b = 1000 s/mm^2 images.

8.0 Study Treatment Details

8.1 Gemcitabine

8.1.1 Other Names

2'-Deoxy-2', 2'-difluorocytidine monohydrochloride, Gemzar

8.1.2 Classification

Antimetabolite (nucleoside analog)

8.1.3 Mechanism of Action

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis.

First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated intoDNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

8.1.4 Storage and Stability

Un-reconstituted drug vials are stored at controlled room temperature. Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; crystallization may occur. The unused portion should be discarded.

8.1.5 Dose Specifics

Gemcitabine is indicated as a single agent for the treatment of pancreatic cancer. In this indication, a dose of 1000mg/m2 over 30 minutes once weekly for up to 7 weeks followed by a week of rest, then once weekly for three weeks of every four weeks is used. Other dosing schedules currently are being studied.

8.1.6 Preparation

Reconstitute the 200mg vial with 5ml and the 1Gm vial with 25ml preservative free normal saline to make a solution containing 38 mg/ml. Shake to dissolve.

8.1.7 Administration

The drug may be administered intravenously as prepared above or further diluted with normal saline to a minimum concentration of 0.1mg/ml. Gemcitabine is commonly diluted in 100 ml or 250ml of saline. Gemcitabine administration may be either over 30 minutes (as in label) or at a rate of 10 mg/m2/minute as recommended by Plunkett and colleagues [43].

8.1.8 Availability

Gemcitabine is commercially available in 200mg and 1Gm vials.

8.1.9 Side Effects

- Hematologic: Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with gemcitabine as a single agent and the risks are increased when gemcitabine is combined with other cytotoxic drugs. In clinical trials, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of subjects receiving single-agent. The frequencies of Grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8 to 28%, and 5 to 55%, respectively, in subjects receiving gemcitabine in combination with another drug.
- Dermatologic: A rash is seen in about 25% of subjects and is associated with pruritus in about 10% of subjects. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Alopecia is reported in <1% of subjects.
- Gastrointestinal: Nausea and vomiting are reported in about two-thirds of subjects and requires therapy in about 20% of subjects. It is rarely (<1%) dose-limiting, and is easily manageable with standard antiemetics. Diarrhea is reported in 8% of subjects, constipation in 6%, and oral toxicity in 7%.
- Hepatic: Abnormalities of hepatic transaminase enzymes occur in two-thirds of subjects, but they are usually mild, non-progressive, and rarely necessitate stopping treatment. Drug-induced liver injury, including liver failure and death, has been reported in subjects receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs. Administration of gemcitabine in subjects with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency.
- Pulmonary: Bronchospasm after injection has been reported in less than 1% of subjects and is usually mild and transient, but parenteral therapy may be required. Dyspnea within a few hours of injection is reported in 10% of subjects. It is usually mild, short-lived, rarely dose limiting, and usually abates without any specific therapy. Cough and rhinitis are also commonly reported. Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine.
- Neurologic: Somnolence has been reported in 10% of subjects, and insomnia is common.
- Cardiovascular: A few cases of hypotension were reported. Some cases of myocardial infarction, congestive heart failure, and arrhythmia have been reported, but there is no clear evidence that gemcitabine causes cardiac toxicity. Peripheral edema is reported in about 30% of subjects. Some cases of facial edema have also been reported. Edema is usually mild to moderate, rarely dose limiting, sometimes painful, and reversible after stopping gemcitabine treatment.
- Hemolytic Uremic Syndrome (HUS): HUS to include fatalities from renal failure or the requirement for dialysis can occur in subjects treated with gemcitabine. In clinical trials, HUS was reported in 6 of 2429 subjects (0.25%). Most fatal cases of renal failure were due to HUS. Renal failure may not be reversible even with discontinuation of therapy.
- Embryofetal Toxicity: Gemcitabine can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If this drug is used during pregnancy, or if a woman becomes pregnant while taking gemcitabine, the subject should be apprised of the potential hazard to a fetus.

- Exacerbation of Radiation Therapy Toxicity: Gemcitabine is not indicated for use in combination with radiation therapy. Concurrent (given together or ≤7 days apart) — Life-threatening mucositis, especially esophagitis and pneumonitis occurred in a trial in which gemcitabine was administered at a dose of 1000 mg/m^2 to subjects with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation.
- Capillary Leak Syndrome: Capillary leak syndrome (CLS) with severe consequences has been reported in subjects receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents.
- Other: Flu-like symptoms are reported for about 20% of subjects. This includes fever, headache, back pain, chills, myalgia, asthenia, and anorexia. Malaise and sweating are also commonly reported.

8.2 Nab-paclitaxel

8.2.1 Other Names

Abraxane

8.2.2 Classification

Mitotic inhibitor (cytoskeletal target)

8.2.3 Mechanism of Action

Nab- paclitaxel is a Cremophor EL-free, albumin-bound paclitaxel particle with a mean size of approximately 130 nm. Nab- paclitaxel is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble particle state.

Paclitaxel is a cytoskeletal drug that targets tubulin. Unlike tubulin-targeting drugs (such as colchicines) that inhibit microtubule assembly, paclitaxel stabilizes the microtubule polymer and protects it from disassembly. Therefore, chromosomes are unable to form a metaphase spindle formation. This blocks progression of mitosis. Prolonged activation of the mitotic checkpoint will then lead to apoptosis or lead the cell to return to G-phase without cell division.

8.2.4 Storage and Stability

Nab-paclitaxel should be stored as vials in original cartons at 20ºC to 25ºC (68º F to 77ºF) and protected from bright light.

8.2.5 Dose Specifics

Nab-paclitaxel is indicated for the first-line treatment of metastatic pancreatic adenocarcinoma in combination with gemcitabine. It is also indicated for breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Additionally, nab-paclitaxel is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in subjects who are not candidates for curative surgery or radiation therapy.

