Phase II trial of paricalcitol and hydroxychloroquine (PH) combination with gemcitabine and nab-paclitaxel in advanced pancreatic cancer

WINSHIP PROTOCOL #: **Winship5079-20**

COORDINATING CENTER: **Winship Cancer Institute of Emory University**

PRINCIPAL INVESTIGATOR: **Olatunji Alese, M.D.**
Associate Professor, Department and Hematology and Medical Oncology
Winship Cancer Institute of Emory University
1365 Clifton Road NE, Suite B4208
Atlanta, GA 30322
e-mail address: *olatunji.alese@emory.edu*

PI for correlatives: **Manoj Bhasin, PhD, MS**
Acting Associate Professor, Department of Biomedical Bioinformatics
Scientific Director, Bioinformatics and Systems Biology Shared Resource
615 Michael Street, Whitehead Biomedical Research Bldg.; Lab 135
Atlanta, GA 30322
E-mail: *manoj.bhasin@emory.edu*

Co-Investigator: **Vikas Sukhatme, MD, ScD**
Dean, Emory University School of Medicine
1520 Clifton Rd. NE, Atlanta, Georgia, United States
e-mail address: *vsukhatme@emory.edu*

Co-Investigators
Walid Shaib, MD
Olumide Gbolahan, MD
Mehmet Akce, MD
Maria Diab, MD
Aaron Jones, NP
Jessica Guadagno, NP
Sujata Kane, PA
Edith Brutcher, NP

Biostatistician
Jeffrey Switchenko, PhD

FUNDING SOURCE: *Internal*

INVESTIGATIONAL PRODUCT (IP): **Paricalcitol and Hydroxychloroquine**
OTHER AGENT(S): Paricalcitol and Hydroxychloroquine

IND #: Exempt

REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	12/21/2021	Change in Principal Investigator

Table of Contents

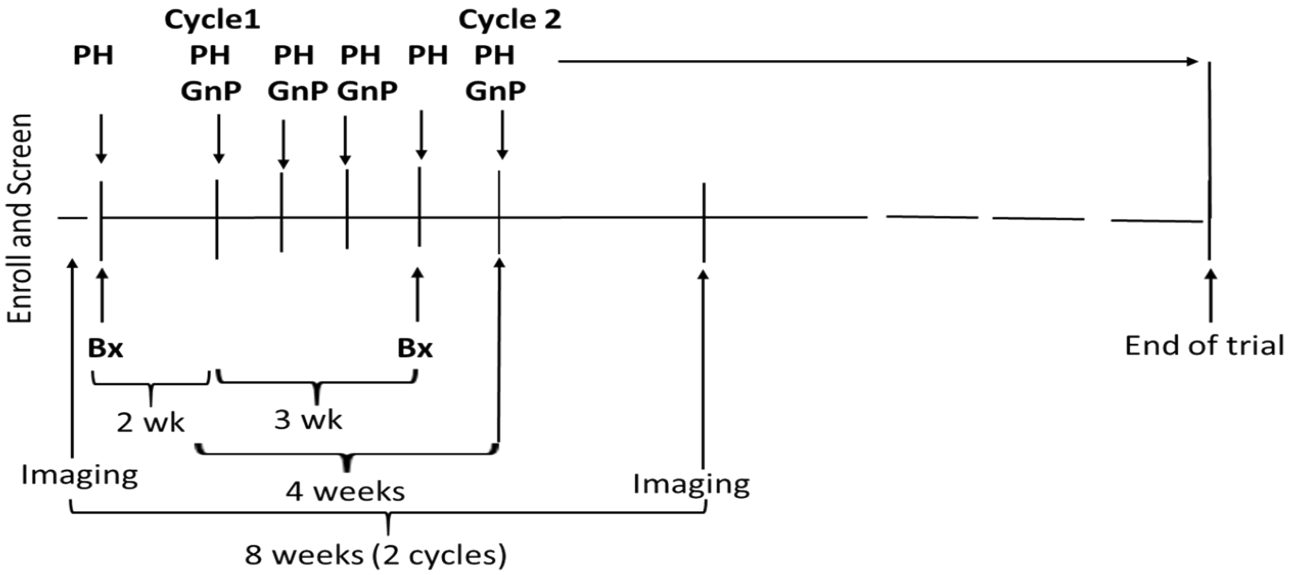
1. Study Summary

1.1 Synopsys

Title:	Phase II trial of paricalcitol and hydroxychloroquine (PH) combination with gemcitabine and nab-paclitaxel in advanced pancreatic cancer.
Study Description:	This research study is an open label, single arm, Phase II study, designed to evaluate the efficacy of the combination **paricalcitol plus hydroxychloroquine (PH)** when added to the commonly-used front-line therapy of gemcitabine/nab-paclitaxel in subjects with previously-untreated, metastatic pancreatic adenocarcinoma.
Objectives:	**Primary Objective**: To evaluate the anti-tumor activity of the combination of paricalcitol plus hydroxychloroquine (PH) when added to gemcitabine and nab-paclitaxel treatment by assessing the Overall Response Rate (ORR) by RECIST 1.1. **Secondary Objectives:** • To evaluate the safety and tolerability of the combination of paricalcitol plus hydroxychloroquine (PH) when added to gemcitabine and nab-paclitaxel treatment in patients with advanced pancreatic cancer. • To evaluate the anti-tumor activity of the combination of paricalcitol plus hydroxychloroquine (PH) when added to gemcitabine and nab-paclitaxel treatment by assessing progression-free survival (PFS) and overall survival (OS). **Exploratory Objective:** • To evaluate the effect of treatment on selected biomarkers in the tumor microenvironment and systemic circulation.
Endpoints:	**Primary Endpoint:** • Efficacy ORR per RECIST 1.1 (Tumor measurements will be performed at **8** weeks) **Secondary Endpoints:** • Safety: adverse events, vital sign measurements, physical examinations, and clinical laboratory test. • Efficacy: Progression Free survival (PFS) and Overall Survival (OS) • Exploratory: Changes in selected biomarkers in tumor microenvironment and circulation before and after treatment with paricalcitol plus hydroxychloroquine (PH) when added to gemcitabine and nab-paclitaxel treatment and their relationship with efficacy.
Study Population:	The patient population consists of subjects ≥18 years of age with biopsy proven pancreatic adenocarcinoma. Eligible patients must have not

	received any prior systemic treatment for metastatic disease. We plan to enroll 21 *evaluable* patients.
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute of Emory University (Atlanta, GA).
Description of Study Intervention:	Patients will receive the following treatment: Paricalcitrol 25 mcg IV three times weekly, Hydroxychloroquine 400 mg BID (1 week) then 600 mg BID (P.O.) Gemcitabine and nab paclitaxel will be given IV every cycle (Days 1, 8, 15) Treatment cycles are 28 days.
Study Duration:	Patients will be treated until unacceptable toxicity, death, or disease progression per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1).

1.2 Schema



PH: Paricalcitrol and hydroxychloroquine
GnP: Gemcitabine and nab-Paclitaxel
Bx: Biopsy- baseline plus day 21
Imaging: Cross sectional imaging of target lesions

1.3 Schedule of Assessments

Trial Period:				**Treatment Cycles** [a]								**End of Treatment**		
Treatment Cycle/Title:	Main Study Screening			1	2	3	4	To be repeated beyond 8 cycles				Discont.	Safety Follow-up	Survival Follow-Up
								5	6	7	8			
Scheduling Window (Days):	-42 to -14	D-14	D-7		± 3	± 3	± 3	± 3	± 3	± 3	± 3	End of treatment (EOT)	30 days post EOT	Every 12 weeks
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X		X		X	X	X	X	X	X	X	X	X	
Prior and Con Med. Review	X		X	X	X	X	X	X	X	X	X	X	X	
PH Treatment		X [b]	X [c]	X	X	X	X	X	X	X	X			
Gemcitabine nab Paclitaxel [d]				X	X	X	X	X	X	X	X			
Post-study anticancer therapy status													X	
Survival Status				X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events			X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X		X	X	X	X	X	X	X	X	X			
Directed Physical Examination			X									X	X	
Vital Signs and Weight	X		X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X[e]		X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG	X													
PT/INR and aPTT	X													
CBC with Differential [f]	X		X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel [g]	X		X	X	X	X	X	X	X	X	X	X	X	
CA19-9	X			X	X	X	X	X	X	X	X			
Urinalysis	X													
ECG	X	X[h]	X[h]	X[h]	X									
Ophthalmic exam [i]	X													
G6PD Testing	X													
Tumor Imaging	X[j]					X[k]			X[k]					
Archival or Newly Obtained Tissue Collection	X													
Correlative Blood Collection[m]	X		X	X	X	X						X		
Research tumor biopsy [l]	X			X										

a. Treatment cycles are 28 days
b. PH will be started on day -14 as detailed in section 5.1.3: Hydroxychloroquine: 400 mg BID (1 week)
c. PH will be started at Paricalcitol: 25 mcg IV three times weekly, hydroxychloroquine 600 mg BID
d. Gemcitabine and nab paclitaxel given days 1, 8, 15 of every cycle
e. ECOG performance status should be done within 10 days or less from day -14 of cycle 1
f. CBC diff will be done day 1, 8, 15 of every cycle
g. Comprehensive chemistry profile will be done day 1 of every cycle
h. ECG will be performed on Day -14 at (2 to 4 hours, 48 (+/-4) and 96 (+/- 4) hours) after first dose, day -7 at 48 (+/- 4) hours, day 1 cycle 1 at 48 (+/- 4) hours
i. Ophthalmic exam will be performed at baseline and every 6 months. Exam will also be performed in patients with visual symptoms.
j. Baseline imaging within 8 weeks of day -14 is acceptable
k. Scans will be done every 2 cycles between day 21 and day 28 of that cycle
l. Paired biopsies will only be obtained at baseline and day 21 (+/-2days) in all patients unless waived by PI.
m. Samples will be collected at baseline, day -7, cycle1 days 1,8,15, cycle 2 day 1 and cycle 3 day. Blood will also be collected at EOT and disease progression.