In metastatic pancreatic cancer, the recommended regimen is 125mg/m^2 administered intravenously over 30-40 minutes on days 1, 8, and 15 of each 28-day cycle. In metastatic breast cancer, the recommended regimen for nab-paclitaxel is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks. In metastatic non-small cell lung cancer, the recommended dose of nab-paclitaxel is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle.

8.2.6 Preparation

Reconstitute each vial containing 100 mg of nab-paclitaxel [Abraxane] by injecting 20 mL of 0.9% Sodium Chloride Injection. Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

8.2.7 Administration

This drug may be administered intravenously as prepared above over 30 minutes. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

8.2.8 Availability

Nab-paclitaxel [Abraxane] is commercially available as 100 mg of paclitaxel in a single-use vial

8.2.9 Side Effects

- Hematologic Disorders Neutropenia was dose dependent and reversible. Among subjects with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm3 (Grade 4) in 9% of the subjects treated with a dose of 260 mg/m2 compared to 22% in subjects receiving paclitaxel injection at a dose of 175 mg/m2. Pancytopenia has been observed in clinical trials.
- Infections Infectious episodes were reported in 24% of the subjects treated with paclitaxel. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

- Hypersensitivity Reactions (HSRs) Grade 1 or 2 HSRs occurred on the day of paclitaxel administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of paclitaxel in subjects previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.
- Cardiovascular Hypotension, during the 30-minute infusion, occurred in 5% of subjects. Bradycardia, during the 30-minute infusion, occurred in <1% of subjects. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. Severe cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 3% of subjects. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported. Electrocardiogram (ECG) abnormalities were common among subjects at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of subjects. Among subjects with a normal ECG prior to study entry, 35% of all subjects developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.
- Respiratory Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with paclitaxel.
- Neurologic the frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of paclitaxel discontinuation in 7/229 (3%) subjects. Twenty-four subjects (10%) treated with paclitaxel developed Grade 3 peripheral neuropathy; of these subjects, 14 had documented improvement after a median of 22 days; 10 subjects resumed treatment at a reduced dose of paclitaxel and 2 discontinued due to peripheral neuropathy. Of the 10 subjects without documented improvement, 4 discontinued the study due to peripheral neuropathy. No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.
- Vision Disorders Ocular/visual disturbances occurred in 13% of all subjects (n=366) treated with paclitaxel and 1% were severe. The severe cases (keratitis and blurred vision) were reported in subjects who received higher doses than those recommended (300 or 375 mg/m2). These effects generally have been reversible. Other possible side effects include conjunctivitis and increased lacrimation.
- Arthralgia/Myalgia The symptoms were usually transient, occurred two or three days after paclitaxel administration, and resolved within a few days.
- Hepatic Grade 3 or 4 elevations in GGT were reported for 14% of subjects treated with paclitaxel.
- Renal Overall 11% of subjects experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.
- Other Clinical Events Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of subjects; no subjects had severe edema. Dehydration and pyrexia were also reported. Nab- paclitaxel is not formulated in Cremophor and thus the risk of hypersensitivity reactions is much less than that of Taxol. Skin reactions including generalized or maculopapular rash, erythema, and pruritus have been observed with paclitaxel. There have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some subjects previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. There have been reports of conjunctivitis, cellulitis, and increased lacrimation with paclitaxel injection.

8.3 Nivolumab

8.3.1 Other Names

Opdivo

8.3.2 Classification

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that targets programmed cell death-1 (PD-1).

8.3.3 Mechanism of Action

Nivolumab selectively inhibits PD-1 activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding. The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted. This releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

8.3.4 Storage and Stability

The product does not contain a preservative. The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

8.3.5 Dose Specifics

240 mg IV over 60 minutes every 2 weeks

8.3.6 Preparation

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab [Opdivo] is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Withdraw the required volume of nivolumab [Opdivo] and transfer into an intravenous container. Dilute nivolumab [Opdivo] with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix diluted solution by gentle inversion. Do not shake. Discard partially used vials or empty vials of OPDIVO.

8.3.7 Administration

Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

8.3.8 Availability

Nivolumab [Opdivo] is commercially available as a 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in a single-dose vial.

8.3.9 Side Effects

- Cardiovascular: Edema, peripheral edema, ventricular arrhythmia, pulmonary embolism, vasculitis
- Central nervous system: Fatigue, headache, peripheral neuropathy, peripheral sensory neuropathy, dizziness, peroneal nerve palsy, motor dysfunction, migraine, myasthenia, encephalitis, facial paralysis, Guillain-Barré syndrome, neuropathy
- Dermatologic: Skin rash, pruritis, vitiligo, exfoliative dermatitis, erythema, erythema multiforme, psoriasis, urticarial, palmar-plantar erythrodysesthesia
- Endocrine and metabolic: Hyponatremia, increased serum triglycerides, hyperkalemia, increased thyroid stimulating hormone level, hypocalcemia, increased serum cholesterol, hypercalcemia, hypothyroidism, hypomagnesemia, hypokalemia, hyperglycemia, hyperthyroidism, adrenocortical insufficiency, diabetes mellitus, diabetic ketoacidosis, weight loss, hypophysitis, pituitary insufficiency
- Gastrointestinal: Diarrhea, colitis, decreased appetite, increased serum lipase, nausea, constipation, vomiting, increased serum amylase, abdominal pain, duodenitis, gastritis, pancreatitis
- Hematologic: Lymphocytopenia, anemia, neutropenia, thrombocytopenia
- Hepatic: Increased serum AST, increased serum ALT, increased serum alkaline phosphatase, increased serum bilirubin, hepatitis, hepatic failure
- Immunologic: Antibody development
- Neuromuscular and skeletal: Weakness, musculoskeletal pain, back pain, arthralgia, spondyloarthropathy, limb pain, polymyalgia rheumatica
- Renal: Increased serum creatinine, renal disease, nephritis, renal insufficiency
- Respiratory: Upper respiratory tract infection, productive cough, cough, dyspnea, dyspnea on exertion, bronchopneumonia, pneumonia, pleural effusion, pneumonitis, respiratory failure, pneumonia due to Pneumocystis jiroveci
- Ophthalmic: Iridocyclitis, iritis
- Miscellaneous: Fever, infusion related reactions, hypersensitivity reaction, sarcoidosis

8.4 Paricalcitol

8.4.1 Other Names

19-nor-1α, 25 –dihydroxyvitamin D2, Zemplar

8.4.2 Classification

Paricalcitol is a vitamin D analog of calcitriol with modifications to the side chain (D2) and the A (19-nor) ring.

8.4.3 Mechanism of Action

Preclinical and *in vitro* studies have demonstrated that paricalcitol's biological actions are mediated through binding of the VDR, which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

8.4.4 Storage and Stability

Paricalcitol injectable is available as a sterile, clear, colorless, aqueous solution for intravenous injection. Each mL contains paricalcitol, 2 mcg or 5 mcg and the following inactive ingredients: alcohol, 20% (v/v) and propylene glycol, 30% (v/v). Contents of the multi-dose vial remain stable up to seven days when stored at controlled room temperature. Store at 25°C (77°F). Excursions permitted between 15° - 30°C (59° - 86°F).

8.4.5 Dose Specifics

Paricalcitol is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. The currently accepted target range for iPTH levels in CKD Stage 5 subjects is no more than 1.5 to 3 times the non-uremic upper limit of normal. The recommended initial IV dose of paricalcitol is 0.04 µg /kg to 0.1 µg/kg (2.8 – 7 µg) administered as a bolus dose no more frequently than every other day at any time during dialysis. If a satisfactory response is not observed, the dose may be increased by 2 to 4 µg at 2- to 4-week intervals.

8.4.6 Preparation

Paricalcitol [Zemplar] injection is available as 2 µg/mL and 5 µg/mL vials. No reconstitution is necessary, dilution to be performed dependent on final concentration for dosing desired.

8.4.7 Administration

Administer 50 µg paricalcitol as IV bolus once weekly (for subjects in Arm A) for one cycle beginning day 1 of therapy until surgery, then on days 1, 8, and 15 of each 28-day cycle for 3-5 cycles post-operatively.

8.4.8 Availability

Paricalcitol [Zemplar] is commercially available for injection as 2 mcg/mL and 5 mcg/mL vials.

8.4.9 Side Effects

- Blood and Lymphatic System Disorders: anemia, lymphadenopathy, bleeding time prolonged
- Cardiac Disorders*:* arrhythmia, atrial flutter, cardiac arrest, heart rate irregular, palpitations
- Sensory Disorders: ear discomfort, conjunctivitis, glaucoma, ocular hyperemia
- Endocrine Disorders: hyperparathyroidism, hypoparathyroidism
- Gastrointestinal Disorders: abdominal discomfort, constipation, diarrhea, nausea, vomiting, dysphagia, gastritis, intestinal ischemia, rectal hemorrhage, gastrointestinal hemorrhage, aspartate aminotransferase increased
- General Disorders and Administration Site Conditions: asthenia, chest discomfort, chest pain, condition aggravated, edema peripheral, fatigue, feeling abnormal, gait disturbance, injection site extravasation, injection site pain, pain, swelling, thirst, chills, fever
- Infections and Infestations: nasopharyngitis, upper respiratory tract infection, vaginal infection, influenza, pneumonia, sepsis
- Metabolism and Nutrition Disorders: decreased appetite, hypercalcemia, hyperkalemia,
- hyperphosphatemia, hypocalcemia, weight decreased
- Musculoskeletal and Connective Tissue Disorders: joint stiffness, muscle twitching, myalgia, arthralgia
- Neoplasms Benign, Malignant and Unspecified: breast cancer
- Nervous System Disorders: cerebrovascular accident, dizziness, dysgeusia, headache, hypoesthesia, myoclonus, paresthesia, syncope, unresponsive to stimuli
- Psychiatric Disorders: agitation, confusional state, delirium, insomnia, nervousness, restlessness
- Reproductive System and Breast Disorders: breast pain, erectile dysfunction
- Respiratory, Thoracic and Mediastinal Disorders: cough, dyspnea, orthopnea, pulmonary edema, wheezing
- Skin and Subcutaneous Tissue Disorders: alopecia, blister, hirsutism, night sweats, rash (pruritic), pruritus, skin burning sensation, urticaria
- Vascular Disorders: hypertension, hypotension, angioedema
- Other: dry mouth

8.5 Cisplatin

8.5.1 Other Names

cisplatinum, CDDP, cis-diamminedichloridoplatinum(II), Platinol

8.5.2 Classification

Cytotoxic platinum chemotherapy

8.5.3 Mechanism of Action

Cisplatin inhibits DNA synthesis by the formation of DNA cross-links; denatures the double helix; covalently binds to DNA bases and disrupts DNA function; may also bind to proteins; the cis-isomer is 14 times more cytotoxic than the trans-isomer; both forms cross-link DNA but cis-platinum is less easily recognized by cell enzymes and, therefore, not repaired. Cisplatin can also bind two adjacent guanines on the same strand of DNA producing intrastrand cross-linking and breakage.

8.5.4 Storage and Stability

Cisplatin Injection is a sterile, multidose vial without preservatives. Store at 15° C to 25°C (59° to 77°F). Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

8.5.5 Dose Specifics

Dosing is as specified above in the protocol regimen. Cisplatin is not FDA-approved for the treatment of pancreatic cancer

8.5.6 Preparation

Cisplatin Injection infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. Each 50 mL or 100 mL amber vial of infusion concentrate contains: 1 mg/mL cisplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50 mL or 100 mL, respectively. Cisplatin Injection infusion concentrate must be further diluted prior to administration

8.5.7 Administration

Cisplatin Injection is administered by slow intravenous infusion

8.5.8 Availability

Cisplatin Injection is commercially available in 50mg and 100mg multidose vials.