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
• To evaluate the anti-tumor activity of the combination of paricalcitol plus hydroxychloroquine (PH) when added to gemcitabine and nab-paclitaxel treatment by assessing the Overall Response Rate (ORR) by RECIST 1.1.k	• Efficacy: ORR per RECIST 1.1 (Tumor measurements will be performed every **8** weeks **± 3 days**).
Secondary	
• To evaluate the safety and tolerability of the combination of paricalcitol plus hydroxychloroquine (PH) when added to gemcitabine and nab-paclitaxel treatment in patients with advanced pancreatic cancer. • To evaluate the anti-tumor activity of the combination of paricalcitol plus hydroxychloroquine (PH) when added to gemcitabine and nab-paclitaxel treatment by assessing progression-free survival (PFS) and overall survival (OS).	• Safety: adverse events, vital sign, physical examinations, clinical laboratory test. • Progression-free Survival (PFS) using RECIST 1.1 • Overall Survival
Tertiary/Exploratory	
• Hypothesis 1: PH inhibits activation of inflammatory cancer associated fibroblasts and increases effector immune cells in the tumor microenvironment • Hypothesis 2: hydroxychloroquine has direct effects on tumor cells through inhibition of growth, modulation of TGF-β and inhibition of autophagy.	• Evaluate the effects of PH on CAF and immune cells using CyTOF to characterize the presence and distribution of these cells. In a subset of patients we can perform single cell RNA assays to characterize the CAF and immune infiltrates • Multiplex IHC to evaluate these pathways including TGF-β1, TGF-β1 RII, SMAD4, LC3 in addition to markers of fibrosis (collagen) and tumor (cytokeratin).

3. Background

Pancreatic cancer is estimated to become the second most common cause of cancer-related death by 2030, and most common by 2050 in the USA (Korc et al., 2017; Rahib et al., 2014). Pancreatic cancer results in approximately 331,000 deaths annually worldwide, making it the seventh most common cause of cancer-related mortality.(Ferlay et al., 2015) More than 90% of all pancreatic cancers are pancreatic ductal adenocarcinoma (PDAC).(Gordon-Dseagu, Devesa, Goggins, & Stolzenberg-Solomon, 2018) For all stages combined, PDAC has a very poor 5-year overall survival (OS) rate of 8%. Despite significant improvements in survival rates in many cancer types, PDAC death rate has increased in recent years (Siegel, Miller, & Jemal, 2018). **Majority of patients with PDAC present with advanced stage disease; therefore, improvement is largely dependent on identification of effective systemic therapies.**

Recent advances in chemotherapy regimens have had a modest impact on median OS, which ranges between 8.5–11.1 months (Conroy et al., 2011; Von Hoff et al., 2013). Development of novel systemic therapies to overcome the resistance of PDAC is an urgent need. Chemotherapy remains the only effective treatment of metastatic pancreatic ductal adenocarcinoma (PDAC) (Ryan, Hong, & Bardeesy, 2014). Both FOLFIRINOX (a combination of 4 drugs) and gemcitabine hydrochloride with nab-paclitaxel (GA) improve overall survival (OS) compared with gemcitabine alone and are associated with occasional long-term survival, suggesting a substantial effect on a subset of patients (Von Hoff et al., 2013),(Conroy et al., 2011). Nonetheless, essentially all patients experience acquired resistance to therapy, as manifested by regrowth of the tumor. Checkp.o.int inhibitors and immune therapies have proven ineffective in PDAC.

The dense extracellular matrix characteristic of PDAC plays a major part in supporting cancer cell proliferation, impeding chemotherapy delivery and preventing immune cells from access to tumor. At least three distinct populations of cancer-associated fibroblasts (CAF's) including pancreatic stellate cells exist in tumor microenvironment. Inflammatory or activated CAF's pro-inflammatory factors and components of the extracellular matrix. Increased number of inflammatory CAF's has been associated with worse clinical outcome. It has been demonstrated that, in pancreatic cancer laboratory models, engagement of the **vitamin D receptor** (VDR) by VDR agonists (such as Paricalcitol) shifts CAFs toward a more quiescent phenotype with reduced tumor growth and improved chemotherapy penetration (Sherman et al., 2014) This has also been shown to promote access of immune cells to the tumor microenvironment. Research clinical data shown autophagy is a common mechanism used by PDAC cells to avoid effects of chemotherapy. Consequently inhibition of **autophagy** has been shown to increase response to chemotherapy for patients with advanced pancreatic adenocarcinoma.

The purpose of this research study is to evaluate the effects of the combining of an autophagy inhibitor (hydroxychloroquine) which enhances the activity of chemotherapy and modulation of tumor microenvironment (synthetic vitamin D analog Paricalcitol) which improves delivery of chemotherapy with standard front-line therapy of pancreatic cancer, gemcitabine and nab-paclitaxel.

3.1 Study Rationale

Autophagy and Pancreatic cancer

Mutational activation of KRAS is the critical genetic driver of pancreatic ductal adenocarcinoma (PDAC) initiation and progression (Hingorani et al., 2003) and is essential for maintenance of PDAC tumorigenic growth (Collins et al., 2012), (Ying et al., 2012). Given that nearly 95% of PDAC harbor activated KRAS mutation, the National Cancer Institute has identified the development of anti-KRAS therapies as one of four priorities for pancreatic cancer research (Ryan et al., 2014),(Waters & Der, 2018). There are at least five major directions of current anti-KRAS drug discovery (Cox, Fesik, Kimmelman, Luo, & Der, 2014),(Papke & Der, 2017), (Stephen, Esposito, Bagni, & McCormick, 2014). One promising strategy aims to target mechanisms that mediate the KRAS-dependent

metabolic functions that support the increased energy needs of PDAC (Bryant, Mancias, Kimmelman, & Der, 2014; Kimmelman, 2015). One such function is autophagy, (or 'self-eating'), a lysosome-mediated cellular defense mechanism whereby cells degrade organelles and macromolecules and recycle cellular waste (Guo & White, 2016).

On activation, autophagy mediates regulated catabolism of cellular organelles, which are encapsulated first in autophagosomes and metabolized when these fuse to lysosomes. When the KRAS oncogene was introduced into mice, it enhanced autophagy, which lead to faster growing, more aggressive tumors (White, 2012). Because of this transformation, pancreatic cancer, more so than other cancers, appears to have a distinct dependence on autophagy, with studies showing increased autophagy activity occurring within these cancer cells (S. Yang et al., 2011). The rapidly dividing cells within tumors require more energy than normal cells to reproduce. When chemotherapy agents attack the pancreatic cancer cells, their ability to conserve energy, through autophagy, becomes especially critical.

Studies of pancreatic cancer cells in laboratories have shown that inhibition of autophagy makes survival of cancer cells more difficult by such processes as increasing reactive oxygen toxins, elevating DNA damage, and causing a metabolic defect leading to decreased mitochondrial oxidative phosphorylation.(S. Yang et al., 2011) Amaravadi et al. (Amaravadi et al., 2007) in 2007 first demonstrated that targeting autophagy with chloroquine derivatives enhanced the efficacy of chemotherapy. Pancreatic cancer, in particular, may be especially reliant on autophagy for growth and survival, and multiple preclinical studies have demonstrated the activity of hydroxychloroquine (HCQ) in pancreatic cancer models.(Perera et al., 2015) (A. Yang et al., 2014)(S. Yang et al., 2011).

In mice studies, decreased autophagy has led to robust tumor regression and prolonged survival of the mice. In a 16-mouse xenograft study, the response to chloroquine was dramatic. Of the 8 mice treated with chloroquine, 7 (88%) survived over 180 days, compared to all 8 untreated mice dying within 140 days (S. Yang et al., 2011). Inhibition of autophagy can be accomplished pharmacologically with hydroxychloroquine sulfate (HCQ), which inhibits the fusion of the autophagosome to the lysosome(Levy, Towers, & Thorburn, 2017). Because autophagy is upregulated in KRAS mutant PDAC(S. Yang et al., 2011) and is critical for tumorigenic growth (A. Yang et al., 2014) the autophagy inhibitor hydroxychloroquine is under clinical evaluation for PDAC treatment (NCT01273805, NCT01506973 and NCT03344172).

Hydroxychloroquine has shown limited activity as a monotherapy (Boone et al., 2015; Wolpin et al., 2014); but has shown promise in combination with preoperative gemcitabine plus nab-paclitaxel (See clinical experience section below). Bryant et al. concluded that inhibitor combinations that concurrently block multiple metabolic processes including autophagy may be an effective therapeutic approach for pancreatic cancer.(Bryant et al., 2014)

Vitamin D deficiency in cancer (Paricalcitol)

Vitamin D deficiency appears common in most cancer patients. One study found that 75% of cancer patients had low vitamin D levels. Low serum vitamin D levels predicted advanced-stage disease. In fact, in patients with levels under 24 ng/mL, the risk of stage 3 disease was almost triple that of those with higher vitamin D levels(Churilla et al., 2011). In another study, cancer patients had a significantly lower mean serum vitamin D level (24.9 ng/mL) relative to a cohort of noncancerous primary care patients (30.6 ng/mL, $P < 0.001$)(Churilla, Brereton, Klem, & Peters, 2012).

In regard to pancreatic cancer, in a study looking at 2 large US cohorts totaling 122,198 people of whom 365 developed pancreatic cancer, higher dietary intake of foods containing vitamin D was associated with a lower

risk for pancreatic cancer(Skinner et al., 2006). In a pooled analysis of 5 prospective cohorts with 451 cases and 1,167 controls, higher plasma levels of vitamin D were associated with a lower risk for pancreatic cancer (P = 0.005)(Wolpin et al., 2012).

Paricalcitol is a modified form of vitamin D that acts as a vitamin D receptor agonist and is not associated with systemic toxicity of vitamin D resulting in conditions such as hypercalcemia. It is currently available intravenously or orally to treat or prevent hyperparathyroidism in dialysis patients. Recently, investigators at the Salk Institute for Biological Studies have found that paricalcitol helps break though the pancreatic tumor's stroma, which acts as a protective shield, incasing the tumor. The stroma is part of an extracellular matrix obstructing the tumor's vasculature and inhibiting chemotherapy delivery to the tumor site. Specifically, the CAF including pancreatic stellate cells (those surrounding the tumor cells) are particularly activated in pancreatic cancer, driving the production of the stroma. These CAF have high levels of vitamin D receptors, and the blocking of these receptors by paricalcitol inactivates the stromal production (Apte & Wilson, 2012). The CAF also produce cytokines and growth factors that enhance local tumor growth, contribute to angiogenesis, and enable metastasis. Furthermore, stellate cells metastasize along with the cancer cells assisting in their seeding, survival, and proliferation (Sherman et al., 2014).

In mice, when paricalcitol was given along with gemcitabine, stromal activation and tumor size were both significantly reduced, resulting in a 57% prolongation of survival(Sherman et al., 2014). In addition to stromal inactivation, vitamin D has been shown to exert anti-proliferative effects, secondary to the upregulation of the cell cycle inhibitors, especially p21 and p27, which control cell proliferation, differentiation, and division. Studies have shown a reduction of several pancreatic tumor lines in mice treated with paricalcitol correlating with the degree of cell cycle kinase inhibition(Schwartz et al., 2008). Lastly, paricalcitol has been shown to increase T cell penetration into the tumor.

3.2 Clinical Experience

Hydroxychloroquine (HCQ)

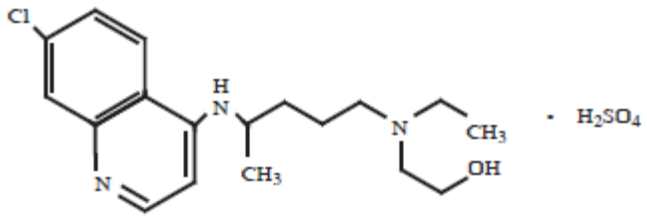


Figure 2. Molecular structure of hydroxychloroquine

HCQ has long been used as a FDA approved treatment for malaria suppression. In addition, it has FDA approved indications for the treatment of discoid and systemic lupus erythematosus and rheumatoid arthritis. It is approved for daily oral administration in either single or divided doses ranging from 200 mg per day up to 800 mg per day, although for longer term daily treatment in the cases of SLE or rheumatoid arthritis, 200-400 mg/day is recommended. As the most striking toxicity is a dose related retinopathy, these lower doses are recommended for longer term daily use. Retinal examination is recommended prior to and during treatment.

A phase 1 trial of gemcitabine and nab-paclitaxel with Hydroxychloroquine (HCQ) found that all agents were tolerable at full doses. (ClinicalTrials.gov Identifier: NCT01506973). Based on these findings a phase I/II trial examining preoperative gemcitabine in combination with oral HCQ for the treatment of patients with high-risk

PDA (NCT01128296)(Boone et al., 2015) was conducted. Clinical outcomes were improved compared to those from a previously established cohort of high-risk patients(Bao et al., 2009).

Based on these promising results, a randomized phase II trial of neoadjuvant gemcitabine/nab-paclitaxel with HCQ (and designated the treatment as PGH) or without HCQ (designated as PG; (NCT01978184)) was launched to better assess the contribution of the inhibition of autophagy by HCQ to gemcitabine/nab-paclitaxel chemotherapy (Zeh et al., 2020). Specifically the study analyzed 54 patients with resectable or borderline resectable pancreatic cancer receiving hydroxychloroquine 1,200 mg daily, in addition to chemotherapy. The trial showed greater pathological tumor response in the hydroxychloroquine group (P = 0.004). Additionally, the CA19-9 tumor marker in patients receiving hydroxychloroquine decreased by 20%, as compared to 10% in the chemotherapy-alone group (P = 0.014), and at the time of surgery, the ratio of positive lymph nodes to total number of lymph nodes was lower in the hydroxychloroquine group vs. the control group (0.03 vs. 0.05; P = 0.02). The hydroxychloroquine group had greater apoptosis in their tumors, less stromal activation, and greater infiltration of CD4 and CD8 T cells (P = 0.016 and P = 0.046, respectively), and greater tumor expression of PD-L1. No adverse effects were noted in this study (Miller-Ocuin et al., 2017).

Paricalcitol

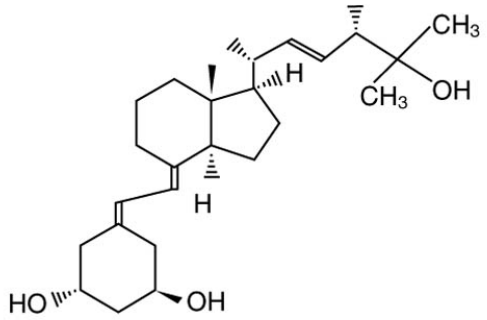


Figure 3. Molecular structure of paricalcitol

In a small Phase I study patients were treated with paricalcitol for 1 month prior to tumor resection. A 10- to 100-fold increase in the number of T cells was observed in and around the tumor (Sherman et al., 2014) (NCT02030860). Vitamin D affects the tumor's immune environment has inspired the start of a Phase II study combining paricalcitol with chemotherapy(Borazanci EH, 2017). The research study consist of a safety run-in phase and a randomized phase 2 study. It includes subjects with previously-untreated, metastatic pancreatic adenocarcinoma. The run-in safety study will evaluate the safety of adding two formulations (IV or Oral) of paricalcitol to a standard chemotherapy program of gemcitabine and nab-paclitaxel. The randomized phase 2 study will evaluate the efficacy of paricalcitol when added to gemcitabine and nab-paclitaxel (NCT03520790). The study is currently ongoing.

4. Study Intervention/Investigational Agent

4.1 Description

Gemcitabine and nab-paclitaxel

The Food and Drug Administration approved the combination of gemcitabine and nab-paclitaxel as a treatment option for pancreatic cancer. The recommended dose is 1000 mg/m^2 for gemcitabine and 125 mg/m^2 for nab-paclitaxel administered intravenously over 30-40 minutes on Day 1, 8 and 15 of each 28-day cycle. https://media2.celgene.com/content/uploads/abraxane-pi.pdf (nab-paclitaxel)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020509s082lbl.pdf (gemcitabine)

Hydroxychloroquine (HCQ)

Hydroxychloroquine (HCQ) is commonly prescribed for rheumatoid arthritis and lupus at doses of 400 mg p.o. daily. A pharmacokinetic/pharmacodynamic study of escalating doses of HCQ at 400 mg/800 mg/1200 mg p.o. daily in patients with rheumatoid arthritis followed by maintenance doses of 400 mg p.o. daily found that doses of up to 1200 mg P.O. daily were well tolerated (Munster et al., 2002).
http://products.sanofi.ca/en/plaquenil.pdf

Paricalcitol

The results of the study of Fountzials *et al.* (Fountzilas et al., 2018) demonstrate that paricalcitol can be combined safely with gemcitabine in patients with advanced cancer in doses up to 7 µg/kg IV weekly.
https://www.rxabbvie.com/pdf/zemplarivpi.pdf

The trial treatment is outlined below in **Table below:**

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Paricalcitol	25 mcg	IV	Three times weekly	28 days (4 weeks)
Hydroxychloroquine	400 mg (1st week D-14) 600 mg	P.O.	Twice daily	
Gemcitabine	1000 mg/m2	IV infusion over 30 min	Days 1, 8, and 15	
nab-paclitaxel	100 mg/m2	IV infusion over 30 min		

Gemcitabine will be administered immediately after nab-paclitaxel on Days 1, 8 and 15 of each 28-day cycle. The cycle will be repeated every 4 weeks. Patients will receive an appropriate anti-emetic regimen according to institutional guidelines prior to administration of chemotherapy.

Paricalcitol
Paricalcitol will be administered intravenously at 25 mcg three times a week. Recommended package insert suggest to initiate at 0.04 mcg/kg to 0.1 mcg/kg (2.8 mcg to 7 mcg) no more frequently than every other day. Ensure serum calcium is not above the upper limit of normal before initiating treatment. Monitor serum calcium weekly.

Hydroxychloroquine (HCQ)
Each dose should be taken with a meal or a glass of milk. Patients will receive 800 mg (400 mg BID) of hydroxychloroquine during the first week of treatment, 1200 mg (600 mg BID) afterwards. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary (Appendix E) will be returned to clinic staff at every patient's visit.

Gemcitabine and nab-paclitaxel
Please refer to the nab-paclitaxel and gemcitabine Product Labels for product description, stability information, storage instructions, and route of administration.
https://media2.celgene.com/content/uploads/abraxane-pi.pdf (nab-paclitaxel)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020509s082lbl.pdf (gemcitabine)

4.1.1 Justification for Dose

Gemcitabine and nab-paclitaxel

The Food and Drug Administration approved the combination of gemcitabine and nab-paclitaxel as a treatment option for pancreatic cancer. The recommended dose is 1000 mg/m^2 for gemcitabine and 100 mg/m^2 for nab-paclitaxel administered intravenously over 30-40 minutes on Day 1, 8 and 15 of each 28-day cycle. https://media2.celgene.com/content/uploads/abraxane-pi.pdf (nab-paclitaxel)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020509s082lbl.pdf (gemcitabine)

Hydroxychloroquine (HCQ)

Hydroxychloroquine (HCQ) is commonly prescribed for rheumatoid arthritis and lupus at doses of 400 mg p.o. daily. A pharmacokinetic/pharmacodynamic study of escalating doses of HCQ at 400 mg/800 mg/1200 mg p.o. daily in patients with rheumatoid arthritis followed by maintenance doses of 400 mg p.o. daily found that doses of up to 1200 mg P.O. daily were well tolerated (Munster et al., 2002).
http://products.sanofi.ca/en/plaquenil.pdf

Paricalcitol

The results of the study of Fountzials *et al.*(Fountzilas et al., 2018) demonstrate that paricalcitol can be combined safely with gemcitabine in patients with advanced cancer in doses up to 7 µg/kg IV weekly.
https://www.rxabbvie.com/pdf/zemplarivpi.pdf

4.2 Drug/Device Handling

Please refer to the Product Labels for product description, stability information, storage instructions, and preparation

Paricalcitol
https://www.rxabbvie.com/pdf/zemplarivpi.pdf

Hydroxychloroquine (HCQ)
http://products.sanofi.ca/en/plaquenil.pdf

Gemcitabine and nab-paclitaxel
https://media2.celgene.com/content/uploads/abraxane-pi.pdf (nab-paclitaxel)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020509s082lbl.pdf (gemcitabine)

4.3 Accountability

The study drug will be provided for this study by IDS and will be used only as directed in the study protocol. The Winship IDS (Investigational Drug Service) personnel will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.
Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.
The Drug Accountability Log may record specifics to study drug dispensation such as:
• Records of product delivery, inventory, temperature monitoring, destruction, and return.
• Dosages prepared, time prepared, doses dispensed.
• Doses and/or vials destroyed.
•
Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

The study drug supply will be disposed of as per Winship's Investigational Pharmacy (IDS) SOP

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

5. Procedures Involved

5.1 Study Design

This open label, single arm phase II trial design will evaluate the clinical activity and safety of combination therapy: paricalcitol plus hydroxychloroquine (PH) added to a standard chemotherapy program of gemcitabine and nab-paclitaxel in subjects with previously untreated metastatic pancreatic adenocarcinoma.