8.5.9 Side Effects

Nephrotoxicity: Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given. Elderly patients may be more susceptible to nephrotoxicity. Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using a 6- to 8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

Ototoxicity: Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). The prevalence of hearing loss in children is particularly high and is estimated to be 40-60%. Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated cisplatin doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Vestibular toxicity has also been reported. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Ototoxicity can occur during treatment or be delayed. Audiometric monitoring should be performed prior to initiation of therapy, prior to each subsequent dose, and for several years post therapy. The risk of ototoxicity may be increased by prior or simultaneous cranial irradiation, and may be more severe in patients less than 5 years of age, patients being treated with other ototoxic drugs (e.g. aminoglycosides and vancomycin), and in patients with renal impairment. Genetic factors (e.g. variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.

Hematologic Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia.

Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression. In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician. The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

Gastrointestinal Marked nausea and vomiting occur in almost all patients treated with cisplatin, and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia maypersist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy. Diarrhea has also been reported.

Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic-uremic syndrome [HUS]), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Serum Electrolyte Disturbances: Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin. Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia: Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity: Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of cisplatin. Cisplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients.

Elderly patients may be more susceptible to peripheral neuropathy. Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Loss of taste, seizures, leukoencephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) have also been reported.

Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-Like Reactions: Anaphylactic-like reactions have been reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity: Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

Other Events: Cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, asthenia, and dehydration have been reported. Local soft tissue toxicity has been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema.

9.0 Statistical Plan

9.1 Registration and Randomization

As illustrated in the Schema, and as described in Sections 2.5 and 3.0, patients will be ***registered*** to this trial before the tumor classification data (Epithelial vs QM) are available, so as to permit the immediate initiation of therapy, should that be desired. Patients whose disease is QM will be removed from the study but followed for outcome.

Patients whose disease is classified as epithelial subtype will be randomized 1:1 to receive or not receive paricalcitol in combination with chemotherapy and nivolumab. At a minimum, the combined treatment will be given for ***one full cycle*** before surgery or else the patient will be replaced. It is expected that most patients will receive three cycles of neo-adjuvant therapy, two with full doses of nivolumab or paricalcitol/nivolumab. This compromise recognizes the overarching clinical imperative to treat the disease in some patients, and will not unduly alter the interpretation of the biological data, which are based on the addition of the investigational interventions.

9.2 Sample Size Determination and Methods

It is estimated that 60% of pancreatic adenocarcinoma patients have tumors of the epithelial subtype and 40% have tumors of the quasimesenechymal subtype. To achieve a target of 10 patients in each randomized arm in the epithelial subgroup, a total of 34 patients is estimated to be necessary for registration.

This trial is directed to establishing feasibility and safety of the approach, and has the primary endpoint of detecting changes in circulating and tumor-infiltrating immune cells, tumor morphology, and stellate cell biology in patients treated with or without paricalcitol along with chemotherapy and nivolumab. The primary endpoints will be descriptive and hypothesis-generative, and no confidence limits surrounding these effects can be defined prospectively. The outcomes of interest will be the immunohistochemical analysis of T cell subpopulations in the tumor microenvironment (generally dominated by fibrosis, which should be reduced by the activation of VDR), T-cell clonal repertoire and neoantigen reactivity, and the expression profiles of the stellate cells, lymphocytes, and tumor which we hypothesize should be reprogrammed by the vitamin D supplementation, as monitored by RNA-Seq and ATAC-Seq. The effect size to be anticipated is as yet unknown, and treatment of 10 patients with and without paricalcitol will provide quantitative data for future larger trials. When applicable, descriptive statistics will be computed such as mean, median to describe central tendency and standard deviation (SD), range, inter-quartile range (IQR) for variability. Due to pilot nature of the study, no formal sample size or power calculation was performed. The feasibility of the approach will be assessed in the completion of the preoperative therapy; success will be defined by at least 90% of the subjects who receive any preoperative therapy on study subsequently undergoing pancreatic resection. The proportion of resections with all surgical margins clear of tumor by at least 1mm (i.e. an R0 resection) will also be assessed.

We will describe the effect of gemcitabine/cisplatin/nab-paclitaxel/nivolumab with and without paricalcitol on tumor response to neoadjuvant chemotherapy by imaging, and report this result. Tumor response will be assessed and reported separately in each arm and defined as the number of subjects achieving a tumor response (CR or PR by RECIST 1.1 criteria) divided by the number of subjects who have been assessed for response. The exact 90% confidence interval based on binomial distribution will be determined.

We will also determine the safety of this neoadjuvant approach by defining the adverse effects in treated subjects – we expect the treatment to be well-tolerated in most subjects, and expect no interaction with paricalcitol administration, as was demonstrated in our initial 14 subject cohort. Safety analysis will occur after accrual of every five subjects. All subjects that have initiated treatment will be considered evaluable for toxicity analysis. The maximum grade for each toxicity will be recorded for each subject, and frequency tables will be reviewed to determine toxicity patterns. DLTs as defined in 5.2.3 will also be summarized and tabulated both over and within major categories. Exact 90% confidence intervals for the event rates will be computed. Due to the nature of this 20 patient study and the complexity of this multi-modality regimen, a single global early termination rule has not been defined. Toxicity attributable to nivolumab will be reviewed by the principal investigator. Paricalcitol, cisplatin, nab-Paclitaxel and gemcitabine-related toxicities (in any cycle) and surgery-related complications will be assessed by the responsible sub-investigators.