The study is divided into a Screening period, Treatment period, End of Treatment (EOT) period, and Follow-up period.

During **screening** period patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam) as long as the procedures were completed within the **28-day screening period** (days -42 and -14 in Section 1.3 SOA). After signing the ICF, patients will be evaluated for entry criteria during the screening period within 28 days before administration of study drug(s).
. Rescreening after screen failure will be allowed

Treatment period will continue until unacceptable toxicity, death, disease progression per RECIST 1.1, Investigator's decision to discontinue treatment, the patient withdraws consent, is lost to follow-up, or Institution decides to terminate the trial. Patients with PD per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section "Treatment beyond progression". Patients with a PR or SD will continue to receive treatment until achievement of a confirmed complete response (CR), disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating patients with a confirmed CR.

5.2 Dosing and Administration

The trial treatment is outlined below in **Table 2.**

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Paricalcitol	25 mcg	IV	Three times weekly	28 days (4 weeks)
Hydroxychloroquine	400 mg (1st week D-14) 600 mg	P.O.	Twice daily	
Gemcitabine	1000 mg/m2	IV infusion over 30 min	Days 1, 8, and 15	
nab-paclitaxel	100 mg/m2	IV infusion over 30 min		

Gemcitabine will be administered immediately after nab-paclitaxel on Days 1, 8 and 15 of each 28-day cycle. The cycle will be repeated every 4 weeks. Patients will receive an appropriate anti-emetic regimen according to institutional guidelines prior to administration of chemotherapy.

5.4 Dose Modification

Hydroxychloroquine, Paricalcitrol, gemcitabine nab-paclitaxel have class-specific safety profiles based on their mechanism of action but may also cause AEs that overlap. **For management of AEs which can be clearly attributed to one agent, independent dose modification for that agent is recommended with no dose adjustment for the other agents.** For AEs attributable to more than one study treatment, management of toxicity should include dose modifications of all possibly causative agents. **No dose adjustment or interruption will be done for clinically insignificant laboratory changes.**

Overall AEs are to be graded according to NCI-CTCAE v5.0 (http://ctep.cancer.gov). All dose interruptions and the reason for the dose interruption must be documented in the eCRF.

Overall, patients with AEs suspected to be related to ***hydroxychloroquine*** include visual changes, skin pigmentation changes, porphyria, arrhythmias, aplastic anemia, agranulocytosis, nausea, fatigue. Dose adjustment of hydroxychloroquine is outlined in Table 3.
Hydroxychloroquine will be initiated on day -14 at a daily dose of 800 mg (two 400 mg tablets) for 1 week.

- If the 800 mg dose *is not tolerated* then treat with 600mg dose for 1 week. If 600 mg dose is not tolerated, then the patient will be off study. If 600 mg dose well tolerated this will be the dose for day 1.
- If the 800mg dose *is well tolerated* then daily dose will be increased to 1200 mg (two 600 mg tablets) for 1 week. If the 1200mg dose is not well tolerated then 800 mg dose will be used on day 1. If the 1200 mg dose is well tolerated then this will be the dose for day 1.

Table 3. Dose modification of hydroxychloroquine

NCI CTCv5.0 Criteria	***Hydroxychloroquine* Dose Modification**
Any Grade 1 toxicity related to HCQ except visual changes and QTc Prolongation	*No dose reduction or interruption*
Any Grade 2 toxicity related to HCQ except visual changes and QTc Prolongation	*First occurrence – dose interruption until grade 1 or lower resumes same dose* *Second occurrence- dose interruption until grade 1 or lower resume 200 mg lower*
Any Grade 3 or higher toxicity related to HCQ except visual changes and QTc Prolongation	*First occurrence- Interrupt until toxicity resolves then resume at a dose 200mg less.* *Second occurrence- Interrupt until toxicity resolves and resume at 200 mg lower* *Third occurrence- discontinue*
Any visual toxicity	*Hold medication* *Ophthalmology exam* *If retinopathy has occurred hold for 2 weeks and resume with 50% dose reduction* *If retinopathy recurs stop drug*

If a subject on study has a QTc interval increase by ≥ 60 ms to an absolute value > 470 ms or an increase to an absolute value of > 500 ms at any evaluation, and if the subject is asymptomatic (does not have palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on electrocardiogram (ECG), or a change in vital signs)	• Hold hydroxychloroquine • Check electrolytes, especially magnesium and potassium; correct abnormalities as clinically indicated • Repeat ECGs hourly until the QTc is < 30 ms increased over the average baseline value Do not re-challenge with hydroxychloroquine
Subjects with QTc prolongation and symptoms	Close monitoring Cardiology consultation is recommended for evaluation and subject management. Do not re-challenge with hydroxychloroquine

Overall, patients with AEs suspected to be related to ***paricalcitol*** include hypercalcemia, edema, and fever.

Table 4. Dose modification of paricalcitol

NCI CTCv5.0 Criteria	***Paricalcitrol* Dose Modification**
Any Grade 1 toxicity related to paricalcitol	***No dose reduction or interruption***
Any Grade 2 toxicity related to paricalcitol	***Dose interruption until grade 1 or lower resume with 20% dose reduction***
Any Grade 3 or higher toxicity related to HCQ except visual changes	***Interrupt until toxicity resolves and resume with 40% dose reduction***

Overall, patients with AEs suspected to be related to ***gemcitabine and/or nab-paclitaxel*** will be dose adjusted as pre institutional guidelines and standard of care pathways in the package insert.

5.5 Concomitant medication

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed.

- Medications to prevent or treat nausea or vomiting.
- Anti-diarrheal medications (e.g., loperamide) for patients who develop diarrhea.
- Pain medication to allow the patient to be as comfortable as possible.
- Treatment with bisphosphonates or denosumab for pre-existing, painful bone/liver metastases, and limited-field palliative radiotherapy or surgery is permitted. Patients requiring initiation of such treatment during the course of the study must be evaluated for disease progression; radiotherapy like any concomitant medication must be listed on the CRF.
- Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF), thrombopoietin mimetics or erythroid stimulating agents as per local or published guidelines; in case of anemia, thrombocytopenia or neutropenia, potential immune mediated etiology should be ruled out
- Nutritional support or appetite stimulants (e.g. megestrol).
- Oxygen therapy and blood products or transfusions.
- Inactivated vaccines.
- The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

Prohibited Concomitant Medications

During the course of the study, patients must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) or any other therapies that may be active against cancer or modulate the immune responses.

- Concomitant administration of high doses of calcium-containing preparations or other vitamin D compounds may increase the risk of hypercalcemia. Thiazide diuretics are known to induce hypercalcemia by reducing excretion of calcium in the urine.
  Paricalcitol is partially metabolized by CYP3A. Exposure of Paricalcitol will increase upon administration with strong CYP3A inhibitors. Dose adjustment may be necessary

- **Hydroxychloroquine** has the potential to prolong the PR, QRS and/or QTc intervals in a concentration-related manner. Caution is recommended if the drug is used concomitantly with other drugs that prolong the PR, QRS and QTc intervals. Current information sources should be consulted for drugs that prolong the QTc interval, the QRS duration, or the PR interval. Caution is recommended if Hydroxychloroquine is used with drugs that have the potential to decrease electrolytes levels. Current information sources should be consulted for drugs that disrupt electrolytes.

Rescue Medications & Supportive Care

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, etc. should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events until start of new antineoplastic medication or 90 days after discontinuation of study drug, whichever is sooner. Suspected SAEs will continue to be collected beyond the 90-Day safety visit. This will be done by return clinic visits, laboratory checks, and phone calls.

5.6 Study Procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purp.o.se of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

Screening Phase

Screening procedures will be performed up to 28 days prior to initiation of therapy with paricalcitol and hydroxychloroquine (Days -42 and -14 in Section 1.3 SOA). Baseline imaging by CT/MRI within 8 weeks of day -14 is acceptable. All subjects must first read, understand, and sign the IRB approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Period**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG
- Ophthalmology exam
- Tumor biopsy
- Review of prior/concomitant medications
- Imaging by CT/MRI (Baseline imaging within 8 weeks of day -14 is acceptable)
- Research blood collection
- Clinical laboratory tests for:
    - Hematology
    - Clinical chemistry
    - Coagulation (PT, aPTT, INR)
    - Serum or urine pregnancy test (for women of childbearing potential)
    - G6PD Testing
    - CA19-9
    - Urinalysis

Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3).

Day -14

- Start Hydroxychloroquine 400 mg BID and Paricalcitol 25 mcg IV
- ECG at 2 (+2), 48 (+/-4) and 96 (+/-4) hours

Day -7

- Full physical examination
- ECOG Performance Status
- Vitals signs, weight
- Review of prior/concomitant medications
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - CA19-9
- Start Hydroxychloroquine 600 mg BID, continue paricalcitol
- ECG 48 (+/-4) hours after hydroxychloroquine
- Research lab sample collection

Day 1 every cycle

- Full physical examination
- Review adverse events
- ECOG Performance Status
- Vitals signs, weight
- Review of prior/concomitant medications
- Pill count and diary collection
- ECG (first and second cycle ONLY)
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - CA19-9
- Gemcitabine and nab paclitaxel in addition to hydroxychloroquine and paricalcitol
- Research blood collection (cycle 1 and cycle 2 ONLY)

Day 8 and 15

- History and physical (cycle 1 ONLY)
- Review of adverse events
- CBC diff
- Research blood collection (cycle 1 ONLY)
- Gemcitabine and nab paclitaxel plus paricalcitol and hydroxychloroquine

Day 21 cycle 1 (+/- 2 days)

- Research Tumor biopsy

Every 8 weeks

- Tumor imaging (every 8 weeks)

Every 6 months

- Ophthalmology exam

End of Treatment

End of treatment is defined as the last planned dosing visit within the dosing period. For subjects who discontinue drug treatment, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 14 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit. Assessments for subjects who have completed treatment and achieved disease control, or have discontinued treatment due to toxicity in the absence of confirmed progressive disease are provided in the Schedule of Event. All subjects will be followed for survival until the end of the study regardless of further treatments, or until the study ends the study.

- Full physical examination
- Review adverse events
- ECOG Performance Status
- Vitals signs, weight
- Review of prior/concomitant medications
- Pill count and diary collection
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - CA19-9
- Research blood collection

5.7 Description of Study Procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedule of Events. Full physical examinations should be conducted at screening/baseline, Day 1 of cycle 1 and beyond, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be reported at each visit, height at screening/baseline visit only.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.

On infusion days, patients receiving treatment will be monitored during and after infusion of IP. If the infusion takes longer than 60 minutes, then BP and pulse measurements should be taken if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with

assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.
At Screening, a single ECG will be obtained on which **QTcF must be <450 ms**.

In case of clinically significant ECG abnormalities, including a QTcF value >450 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding. The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE.

Tumor and Radiographic Assessments

Tumor assessments for all patients will be performed at Screening and every 8 weeks (± 3 days) until the patient withdraws consent or starts a new antineoplastic regimen. Assessments will become less frequent during the long-term follow-up period. Tumor response will be evaluated using RECIST 1.1 (See Appendix F).

Radiographic assessments (chest/abdomen/pelvis, and other known affected anatomical areas) are required for all patients for tumor measurements. Additional scan assessments may be collected based on clinical symptoms, as appropriate. Documented tumor measurements are required using CT scans, MRI, physical examination, and/or digital photography, as appropriate. Any imaging used to assess disease at any time p.o.int will be submitted for an independent radiology review. The same method of assessment (CT or MRI and/or digital photography) and the same technique for acquisition of images must be used for all study assessments (contrast must be used unless medically contraindicated). Baseline imaging should be done at the same institution/facility which will be used to measure response during the patient's participation in the study. Radiographic assessments and efficacy analyses will be conducted by the Investigator site as well as the independent radiology review committee.

Ophthalmic exam

Ophthalmic exam will consist of assessment of ocular/visual signs and symptoms, visual acuity and slit lamp exam. Ophthalmologic exam will be performed prior to start of study and every 6 months. In case of ocular toxicity during study treatment, these tests will be repeated until resolution to grade <1.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Hematology and Clinical Chemistry
- Urinalysis
- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
    - Urine human chorionic gonadotropin (at screening only)
    - Serum beta-human chorionic gonadotropin
- Other laboratory tests
    - CA19-9
    - G6PD Testing

6. Data and Specimen Banking

Hypothesis 1: **PH will inhibit activation of inflammatory cancer associated fibroblasts (CAF) and increase effector T-cell immune microenvironment.**
Test: we plan to evaluate the effects of PH on tumor, CAF, immune cells and stroma using Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-Seq) to characterize tumor and immune infiltrate. We will also evaluate anti-tumor T cell immunity by performing T cell receptor sequencing on tissue and temporal blood samples.

Hypothesis 2: **Hydroxychloroquine has direct effects on tumor cells through inhibition of growth, modulation of TGF beta and inhibition of autophagy.**
Test: we will use multiplex IHC to evaluate these pathways including TGF-β1, TGF-β1 RII, SMAD4, LC3 in addition to markers of fibrosis (collagen) and tumor (cytokeratin).

Tumor Biopsy: Tumor specimens from patients enrolled in the study will be obtained at baseline (**Pre-treatment Tumor samples**) within 21 days before starting treatment with Paricalcitrol and Hydroxychloroquine (PH). The 2nd biopsy will be on day 21 (+/- 2days). **PI may waive paired biopsies if the biopsies cannot be safely obtained.**

The research biopsies each with 3 cores will be handled in the following way:
1) One core will be formalin-fixed and paraffin embedded for immunohistochemistry and H&E staining
2-3) Single cell suspensions will be prepared from the other two cores and cryo-preserved in liquid nitrogen for correlative assays.

All collected tissues will be sent fresh to Dr. Alese's lab, Building C 3rd floor. One core will be stabilized and stored in -80°C freezers (OCT embedded, short term storage). Two cores will be processed for preparing single cell suspension and stored as single use aliquots in a liquid nitrogen freezer. The protocols for preparation of single cell suspensions will be obtained from Dr. Bhasin's lab which has extensive experience in the area of single cell profiling. All FFPE tissue blocks will be stored in a climate controlled storage room that is temperature (less than 27ºC) and humidity controlled.

We plan to evaluate the effects of PH on CAFs, tumor, immune cells and stroma using CITE-Seq. Tissue will be also be evaluated using multiplex IHC to evaluate pathways including TGF-β1, TGF-β1 RII, SMAD4, LC3 in addition to markers of fibrosis (collagen) and tumor (cytokeratin).

Blood samples:
Peripheral blood will be collected for correlative assays at baseline, Day -1, Day 7 and at 1 and 2 months (Day 1 of cycle 1, 2, and 3) and time of progression. Approximately **40 mL of blood** will be obtained for correlative studies at each time points. Blood samples must be processed within **8 hours** of the blood draw by courier to the central site (Winship Cancer Institute, Olatunji Alese Lab Winship Bldg. C 3rd floor). Blood samples will be processed, and the plasma layer will be aliquoted, snap frozen (dry ice or liquid nitrogen) and stored at ≤-70°C until analysis. Plasma samples from individual patient cohorts will be batched and analyzed simultaneously. Table 1 summarizes all clinical sample and correlative assays for this study.

Peripheral blood mononuclear cells (PBMC) will be isolated from these same blood samples following removal of the plasma layer via standard methods using density gradient centrifugation with Ficoll-paque plus as described in the laboratory manual. Following isolation PBMCs will undergo single cell RNA-sequencing and immune-

repertoire analysis using T cell receptor (TCR) sequencing in Dr. Bhasin's lab. Quantification of autophagy will be carried out by one of several methods (Alonzi, Petruccioli, Vanini, Fimia, & Goletti, 2019).

The following studies are planned for these biospecimens collected: 1. Flow cytometry (at least to assess proliferating and activated T-cells in blood); 2. TCR sequencing to assess diversity of the T cell repertoire intra-tumorally and in blood; and 3. Single cell CITE-Seq in the blood. Collectively these assays will help in characterizing the impact of treatment on tumor cells and on the micro-environment. The correlative CITE-Seq and TCR sequencing studies will be performed by Dr. Bhasin's lab.

Plasma analysis: We will measure CRP, cytokines and a number of interleukins to determine the impact of treatment on key immune regulators that correlate with prognosis in pancreatic cancer. Assays will be carried out using the Stanford Human Immune Monitoring Center Core.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence.
Samples and data will only be used for research.

Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, de-identified data and/or specimens might be provided to other researchers. In this case, information that could identify the subject will not be included.

8. Study Timelines

8.1 Duration of therapy

In the absence of treatment delays due to adverse event(s), **patients will be treated until** any one of the following:

- Tumor progression per RECIST 1.1
- Death
- Unacceptable toxicity
- Symptomatic deterioration
- Achievement of maximal response
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment
- Patient withdraws consent
- Lost to follow up

In the event of a patient's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events.

8.2 Duration of follow-up

Patients will be followed for approximately 28 days (Safety Follow-up) after the last dose of study drug or before initiation of new antineoplastic or investigational therapy whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Survival follow-up should continue every 12 weeks.
- All patients will be contacted for survival every 12 weeks following the End of Treatment (EOT) visit.

Patients who have not initiated a new antineoplastic regimen will have the following assessments:
- In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Inclusion and Exclusion Criteria

Inclusion Criteria

Study candidates must meet all of the following inclusion criteria to be eligible for participation in this study:

a) Patients must have histologically confirmed advanced or metastatic adenocarcinoma of the pancreas (Stage IV).
b) Patients must have measurable disease as defined by RECIST criteria 1.1 as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded as ≥10 mm (≥1 cm) on CT scan, MRI.
c) Patients may have had prior neoadjuvant or adjuvant treatment for pancreatic cancer. The last dose of chemotherapy must have been 12 months prior to study entry. No prior systemic therapy for metastatic disease.
d) Patients must be Age ≥18 years.
e) ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
f) Patients must have adequate organ and marrow function, within 28 days of Cycle 1 Day 1, as defined below:

Hematology	
Hemoglobin	≥ 9.0 g/dl (no transfusions allowed within 7 days of Cycle 1 Day 1 to meet entry criteria)
Absolute neutrophil count (ANC)	≥ 1,500/mcL (after at least 7 days without growth factor support or transfusion)
Platelets	≥ 100,000/mcL (no transfusions allowed within 7 days of Cycle 1 Day 1 to meet entry criteria)
Coagulation	
International Normalized Ratio (INR)	≤1.5
Partial thromboplastin time (PTT)	< 1.5 x upper limits of normal (ULN)
Chemistry	
Total bilirubin	≤1.5 times the institutional upper limit of normal (ULN)
AST/ALT	≤ 5.0 times the ULN.
Serum creatinine	≤ 1.5× ULN or Creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels >1.5 x ULN. Creatinine clearance should be calculated per institutional standard
Calcium (corrected for albumin)	≤1 × institutional upper limit of normal

g) Patients with prior radiotherapy are acceptable. It must be at least 21 days since administration of radiation therapy and all signs of toxicity must have abated.
h) Patient must have a primary or metastatic non-bone site that is amenable to safe biopsy. Bone only lesions are not suitable for biopsy.