Progression-free survival and overall survival will be evaluated using the method of Kaplan Meier and described for future bench-marking. Disease-free survival will be evaluated in patients undergoing resection. Subjects who turn out not to be operative candidates (for various reasons, including metastatic disease coming to light before or during the operation) will be replaced.

9.3 DCE- and DW-MRI analyses

Following the baseline DCE-MRI, the 2nd DCE-MRI will be performed after the completion of 3 cycles of neoadjuvant therapy and prior to surgery. Sensitivity and specificity of the imaging markers to stroma-treatment will be estimated. To do this, we define the treatment responders as those with the fraction of HA-positive staining from the post-treatment biopsy to be ≤50% of that from pre-treatment biopsy. Given a pre-specified cutoff value for imaging biomarkers, the sensitivity is computed as the proportion of patients with imaging marker value above the threshold among the responders, and the specificity is computed as the proportion of patients with imaging marker value below the threshold among the non-responders. if 13 respond and the marker sensitivity is 80%, 10 patients will have the marker value above the threshold. We will pay attention to the specificity. For the remaining 7 non-responders, if the specificity is above 90%, then at least 6 patients will have marker value below the threshold. We will generate the receiver operating characteristic curve (ROC) to guide the selection of cut-off values.

Immunohistochemistry (IHC) analyses will be compared with DCE- and DW-MRI derived parameters. We will evaluate whether and what specific imaging markers (e.g., K^{trans}, ADC and so on) derived from DCE- and DW-MRI changes will be correlated with IHC-based outcomes.

10.0 Safety and Adverse Events

10.1 Definitions

10.1.1 Unanticipated Problems Involving Risk to Subjects or others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

10.1.2 Adverse Event

An **adverse even**t (AE) is any unfavorable symptom, sign, illness or experience that occurs at any dose and develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

10.1.3 Adverse Events of Special Interest

AESIs (serious or non-serious) are defined as AEs of scientific and medical concern specific to the investigational product or program, for which ongoing monitoring and rapid communication by the Principal Investigator to drug manufacturer can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Principal Investigator to other parties (eg, regulators) might also be warranted.

Details on currently agreed list of AESIs for investigational agents can be found in the current IB. These AESIs are to be reported to drug manufacturer expeditiously within 24 hours of knowledge of the event, during the study through 30 days after receiving the last dose of study treatment, according to the procedures below

10.1.4 Serious Adverse Even**t**

Adverse events are classified as serious or non-serious. A serious adverse event is any AE, that is:

- fatal
- life-threatening

- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events.**

Events or Outcomes Not Qualifying as Serious Adverse Events
The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/ or convenience situations (eg, respite care)
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward)
- Overdose of study drugs or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a nonserious AE
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTC Grade 5 (fatal outcome) indicated.

10.2 Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 100 days following the last administration of study treatment.

10.3 Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period

10.4 General Physical Examination Finding
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

10.5 Post-Study Adverse Event

All unresolved AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the Principal Investigator of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The Principal Investigator should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

10.6 Abnormal Laboratory Values

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

10.7 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:
Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.8 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis. All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.9 Reporting of Adverse Events

Investigators must conform to the AE reporting timelines, formats and requirements of the various entities to which they are responsible using a MedWatch Form, but at a minimum those events that must be reported are those that are:

- Related to study participation,
- Unexpected, and
- Serious or involve risks to subjects or others

If the AE is considered serious, Principal Investigator should report this event to to their IRB. An event may qualify for expedited reporting to regulatory authorities if it is a suspected unexpected serious adverse reaction (SUSAR) in line with relevant regulations.

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study center
- Subject number
- Investigational study product
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment.

10.9.1 Investigator Reporting: Notifying Drug Manufacturer

All SAEs, AESIs, and pregnancies, regardless of relationship to study drug, must be reported using a MedWatch Form to BMS within 24hours/ 1 business day of becoming aware of the event during the study through100 days after receiving the last dose of study treatment, according to the procedures below. After the 100 day specified window, only SAEs considered to be treatment related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report.

MedWatch Report should be sent to:
SAE Email Address: Worldwide.Safety@BMS.com
OR
SAE Facsimile Number: +1 609-818-3804

10.9.2 Investigator Reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:
Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable Events:

For clinical drug trials, the following events are also reportable to the Penn IRB:
Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.

A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
Breach of confidentiality
Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

10.9.3 Abramson Cancer Center Data Safety Monitoring Committee (DSMC):
Every effort should be made to report an event as a diagnosis, not as a list of symptoms. Symptoms that led to the diagnosis should be included in the event description, but should not be the actual event.

- All grade 3 or higher events regardless of attribution or expectedness within 10 business days of knowledge.
- All unexpected deaths within two business day of knowledge.
- All others deaths within 30 days of knowledge. Deaths of subjects greater than 90 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol

SAEs will be submitted to the DSMC through the Velos Clinical Trial Management System.

Reportable Events

Exception
A one time, intentional action (planned prospectively) or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. Advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.
The following information must be contained in your exception request:

- When it is needed and why it is needed in that timeframe
- Has the Medical Monitor or Sponsor approved and provide the documentation of approval
- Is this an exception from eligibility, treatment, disease progression, study calendar windows, etc.
- Why the exception is needed (cite the section(s) of the protocol) along with the full clinical details of the subject. This must be determined by the sub-Investigator or PI.

- The reason why the protocol currently doesn't allow the situation for which an exception is being requested. This must be determined by the sub-Investigator or PI.
- If there are plans to amend the protocol and if not, why not.
- If additional follow-up or interventions will be required in order to protect the subject as a result of this exception.

Study Exceptions the DSMC may Reject:
Exceptions to eligibility, treatment/dosing, contraindicated treatment/therapies/interventions or safety tests for the following types of studies may be rejected by the DSMC:

- Any investigator-initiated treatment study.
- Any treatment study involving on-campus manufacturing of any component, regardless of sponsor.

To seek approval, you must provide the DSMC with strong and compelling scientific and clinical information to support your request. You should also include a statement explaining whether or not the protocol will be amended. If the protocol will not be amended your reasoning must be provided. If this situation is likely to happen again, the DSMC will require a protocol amendment.

Deviation
Any unintentional action or process that departs from IRB approval and is identified retrospectively. The deviation is reportable to the DSMC and the IRB within 10 days from the time the event becomes known to the study team only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

If the PI determines that a deviation has **any potential** to impact participant safety (harm and/or risk), or the integrity of data produced from the participant, or some other overall impact on the study, the PI must report the deviation to the IRB and DSMC as described above. The IRB will make the final assessment of the impact. The DSMC will assess for additional safety and scientific integrity concerns.

The following information must be contained in your deviation report:

- When it happened? When the study team (any member) became aware
- The full description of the deviation including important dates, test results, actions taken towards the subject, etc. Also, why it happened and how it was identified.
- Was the Medical Monitor or Sponsor notified. If so, their response?
- The PIs assessment of the impact on risk, safety and/or outcome. If no impact, why. If impact, what and what will happen next.
- The corrective actions that have been implemented to date and the impact of those corrective action plans.
- Future corrective action plans (if applicable) and the impact of those plans.
- If there are plans to amend the protocol (if applicable to prevent future deviations) and if not, why not.

If the PI determines that the event had no potential to impact participant safety (harm and/or risk) or the integrity of data produced from the participant, the PI must fully document his/her rationale for each category (risk, harm, and participant data).

10.11 Data Handling and Record Keeping

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

11.2 Data Collection and Management

This study will use Velos as the data management system. The study case report form (CRF) is the primary data collection instrument for the study and will be electronically created and completed in Velos. CRFs will be provided for each patient. Subjects must not be identified by name on any CRFs. Subjects will be identified by their patient identification number (PID). All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A.”.)

12.0 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. This monitoring will include a regular assessment of the number and type of serious adverse events.

This study will be monitored in accordance with the Cancer Center's Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) Plan, approved by NCI during the Core Grant's most recent review. This plan requires that the investigator submit a study-specific plan outlining how data will be reviewed In addition, the CTSRMC plan calls for an internal audit by the Cancer Center's Data Safety Committee twice yearly. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12.0 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 parts 50 and 56 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent IRB, in agreement with local legal prescriptions, for formal approval of the study conduct.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This clinical study, including correlative work will be supported by funds provided by National Science Foundation and Stand Up to Cancer.

DCE- and DW-MRIs will be supported by funds from an NIH U24 grant (1-U24-CA231858-01, PI Rong Zhou).

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14.0 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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16.0 Schedule of Events

Note: study timepoints may be performed within a +/- 3-day window.

	Screening [1]	**Cycle 1** (21D)		**Cycles 2, 3** (21D)			**Pre-Surgery**	**Surgery**	**Cycles 4-9**[6] (21D)			**End of Study Visit**[10]	**Follow-up**
		1	8	1	8	15			1	8	15		
Treatments													
Gemcitabine		X	X	X	X				X	X			
Cisplatin		X	X	X	X				X	X			
Nab-paclitaxel		X	X	X	X				X	X			
Nivolumab				X					X				
Paricalcitol IV (Arm A)				X	X	X	X[12]		X	X	X		
Tests and Observations													
Informed Consent[2]	X												
Medical History	X												X[7]
Physical Exam and Performance Status	X	X		X					X			X	
AE Assessment		X	X	X	X		X		X	X		X	
CBC w/ differential	X	X	X	X	X				X	X			
Serum Chemistry[4]	X	X	X	X	X				X	X		X	
Serum Calcium/Phosphate (Arm A only except at screening)[11]	X	X	X	X	X	X	X		X	X		X	
TSH[13]	X			X					X			X	
iPTH	X	X		X					X			X	
CA19-9	X	X		X			X		X			X	
Serum vitamin D	X												
Pregnancy test[5]	X	X		X					X[5]			X	
Disease Assessment (routine CT/MRI)[3]	X						X		X[3]			X[9]	X[8]
Research Correlates													
50mL PBMCs and plasma[14]		X		X	X				X			X	

Fresh Tumor Biopsy Sample[15]	X[15]												
Tumor Tissue for Research from Surgical Procedure[16]								X[16]					
DCE-/DW-MRI[17]	X[17]						X[17]						

[1] Screening laboratory evaluations must be conducted within 14 days prior to start of protocol therapy or repeated on cycle 1 day 1 to confirm eligibility. Disease assessment must be conducted within 28 days prior to start of protocol therapy.

[2] Informed consent will be documented prior to initiation of any other research related activity. If there have been tests/procedures that have been performed as part of subject's work-up or routine practice prior to informed consent, those tests/procedures do not have to be repeated

[3] CT/MRI, and/or PET/CT in the event that PET/CT is determined to be standard of care. Restaging scans should be completed prior to surgery and before resuming adjuvant therapy.

[4] Sodium, potassium, BUN, serum creatinine, glucose, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, magnesium, albumin

[5] In women of childbearing potential only. At screening, within 24 hours prior to first dose of cycles 1, 3, 4, 6, and 8 and at the end of treatment visit. Men and women of childbearing potential must agree to use a medically accepted form of birth control (see Appendix A) OR must agree to completely abstain from intercourse for two weeks before beginning study treatment, during participation in this study, and for 5 months for females and 7 months for males after the final study treatment.

[6] To begin 4-12 weeks post surgical resection (at the discretion of the physician).

[7] Limited to following of survival and disease recurrence through review of the medical record for up to 5 years after the end of study visit (every 6 months for the first year, then annually).

[8] MRI/CT scan will be performed at frequency determined by clinical care with data to be collected from the medical record for the purposes of the research.

[9] End of study CT/MRI should be conducted approximately 2-6 weeks after the completion of adjuvant study therapy.

[10] End of study visit should be conducted approximately 2-6 weeks after the completion of study therapy and after end of study imaging.

[11] This is a lab-only assessment for calcium and phosphate and does not require a clinic visit. Assessment has a +/- 2 day window

[12] Paricalcitol IV will continue weekly up until the day prior to surgery (expected 1-4 weeks after cycle 3)

[13]TSH will be checked at screening, prior to cycles 2, 4, 6, and 8, and at the end of treatment visit.

[14]Research blood for plasma and PBMCs will be drawn on cycle 1 day 1 prior to treatment, on day 1 of cycles 2, 3, and 4, cycle 2 day 8, and at the end of treatment visit

[15] Imaging will be reviewed by Surgeon/Radiologist/Interventional GI to determine the safest tumor location and type of procedure to obtain sample. Collect Core biopsy according to local institutional standards. Most biopsies will be via endoscopic ultrasound using a Sharkcore or similar device. Tumor samples obtained prior to screening as part of standard of care may be evaluated by surgical pathology and utilized if adequate. A fine-needle aspirate (FNA) biopsy should not be used for this tissue biopsy. If prior FNA obtained and material sufficient for cell block, slides can be reviewed by pathology for adequacy, but repeat biopsy will likely be necessary

[16] Fresh Surgical Tumor Samples: The surgical material will be handled, processed, and analyzed according to standard-of-care practices in the Department of Pathology at participating institutions and a standard pathology report will be issued. Material will be made available for research purposes but number and extent of assays to be performed will depend on the amount of tissue available. Material may include primary tumor, associated stroma, and peripancreatic lymph nodes. Assays by priority: (refer to study lab manual)

[17] DCE/DW-MRI: **Research MRIs**

Patients will undergo paired research MRIs. The first MRI will take place during the screening period and the second will occur after the completion of cycle 3 of chemotherapy and prior to surgery.

At the screening visit, study team will place order for MRI abdomen w/ and w/o contrast billed to research account and contact MRI coordinator Jessica Nunez (jessica.nunez@pennmedicine.upenn.edu) who will contact the patient to schedule the scan.

Baseline chest and pelvic imaging are encouraged but not required if not felt to be standard of care by the treating investigator. PET-CT is an acceptable substitute for CT/MRI if determined to be the standard of care by the treating physician.

Screening biopsy and MRI should not be scheduled on the same day, and performing the MRI at least several days after biopsy is optimal to avoid any changes in MRI due to procedural complications. MRI can be scheduled on cycle 1 day 1 prior to treatment when necessary.

Appendix A: Definition of Non-Childbearing Potential and Medically Acceptable Methods of Birth Control

Non-childbearing potential is defined as any of the following (by other than medical reasons):

1. ≥45 years of age and has not had menses for >2 years
2. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pre-study (screening) evaluation
3. Post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by imaging. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the patient must be willing to use 2 other adequate methods.

Females:

Women of child-bearing potential must agree to use 2 of the following forms of contraception OR completely refrain from intercourse during the study and for at least 5 months following the last dose of study drug.

Males:

Men with partners of child-bearing potential must agree along with their partner to use 2 of the following forms of contraception OR completely refrain from intercourse during the study and for at least 7 months following the last dose of study drug.

Acceptable methods include:

- Condoms
- Diaphragm
- Cervical cap
- Intra-uterine device
- Surgical sterilization (tubal ligation or vasectomy)
- Oral contraceptives

Abstinence at certain times of the cycle, such as during ovulation or after ovulation, or withdrawal are not acceptable methods. The list of methods above is not exhaustive and additional contraception methods may also be acceptable. The study doctor must approve the contraceptive methods in subjects with child-bearing potential.

Appendix B: Nivolumab Toxicity Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Principal Investigator. The guidance applies to all immuno-oncology agents and regimens. A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN -2.5 x ULN and/or T. bili > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 2.5 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

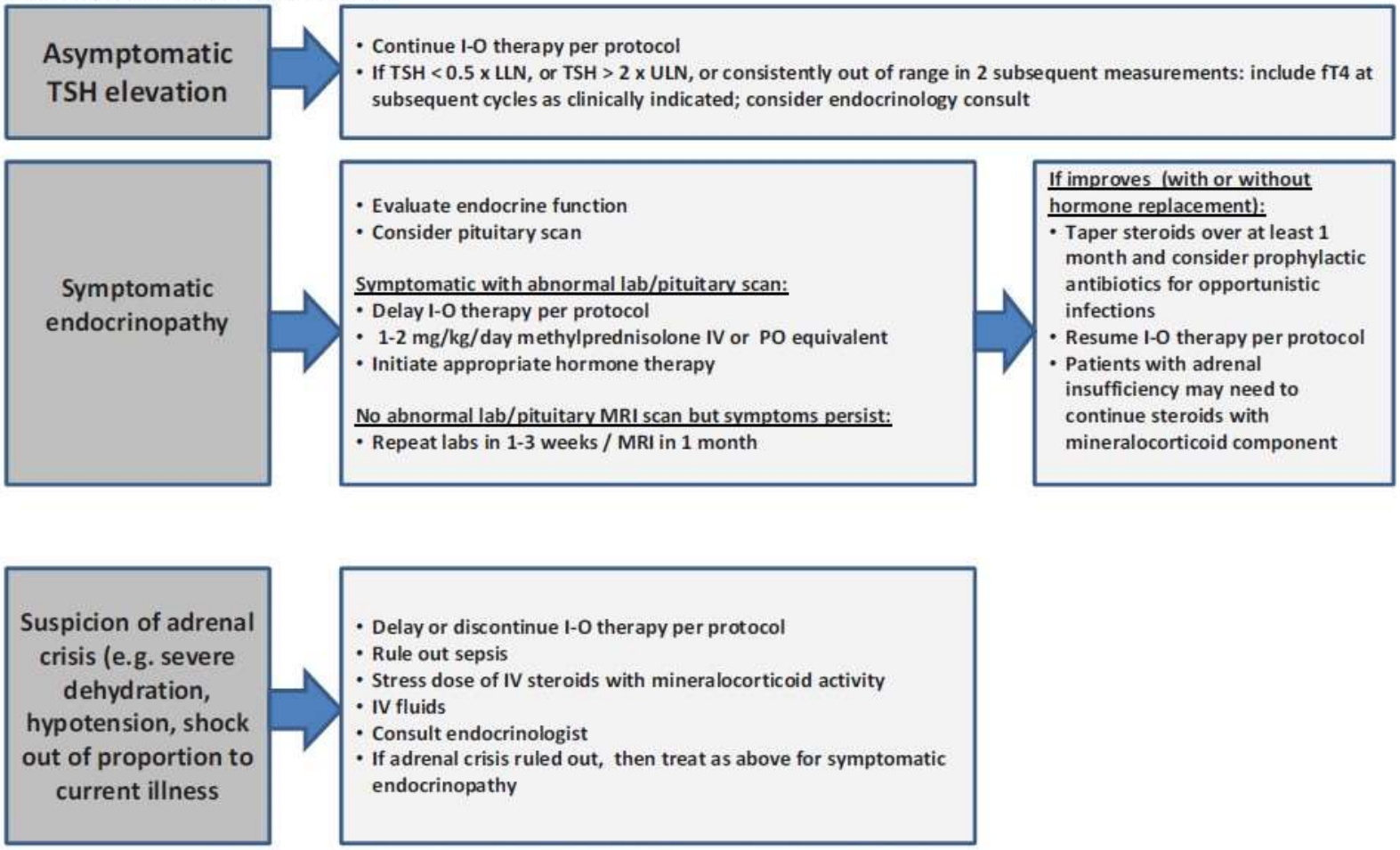
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

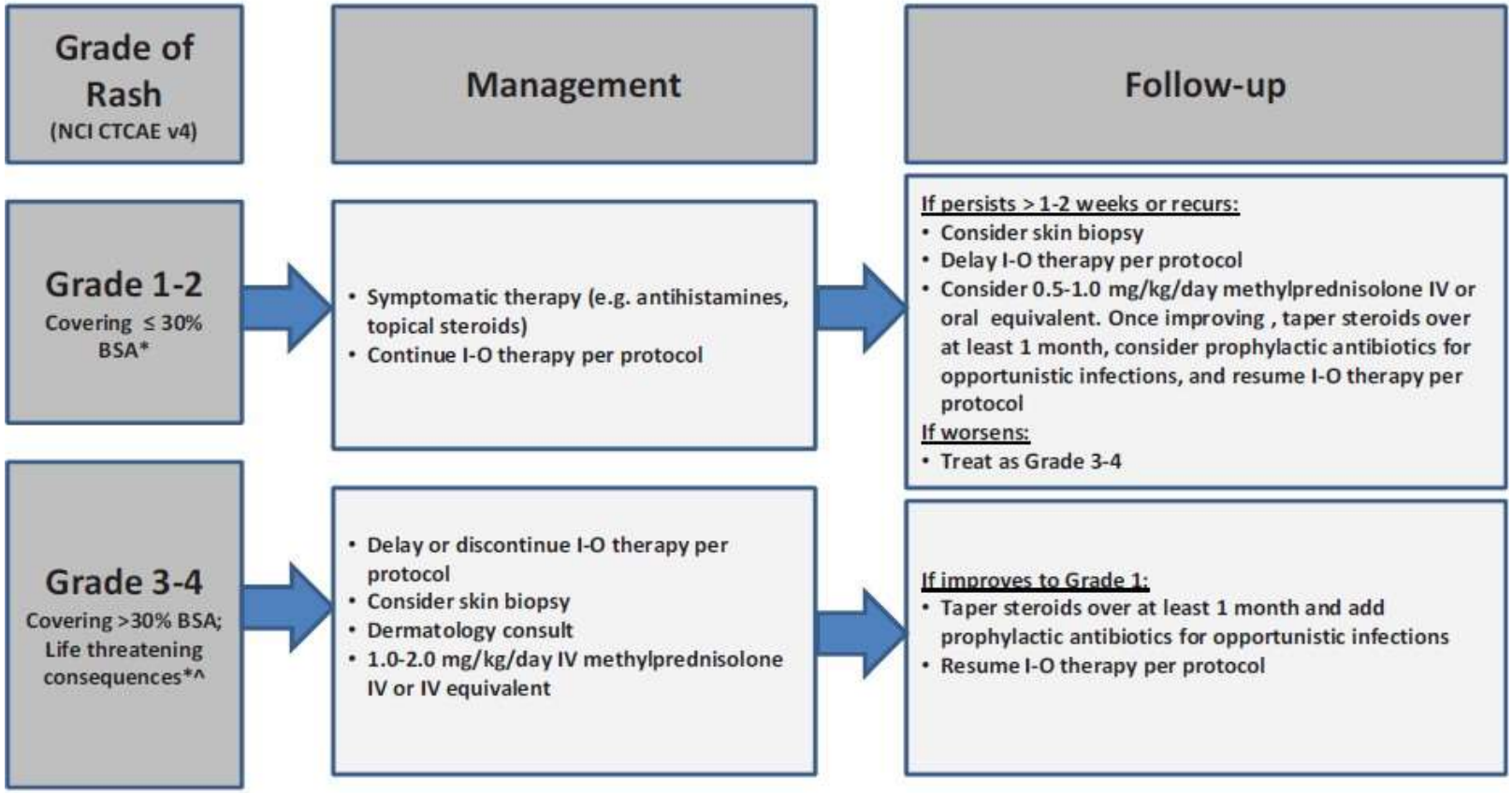
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.