i) Patients with known G6PD deficiency, severe psoriasis, porphyria, macular degeneration or severe diabetic retinopathy are ineligible because of the potential for greater HCQ toxicity.
j) Patients with known history or current symptoms of cardiac disease, or history of treatment with cardio-toxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
k) The effects of study drugs used in this study on the developing human fetus are unknown. For this reason, female of child-bearing potential (FCBP) must have a negative serum or urine pregnancy test prior to starting therapy.
l) FCBP and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 1 months after completion of drug administration.
m) Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.
n) Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

a) Prior chemotherapy or any other investigational agents for the treatment of metastatic pancreatic cancer.
b) Concurrent use of any other anti-cancer therapy, including chemotherapy, targeted therapy, immunotherapy, or biological agents.
c) History of use of HCQ (aminoquinolines) or Paricalcitol in the 6 months prior to study entry.
d) Pre-existing hypercalcemia, defined as baseline serum calcium (corrected for albumin) above the institutional upper limit of normal.
e) After signing consent, vitamin D or calcium containing supplements must be stopped and no vitamin D or calcium supplements can be taken while the patient is enrolled to the study due to increased risk for hypercalcemia.
f) Pre-existing, clinically significant peripheral neuropathy, defined as CTCAE grade 2 or higher neurosensory or neuro-motor toxicity, regardless of etiology.
g) Participants with uncontrolled brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
h) Current use of medications that prolong QT interval unless approved by PI or substances that are strong inhibitors or inducers of CYP450 3A enzyme(s)- unless approved by PI.
i) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

j) Patients with known G6PD deficiency, severe psoriasis, porphyria, macular degeneration or severe diabetic retinopathy are ineligible because of the potential for greater HCQ toxicity.

k) Pregnant women are excluded from this study because the use of agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with study drugs, breastfeeding should be discontinued.
l) Participant must be able to swallow and absorb pills.

10. Local Number of Participants

We will be recruiting **21 participants** at Winship. We are expecting to have to consent 24 number of participants to reach our recruitment goal of 21 subjects at Winship. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

11. Recruitment Methods

Investigators, nurses, and/or data managers review lists of cancer patients who have cancer and will determine if there are patients who might be eligible for a clinical trial. The nurse/data manager reviews accessible medical records to screen further for eligibility. The nurse reviews the eligibility with the physician.

Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options. Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.

No incentives are provided to patients for trial participation.

Registration process

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore® Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator. When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-

investigator, Co-Investigator) has signed the eligibility checklist, enrollment may proceed. OnCore® and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

Subjects who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, will not be enrolled into the study and are considered **screen failures**. All subjects which have signed informed consent, and were deemed ineligible will be recorded in a log with the reason of ineligibility and their enrollment status will be updated in OnCore. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants and to respond to queries from regulatory authorities. Minimal information includes demography, informed consent date, screen failure details, eligibility criteria, study discontinuation date.

12.Withdrawal of Participants

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment.

The EOT visit will occur **30** days after the last dose of the study drug or before a new antineoplastic regimen has been initiated.
Reasons for EOT are:

- PD in the absence of clinical benefit as determined by the Investigator.
- Occurrence of a clinically significant AE found to be unacceptable or non-resolution of clinically significant AEs for > 4 weeks.
- Symptomatic deterioration.
- Achievement of maximal response.
- Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and PI.
- Continued participation is no longer in the patient's best interest in the opinion of the Investigator.
- Withdrawal of consent.

Patient remain on treatment phase until discontinuation of all study drugs, In the event of a patient's withdrawal, the Investigator will promptly notify the PI and make every effort to complete the EOT procedures specified in the Schedule of Events

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

Subjects who sign the informed consent form and are assigned but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are assigned and receive the study intervention,

and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced. *Please refer to the Schedule of assessment for assessments to be performed at the time of discontinuation.*

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study drugs for 4 consecutive weeks.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are eligible but do not receive any of the study intervention will be replaced.

13. Risks to Participants

Risk associated with paricalcitol
In terms of safety, as stated, paricalcitol is less likely to produce hypercalcemia, hyperphosphatemia, or elevations in calcium and phosphorus levels compared to other forms of vitamin D, primarily due to its decreased effect on intestinal absorption of calcium and phosphorus (Sprague, Llach, Amdahl, Taccetta, & Batlle, 2003). Hypercalcemia can occur during treatment with ZEMPLAR and can lead to cardiac arrhythmias and seizures. Severe hypercalcemia may require emergency attention. The risk may be increased when paricalcitol is used concomitantly with high dose calcium preparations, thiazide diuretics, or vitamin D compounds. Inform patients about symptoms of hypercalcemia and monitor serum calcium prior to initiation and during treatment and adjust dose accordingly.

In a Phase I dose-escalating trial of IV paricalcitol in men with advanced prostate cancer, patients received as much as 25 µg 3×/week intravenously. Significant hypercalcemia was rare, and the maximally tolerated dose of paricalcitol was not reached in that study, indicating that even higher doses may be free of significant side effects.(Schwartz et al., 2008). Paricalcitol has also been shown to be well tolerated in mice at relatively high levels.
In summary, paricalcitol given intravenously at a dose of 25 µg, 3×/week, appears to be well tolerated with little risk of serious adverse side effects in humans. It has worked well in vitro and in vivo (mouse studies) indicating possible benefit in combination with chemotherapy in human pancreatic cancer. Large-scale studies in humans are just beginning. The most common adverse reactions (> 5% and more frequent than placebo) are nausea, vomiting and edema

Risk associated with hydroxychloroquine
The major risk associated with hydroxychloroquine is retinopathy, potentially leading to blindness. At the typical dose of 200 mg 2×/day (for autoimmune diseases), the risk is exceedingly small with <2% of patients developing retinopathy after 20 years. The higher doses being tested to prevent autophagy (800–1,200 mg daily dosages are currently in clinical trials) carry a higher risk. Two small studies have shown some degree of retinal damage

occurring in under 2 years.(Leung, Neal, Wakelee, Sequist, & Marmor, 2015). Therefore, at high doses, screening by an ophthalmologist is recommended every 6 months, as early detection is the only method to prevent serious retinal damage.
Other toxicities reported with hydroxychloroquine include nausea, fatigue, and possible potentiation of chemotherapy-induced myelosuppression. Dose limiting toxicities of nausea, vomiting and abdominal pain were observed at 800 and 1200 mg p.o. daily.

Cases of cardiomyopathy resulting in cardiac failure, in some cases with a fatal outcome, have been reported in patients treated with hydroxychloroquine. It can also prolong the PR, QRS and QTc intervals, especially in patients with underlying risk factors. QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. It is not recommended for use in patients with baseline QTc prolongation (e.g., congenital or acquired Long QT Syndrome), second-or third-degree atrioventricular block. Electrolyte imbalances (e.g. hypokalemia/hypomagnesemia/hypocalcemia) must be corrected prior to use.

Hydroxychloroquine has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients treated with hydroxychloroquine should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia during treatment with hydroxychloroquine should have their blood glucose level checked and the need for hydroxychloroquine treatment reviewed as necessary. Periodic blood counts should be obtained in patients requiring prolonged therapy due to the risk of bone marrow depression.

Risk associated with chemotherapy
The most common (≥ 20%) adverse reactions of nab-paclitaxel in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common adverse reactions for the single agent (≥20%) are nausea/vomiting, anemia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema.

14. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol.

15. Statistical Design

15.1 Statistical consideration:

Primary Endpoint:

- Efficacy: ORR per RECIST 1.1 (Tumor measurements will be performed every 8 weeks)

Secondary Endpoints:

- Safety: adverse events, vital sign measurements, physical examinations, and clinical laboratory test.
- Efficacy: Progression Free survival (PFS) and Overall Survival (OS)

- Exploratory: Changes in selected biomarkers in tumor microenvironment and circulation before and after treatment with paricalcitol plus hydroxychloroquine (PH) when added to gemcitabine and nab-paclitaxel treatment and their relationship.

15.2 Sample Size/ Accrual Rate

Primary safety and efficacy analysis will be conducted on all patient data at the time all patients who are still receiving study treatment will have completed at least 4 cycles of treatment. The additional data for any patients continuing to receive study treatment past this time, as allowed by the protocol, will be further summarized in a final study report once these patients completed the study. Patients are considered evaluable if they receive day 1 cycle 1 of treatment. Patients unable to tolerate PH alone (day -14 to day -1) will still be included in analysis of outcome and toxicity but will be replaced for the primary endpoint assessment.

The study will proceed using Simon's two-stage Minimax design. Response rate for gemcitabine and nab paclitaxel is 23% (Von Hoff et.al. NEJM 2013; 369:1691-1703). An overall response rate of the combination of gemcitabine and nab paclitaxel with paricalcitol plus hydroxychloroquine (PH) of 45% would be considered clinically significant and interesting for further development. The null hypothesis that the true response rate is 23% will be tested against a one-sided alternative. In the first stage, 15 evaluable patients will be accrued. If there are 3 or fewer response in these 15 patients, the study will be stopped. Otherwise, 6 additional evaluable patients will be accrued for a total of 21 evaluable patients. The null hypothesis will be rejected if 8 or more responses are observed in 21 evaluable patients. This design yields a type I error of 0.1 and power of 80% when the true response rate is 45%.

15.3 **Statistical analysis and plan**

All subjects who receive any amount of study drug will be included in the evaluation of safety and efficacy. Response rate will be estimated, and a 90% exact confidence interval will be reported using the Clopper-Pearson method. Summary statistics will be presented for all safety, efficacy and biomarker parameter analyses. The purp.o.se of these analyses is hypothesis generating and therefore, formal statistical testing will not be performed. Various exploratory statistical tests may be applied to data generated from this trial to generate hypotheses to be tested in subsequent trials. In general, data for continuous parameters will be presented using descriptive statistics including sample size, mean, and median; standard deviation; and minimum and maximum. Categorical parameters (such as pathologic response rate) will be displayed using counts and percentages. Toxicities will be presented as worst toxicity per patient and will be reported as percent toxicity. The number of subjects with skipped doses, dose delays and dose reductions as well as major reasons for dose modifications will be summarized. Time-to-event endpoints such as overall survival and progression-free survival will be estimated using the Kaplan-Meier method.

Adverse events will be classified using MedDRA System Organ Classes and Preferred Terms. Furthermore, SAEs, AEs with a severity grade of 3 or above using NCI CTCAE version 5.0, AEs deemed related to study drug, AEs leading to discontinuation of study drug, and AEs leading to death will also be summarized in preferred term by system organ class and listed on an individual subject basis.

Descriptive statistics for worst grade of each treatment related laboratory parameter by the NCI CTCAE scale version5.0 at baseline and follow-up will be presented along with change from Baseline. Additionally, laboratory values ≥ Grade 3 severity will be tabulated and listed on an individual subject basis.

15.4 Data/specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the PI and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics.

All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study pancreatic cancer. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

16.Provisions to Monitor the Data to Ensure the Safety of Participants

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Classification of an Adverse Event

<u>Severity of Event</u>

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

<u>Relationship to Study Intervention</u>

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result,

occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Adverse Event and Serious Adverse Event Reporting

Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment start through **28** days following cessation of treatment, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.
The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.
Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study.

Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1-5)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Whether it is serious, where a serious adverse event (SAE) is defined previously and which seriousness criteria have been met.
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.
Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.
Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Serious Adverse Event Reporting

For the time period beginning with treatment initiation on trial (day 1) through 21 days following cessation of treatment, or until subject initiates new anticancer therapy, whichever is earlier. Any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug,

must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, or FDA .

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study PI and should be provided as soon as possible. All subjects with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

Second and secondary malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through **ONCORE.**

Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol. A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("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); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP). The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data. The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

17. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the PI and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence..

The study monitor, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

18. Economic Burden to Participants

Research study drugs (hydroxychloroquine and paricalcitol) used in this study will be free of charge to the participants. Any costs associated with the research biopsies will be paid for by the study and no cost to the patient. The study will not pay for patient`s regular medical care, standard chemotherapy (gemcitabine, nab-paclitaxel) and standard of care studies, procedures, examinations.

Subjects will have to pay for the items or services for which the study does not pay. The study budget will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the study does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the study has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be.

19. Consent Process

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic.
At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purp.o.se, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation. Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.

It will be explained to prospective participants that the study involves research, the purp.o.se of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The

study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time. Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent.
Prospective participants will be provided with a description of any reasonably foreseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.

Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, their representatives, and possibly the FDA or OHRP.

Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., subject, insurer). The participant is told the source of the study's funding. All participants will be told of any additional costs that may result from participation in the research.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use.

Process to Document Consent in Writing:

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product

Winship SOP 2.1:”Obtaining Informed consent for Greater than Minimal Risk Interventional clinical trial” will be followed.

Participants who are not yet adults (infants, children, teenagers)

N/A

Cognitively Impaired Adults

N/A

Adults Unable to Consent

N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

20. Setting

The research will be conducted at Emory University. Potential participants will be identified in gastrointestinal medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, multidisciplinary tumor board, and multidisciplinary gastrointestinal tumor board at Emory University.

21. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, and its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

22. Multi-Site Research when Emory is the Lead Site

N/A

23. References

Alonzi, T., Petruccioli, E., Vanini, V., Fimia, G. M., & Goletti, D. (2019). Optimization of the autophagy measurement in a human cell line and primary cells by flow cytometry. *Eur J Histochem, 63*(2). doi:10.4081/ejh.2019.3044

Amaravadi, R. K., Yu, D., Lum, J. J., Bui, T., Christophorou, M. A., Evan, G. I., . . . Thompson, C. B. (2007). Autophagy inhibition enhances therapy-induced apoptosis in a Myc-induced model of lymphoma. *J Clin Invest, 117*(2), 326-336. doi:10.1172/JCI28833

Apte, M. V., & Wilson, J. S. (2012). Dangerous liaisons: pancreatic stellate cells and pancreatic cancer cells. *J Gastroenterol Hepatol, 27 Suppl 2*, 69-74. doi:10.1111/j.1440-1746.2011.07000.x

Bao, P., Potter, D., Eisenberg, D. P., Lenzner, D., Zeh, H. J., Lee Iii, K. K., . . . Moser, A. J. (2009). Validation of a prediction rule to maximize curative (R0) resection of early-stage pancreatic adenocarcinoma. *HPB (Oxford), 11*(7), 606-611. doi:10.1111/j.1477-2574.2009.00110.x

Boone, B. A., Bahary, N., Zureikat, A. H., Moser, A. J., Normolle, D. P., Wu, W. C., . . . Zeh, H. J., 3rd. (2015). Safety and Biologic Response of Pre-operative Autophagy Inhibition in Combination with Gemcitabine in Patients with Pancreatic Adenocarcinoma. *Ann Surg Oncol, 22*(13), 4402-4410. doi:10.1245/s10434-015-4566-4

Borazanci EH, J. G., Borad MJ, et al. . (2017). A phase II pilot trial of nivolumab + albumin bound paclitaxel + paricalcitol + cisplatin + gemcitabine (NAPPCG) in patients (pts) with previously untreated metastatic pancreatic ductal adenocarcinoma. *J Clin Oncol., 35 (Suppl4)*.

Bryant, K. L., Mancias, J. D., Kimmelman, A. C., & Der, C. J. (2014). KRAS: feeding pancreatic cancer proliferation. *Trends Biochem Sci, 39*(2), 91-100. doi:10.1016/j.tibs.2013.12.004

Churilla, T. M., Brereton, H. D., Klem, M., & Peters, C. A. (2012). Vitamin D deficiency is widespread in cancer patients and correlates with advanced stage disease: a community oncology experience. *Nutr Cancer, 64*(4), 521-525. doi:10.1080/01635581.2012.661515

Churilla, T. M., Lesko, S. L., Brereton, H. D., Klem, M., Donnelly, P. E., & Peters, C. A. (2011). Serum vitamin D levels among patients in a clinical oncology practice compared to primary care patients in the same community: a case-control study. *BMJ Open, 1*(2), e000397. doi:10.1136/bmjopen-2011-000397

Collins, M. A., Bednar, F., Zhang, Y., Brisset, J. C., Galban, S., Galban, C. J., . . . Pasca di Magliano, M. (2012). Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. *J Clin Invest, 122*(2), 639-653. doi:10.1172/JCI59227

Conroy, T., Desseigne, F., Ychou, M., Bouche, O., Guimbaud, R., Becouarn, Y., . . . Intergroup, P. (2011). FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med, 364*(19), 1817-1825. doi:10.1056/NEJMoa1011923

Cox, A. D., Fesik, S. W., Kimmelman, A. C., Luo, J., & Der, C. J. (2014). Drugging the undruggable RAS: Mission possible? *Nat Rev Drug Discov, 13*(11), 828-851. doi:10.1038/nrd4389

De Henau, O., Rausch, M., Winkler, D., Campesato, L. F., Liu, C., Cymerman, D. H., . . . Merghoub, T. (2016). Overcoming resistance to checkpoint blockade therapy by targeting PI3Kgamma in

myeloid cells. *Nature, 539*(7629), 443-447. doi:10.1038/nature20554

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., . . . Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer, 136*(5), E359-386. doi:10.1002/ijc.29210

Fountzilas, C., Javle, M., Tan, W., Ma, Y., Fetterly, G., Iyer, R., & Johnson, C. (2018). A phase 1, open-label, dose escalation study of intravenous paricalcitol in combination with gemcitabine in patients with advanced malignancies. *Cancer, 124*(19), 3890-3899. doi:10.1002/cncr.31676

Gordon-Dseagu, V. L., Devesa, S. S., Goggins, M., & Stolzenberg-Solomon, R. (2018). Pancreatic cancer incidence trends: evidence from the Surveillance, Epidemiology and End Results (SEER) population-based data. *Int J Epidemiol, 47*(2), 427-439. doi:10.1093/ije/dyx232

Guo, J. Y., & White, E. (2016). Autophagy, Metabolism, and Cancer. *Cold Spring Harb Symp Quant Biol, 81*, 73-78. doi:10.1101/sqb.2016.81.030981

Hingorani, S. R., Petricoin, E. F., Maitra, A., Rajapakse, V., King, C., Jacobetz, M. A., . . . Tuveson, D. A. (2003). Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. *Cancer Cell, 4*(6), 437-450. doi:10.1016/s1535-6108(03)00309-x

Kimmelman, A. C. (2015). Metabolic Dependencies in RAS-Driven Cancers. *Clin Cancer Res, 21*(8), 1828-1834. doi:10.1158/1078-0432.CCR-14-2425

Korc, M., Jeon, C. Y., Edderkaoui, M., Pandol, S. J., Petrov, M. S., Consortium for the Study of Chronic Pancreatitis, D., & Pancreatic, C. (2017). Tobacco and alcohol as risk factors for pancreatic cancer. *Best Pract Res Clin Gastroenterol, 31*(5), 529-536. doi:10.1016/j.bpg.2017.09.001

Leung, L. S., Neal, J. W., Wakelee, H. A., Sequist, L. V., & Marmor, M. F. (2015). Rapid Onset of Retinal Toxicity From High-Dose Hydroxychloroquine Given for Cancer Therapy. *Am J Ophthalmol, 160*(4), 799-805 e791. doi:10.1016/j.ajo.2015.07.012

Levy, J. M. M., Towers, C. G., & Thorburn, A. (2017). Targeting autophagy in cancer. *Nat Rev Cancer, 17*(9), 528-542. doi:10.1038/nrc.2017.53

Miller-Ocuin, J. L., Zenati, M. S., Ocuin, L. M., Varley, P. R., Novak, S. M., Winters, S., . . . Hogg, M. E. (2017). Failure to Treat: Audit of an Institutional Cancer Registry Database at a Large Comprehensive Cancer Center Reveals Factors Affecting the Treatment of Pancreatic Cancer. *Ann Surg Oncol, 24*(8), 2387-2396. doi:10.1245/s10434-017-5880-9

Munster, T., Gibbs, J. P., Shen, D., Baethge, B. A., Botstein, G. R., Caldwell, J., . . . Furst, D. E. (2002). Hydroxychloroquine concentration-response relationships in patients with rheumatoid arthritis. *Arthritis Rheum, 46*(6), 1460-1469. doi:10.1002/art.10307

Papke, B., & Der, C. J. (2017). Drugging RAS: Know the enemy. *Science, 355*(6330), 1158-1163. doi:10.1126/science.aam7622

Perera, R. M., Stoykova, S., Nicolay, B. N., Ross, K. N., Fitamant, J., Boukhali, M., . . . Bardeesy, N. (2015). Transcriptional control of autophagy-lysosome function drives pancreatic cancer metabolism. *Nature, 524*(7565), 361-365. doi:10.1038/nature14587

Rahib, L., Smith, B. D., Aizenberg, R., Rosenzweig, A. B., Fleshman, J. M., & Matrisian, L. M. (2014). Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res, 74*(11), 2913-2921. doi:10.1158/0008-5472.CAN-14-0155

Ryan, D. P., Hong, T. S., & Bardeesy, N. (2014). Pancreatic adenocarcinoma. *N Engl J Med, 371*(22), 2140-2141. doi:10.1056/NEJMc1412266

Schwartz, G. G., Eads, D., Naczki, C., Northrup, S., Chen, T., & Koumenis, C. (2008). 19-nor-1 alpha,25-dihydroxyvitamin D2 (paricalcitol) inhibits the proliferation of human pancreatic cancer cells in vitro and in vivo. *Cancer Biol Ther, 7*(3), 430-436. doi:10.4161/cbt.7.3.5418

Sherman, M. H., Yu, R. T., Engle, D. D., Ding, N., Atkins, A. R., Tiriac, H., . . . Evans, R. M. (2014).

Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. *Cell, 159*(1), 80-93. doi:10.1016/j.cell.2014.08.007

Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. *CA Cancer J Clin, 68*(1), 7-30. doi:10.3322/caac.21442

Skinner, H. G., Michaud, D. S., Giovannucci, E., Willett, W. C., Colditz, G. A., & Fuchs, C. S. (2006). Vitamin D intake and the risk for pancreatic cancer in two cohort studies. *Cancer Epidemiol Biomarkers Prev, 15*(9), 1688-1695. doi:10.1158/1055-9965.EPI-06-0206

Sprague, S. M., Llach, F., Amdahl, M., Taccetta, C., & Batlle, D. (2003). Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int, 63*(4), 1483-1490. doi:10.1046/j.1523-1755.2003.00878.x

Stephen, A. G., Esposito, D., Bagni, R. K., & McCormick, F. (2014). Dragging ras back in the ring. *Cancer Cell, 25*(3), 272-281. doi:10.1016/j.ccr.2014.02.017

Von Hoff, D. D., Ervin, T., Arena, F. P., Chiorean, E. G., Infante, J., Moore, M., . . . Renschler, M. F. (2013). Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med, 369*(18), 1691-1703. doi:10.1056/NEJMoa1304369

Waters, A. M., & Der, C. J. (2018). KRAS: The Critical Driver and Therapeutic Target for Pancreatic Cancer. *Cold Spring Harb Perspect Med, 8*(9). doi:10.1101/cshperspect.a031435

White, E. (2012). Deconvoluting the context-dependent role for autophagy in cancer. *Nat Rev Cancer, 12*(6), 401-410. doi:10.1038/nrc3262

Wolpin, B. M., Ng, K., Bao, Y., Kraft, P., Stampfer, M. J., Michaud, D. S., . . . Fuchs, C. S. (2012). Plasma 25-hydroxyvitamin D and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev, 21*(1), 82-91. doi:10.1158/1055-9965.EPI-11-0836

Wolpin, B. M., Rubinson, D. A., Wang, X., Chan, J. A., Cleary, J. M., Enzinger, P. C., . . . Kimmelman, A. C. (2014). Phase II and pharmacodynamic study of autophagy inhibition using hydroxychloroquine in patients with metastatic pancreatic adenocarcinoma. *Oncologist, 19*(6), 637-638. doi:10.1634/theoncologist.2014-0086

Yang, A., Rajeshkumar, N. V., Wang, X., Yabuuchi, S., Alexander, B. M., Chu, G. C., . . . Kimmelman, A. C. (2014). Autophagy is critical for pancreatic tumor growth and progression in tumors with p53 alterations. *Cancer Discov, 4*(8), 905-913. doi:10.1158/2159-8290.CD-14-0362

Yang, S., Wang, X., Contino, G., Liesa, M., Sahin, E., Ying, H., . . . Kimmelman, A. C. (2011). Pancreatic cancers require autophagy for tumor growth. *Genes Dev, 25*(7), 717-729. doi:10.1101/gad.2016111

Ying, H., Kimmelman, A. C., Lyssiotis, C. A., Hua, S., Chu, G. C., Fletcher-Sananikone, E., . . . DePinho, R. A. (2012). Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell, 149*(3), 656-670. doi:10.1016/j.cell.2012.01.058

Zeh, H., Bahary, N., Boone, B. A., Singhi, A. D., Miller-Ocuin, J. L., Normolle, D. P., . . . Lotze, M. T. (2020). A Randomized Phase II Preoperative Study of Autophagy Inhibition With High-Dose Hydroxychloroquine and Gemcitabine/Nab-Paclitaxel in Pancreatic Cancer Patients. *Clin Cancer Res*. doi:10.1158/1078-0432.CCR-19-4042

APPENDIX A PERFORMANCE STATUS CRITERIA

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

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

APPENDIX B POTENT INHIBITORS AND INDUCERS OF CYP3A4

Effect on CYP3A	Drug Class	Medications
Moderate to Strong CYP3A Inhibitors	Antibiotics	chloramphenicol, ciprofloxacin, clarithromycin, erythromycin, telithromycin
	Antiemetic	aprepitant
	Antifungals	ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole
	Antiviral protease inhibitors	amprenavir, atazanavir, boceprevir, cobicistat, darunavir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir
	Calcium-channel blockers	diltiazem, mibifradil, verapamil
	Foods/herbs	grapefruit, grapefruit juice, Seville oranges
	Serotonin antagonist	nefazodone
	Tyrosine kinase inhibitor	imatinib
	Vasopressin antagonist	conivaptan
Moderate to Strong CYP3A Inducers	Antibiotics	nafcillin, rifampin
	Anticonvulsants	carbamazepine, phenobarbital, phenytoin
	Antiviral reverse transcriptase inhibitors	efavirenz, etravirine
	Endothelin receptor antagonist	bosentan
	Foods/herbs	St. John's wort
	Wakefulness-promoting agent	modafinil

Reference: [FDA 2014]

Abbreviation: CYP=cytochrome P450 enzyme

APPENDIX C DRUGS KNOWN TO PROLONG THE CARDIAC QT INTERVAL

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox®	Anticancer	Cancer (leukemia)
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection
Chloroquine	Aralen®	Antimalarial	Malaria
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic / Antiemetic	Schizophrenia, nausea,
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection
Citalopram	Celexa®, Cipramil®	Antidepressant, selective serotonin reuptake inhibitor	Depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace®	Antiarrhythmic	Abnormal heart
Dofetilide	Tikosyn®	Antiarrhythmic	Abnormal heart
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's
Dronedarone	Multaq®	Antiarrhythmic	Abnormal heart
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery- Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection, increase gastrointestinal motility
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Rep.o.sil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	Antidepressant, selective serotonin reuptake inhibitor	Depression (major), anxiety disorders

APPENDIX D Drug diary

Study ID:

Subject Initials:___ Subject ID: _____ Cycle: _____

Instructions:
Planned Daily Dose: __**mg**
REMINDERS:

Day	Date	Time	# of Tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				

Name of Medication	**Why did you take the medication?**	**Date Medication Started**	**Date Medication Stopped**

APPENDIX E (RECIST Criteria v. 1.1)

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described in the following subsections.
For the purposes of this study, patients should be re-evaluated for response every *8 weeks*.

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. (*This can be changed according to disease specific response criteria, i.e. Cheson, Olson*).

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on the trial.

Evaluable for objective response. Only those patients who have received any trial related therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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

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

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions **Clinical** lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray **Lesions** on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as

was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endp.o.int.

Tumor markers Tumor markers alone cannot be used to assess response.

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

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

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

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical

literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion. When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions, respectively, will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

Evaluation of Target Lesions

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

Partial Response (De Henau et al.): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

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

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

Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endp.o.int.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

"*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endp.o.int for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

Progression-Free Survival

PFS is defined as the time from the date of first dose to the date of the first objectively documented progressive disease per RECIST 1.1 or death, whichever is earlier. Patients who do not have the date of disease progression per RECIST 1.1 or date of death will be censored on the date of the last evaluable tumor assessment. Patients who started a new antineoplastic regimen prior to disease progression per RECIST 1.1 will be censored on the date of the last evaluable tumor assessment prior to receiving the new antineoplastic regimen. Patients whose disease progression or death appears after missing two consecutive tumor assessments will be censored on the date of the last evaluable tumor assessment. Patients who are lost to follow up will be censored on the date of their last evaluable tumor assessment. PFS will be estimated using the Kaplan-Meier method. The median and its 95% CI, along with the 25% and 75% quartiles will be summarized for all treated patients. OS will be defined as the date of first dose to the date of death. Patients who do not have a date of death will be censored on the last date for which the patient was known to be alive. OS will be analyzed similarly to PFS.

APPENDIX F abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
IB	Investigator's Brochure

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IL	Interleukin
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction

Abbreviation or special term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SoC	Standard of Care
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal