UPMC | HILLMAN CANCER CENTER

Investigator Initiated Trial

HCC 22-194: A Phase 2 Study of 9-ING-41, a Glycogen Synthase Kinase 3-beta (GSK-3β) inhibitor, combined with Retifanlimab, a PD-1 inhibitor, plus Gemcitabine/Nab-Paclitaxel as frontline therapy for patients with advanced Pancreatic Adenocarcinoma (RiLEY)

SPONSOR – INVESTIGATOR

Anwaar Saeed, MD
Associate Professor of Medicine
Chief – Gastrointestinal Medical Oncology
UPMC Hillman Cancer Center.
UPMC Cancer Pavilion, 5th Floor Room 556
5150 Centre Avenue, Pittsburgh, PA 15232
P: 412-623-2091 | E: saeeda3@upmc.edu

Protocol Number:	**HCC 22-194 (formely IIT-2021-RiLEY)**
NCT Number:	NCT05239182
IND Number:	IND 157852
Study Drug(s):	9-ING-41 – Provided by Actuate Therapeutics Retifanlimab (INCMGA00012, MGA012) – Provided by Incyte Corporation Gemcitabine / Nab-Paclitaxel – Commercially Available
Initial Version:	1.1 dated 09-27-2021 (University of Kansas Cancer)
Amendments:	2.0 dated 02-04-2023 (UPMC Hillman Cancer Center)

LIST OF COLLABORATORS

STATEMENT OF COMPLIANCE / PROTOCOL AGREEMENT

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Protocol Number	**IIT-2021-RiLEY**
Protocol Title	**A Phase 2 Study of 9-ING-41, a Glycogen Synthase Kinase 3-beta (GSK-3β) inhibitor, combined with Retifanlimab, a PD-1 inhibitor, plus Gemcitabine/Nab-Paclitaxel as frontline therapy for patients with advanced Pancreatic Adenocarcinoma (RiLEY)**
Sponsor/Investigator	**Anwaar Saeed, MD**

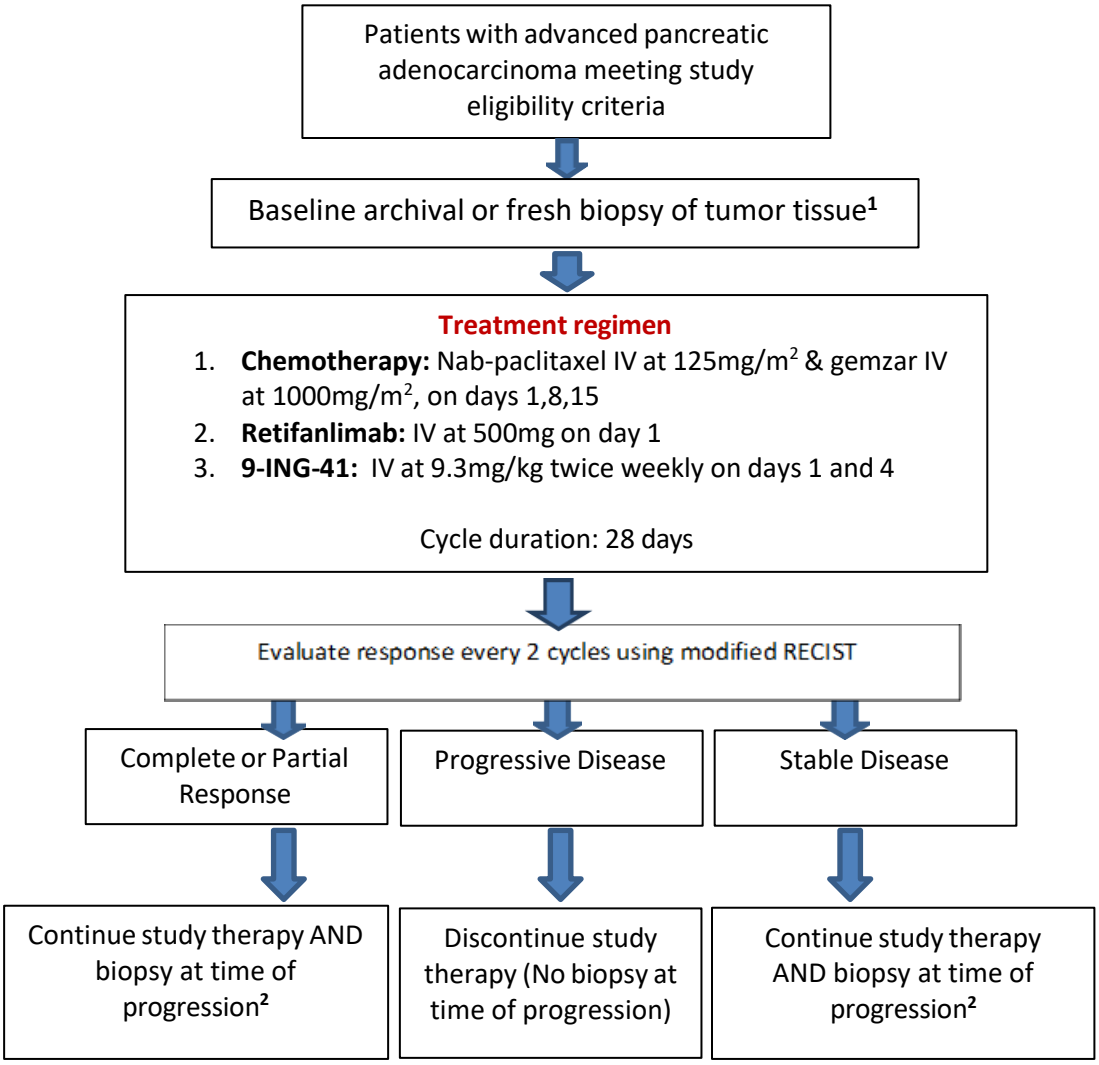
Protocol Version and Date: Version 2.0, dated 02-04-2023

Sponsor-Investigator Signature: Anwaar Saeed *Electronically signed by: Anwaar Saeed Reason: I approve this agreement. Date: Oct 24, 2023 11:13 EDT* 10/24/2023
Date

Print Name: Anwaar Saeed, MD

TABLE OF CONTENTS

SCHEMATIC OF STUDY DESIGN



1- Metastatic tissue preferred to primary tissue. (Archival tissue if available and adequate could be used for testing).
2- Standard biopsy at progression will be used for longitudinal evaluation of exploratory biomarkers and exploration of mechanism of resistance to the drug combination is no longer required.

PROTOCOL SUMMARY

Title	A Phase 2 Study of 9-ING-41, a Glycogen Synthase Kinase 3-beta (GSK-3β) inhibitor, combined with Retifanlimab, a PD-1 inhibitor, plus Gemcitabine/Nab-Paclitaxel as frontline therapy for patients with advanced Pancreatic Adenocarcinoma (RiLEY)
Protocol Number	IIT-2021-RiLEY
Phase	2, preceded by a safety lead-in
Design	Open label, single-arm, Simon 2-stage, Phase 2 design
Study Duration	Study treatment will continue until disease progression and/or unacceptable toxicity for a maximum duration of 2 years. Patients will be followed for survival for up to 18 months after the last day of study drug.
Study Center(s)	UPMC Hillman Cancer Center
Objectives	**Primary:** • To determine the rate of disease control of the combination of 9-ING-41 and retifanlimab plus gemcitabine/nab-paclitaxel in patients with pancreatic cancer without prior systemic therapy for advanced disease. **Secondary:** • To further assess the efficacy (Overall response rate (ORR), median Progression Free Survival (PFS) and median Overall Survival (OS)) of the combination of 9-ING-41 and retifanlimab plus gemcitabine/nab-paclitaxel in patients with advanced pancreatic cancer. • To assess the safety and tolerability of the combination of 9-ING-41 and retifanlimab plus gemcitabine/nab-paclitaxel in patients with advanced pancreatic cancer.
Correlative/Exploratory studies	• Correlation of disease control rate with specific molecular and immunologic tumor profiles. • Correlation of disease control rate with cancer antigen (CA) 19-9 levels.
Number of Participants	32 patients (including 6-9 patient safety lead-in)
Diagnosis and Main Inclusion Criteria	• Patients ≥ 18 years of age with pathologically confirmed advanced, recurrent, or metastatic pancreatic cancer previously untreated with systemic agents in the advanced/metastatic setting. • At least one measurable lesion per RECIST v1.1 • Available archived tumor tissue at study entry or willing to provide a fresh tumor biopsy prior to start of study treatment.

Study Product(s), Dose, Route, Regimen	• 30- to- 40–minute intravenous (IV) infusion of nab-paclitaxel at a dose of 125 mg per square meter, followed by an infusion of gemcitabine according to the gemcitabine label at a dose of 1000 mg per square meter, on days 1, 8, 15 of a 28-day cycle. • Retifanlimab 500 mg IV on day 1 of a 28-day cycle. (Retifanlimab will be administered following gemcitabine/nab-paclitaxel.) • 9-ING-41 administered at a dose of 9.3 mg/kg by IV infusion twice weekly on Days 1 and 4 of each week of a 28-day cycle. (9-ING-41 will be administered following retifanlimab.)
Duration of Administration	Study treatment will continue until disease progression and/or unacceptable toxicity for a maximum duration of 2 years.
Interim Monitoring	Investigator/sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, serious adverse events (SAEs), subject safety issues, recruitment issues, accrual, protocol deviations, unanticipated problems, breaches of confidentiality. Minutes of the disease center DSMB meetings are available to those who are unable to attend in person.
Statistical Methodology	The primary objective of the study is to assess the disease control rate of 9-ING-41 administered in combination with retifanlimab plus gemcitabine/nab-paclitaxel. Secondary objectives include the assessment of other efficacy variables as well as evaluation of toxicities. A Simon 2-stage design will be employed as follows: <u>Endpoint:</u> The primary endpoint for the study is DCR defined as: stable disease for ≥ 16 weeks, confirmed CR, or confirmed PR. <u>Sample Size:</u> The minimum number of responders needed to continue to the next stage, is determined based on the Simon's 2-stage design, with 80% power and one-sided significance level of 0.10. A disease control rate of 70% is hypothesized. A disease control rate of 50% is considered the lower threshold activity (null hypothesis), based on historical data.[1] Based on the design elements specified above, up to 12 patients will be enrolled during Stage 1. If >6 patients achieve disease control, 20 additional patients will be enrolled during Stage 2. Otherwise, enrollment will be terminated. Upon completion of Stage 2, if ≥20 of 32 patients achieve disease control, further evaluation may be pursued. If the DCR is 50% or less, the probability of terminating enrollment after Stage 1 is 61%.

	The phase 2 trial will be preceded by a safety lead-in of 6-9 patients.
Stopping Rules	Safety lead-in part of the trial has safety stopping rules built within the design and as highlighted here: If ≥ 5/6 participants do not experience Dose limiting toxicities (DLTs) within the DLT window of 28 days, the study will proceed to the phase 2 part. If > 1/6 participants experience DLTs, de-escalation to a lower dose level will follow. Participants enrolled to this lower dose level will receive the drug doses per the dose de-escalation scheme described in section 15 under statistical consideration. Three participants will be enrolled to this dose level. If 0/3 participants do not experience DLTS, the study will proceed to the phase 2 part. The study will be terminated if ≥ 1/3 patients experience DLTs at this lower dose level. Efficacy related stopping rules for Phase 2 is as detailed per the Simon's 2 stage design described in the statistical methodology. Additionally, we will also follow the following safety stopping rules: Taking into account participant safety considerations, study will be stopped if 30% or greater of the currently enrolled and registered participants experience Grade 3 or greater 9-ING-41 or Retifanlimab related AEs. Thus, based on a Binomial calculator: P (toxicity > 30% data from the trial) > 0.95, the following stopping rules will be implemented: • > 4 of the first 10 participants experiencing Grade 3 or greater investigational agents related AEs • > 7 of the first 15 participants experiencing Grade 3 or greater investigational agents related AEs • > 8 of the first 20 participants experiencing Grade 3 or greater investigational agents related AEs (if more than 20 participants are recruited in the study)

1 INTRODUCTION

1.1 Pancreatic Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive tumor arising from the ductal and acinar epithelium of the exocrine pancreas which accounts for 95% of malignant neoplasms of the pancreas. In the United States, PDAC accounts for ~60,000 newly diagnosed cases per-year and ~48,000 deaths per-year which make up 3% of all cancers and 7% of all cancer deaths, respectively.[2] PDAC has an abysmal prognosis including a 5-year survival rate of 10% in all stages combined. In metastatic disease, the 5-year survival is 3% and median survival is ~6 months.[3] Furthermore, only 20% of newly diagnosed patients are eligible for curative resection and the rest must be treated with palliative systemic chemotherapy.[4]

The standard of care systemic therapy for advanced, metastatic disease is limited to combination cytotoxic chemotherapy including gemcitabine plus nab-paclitaxel or FOLFIRINOX.[5] In the pivotal Phase 3 trial, FOLFIRINOX treatment was associated with a median overall survival (OS) of 11.1 months compared with 6.8 months in gemcitabine alone (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P < 0.001).[6] However, due to the toxicities of this regimen, it is not appropriate for all patients with newly diagnosed pancreatic cancers. Gemcitabine/nab-paclitaxel was approved in the first-line setting in metastatic disease based on a median OS of 8.5 months, as compared with 6.7 months in patients receiving gemcitabine alone (hazard ratio for death, 0.72; 95% CI, 0.62 to 0.83; P < 0.001).[7] The rate of disease control (confirmed response or stable disease for ≥ 16 weeks) was 48% (95% CI, 43 to 53) in the nab-paclitaxel–gemcitabine group and 33% (95% CI, 28 to 37) in the gemcitabine group (rate ratio for disease control, 1.46; 95% CI, 1.23 to 1.72; P < 0.001). Therefore, there is a great unmet need for finding novel treatment options and improving survival outcomes.

1.2 Glycogen Synthase Kinase-3 (GSK-3)

Glycogen synthase kinase-3 (GSK-3) is a serine (S)/threonine (T)(ST) kinase initially described as a key regulator of metabolism, specifically glycogen biosynthesis.[8] It has since been shown to play a role in several disease processes including cancer. GSK-3 has two ubiquitously expressed and highly conserved isoforms, glycogen synthase kinase-3 alpha (GSK-3α) and glycogen synthase kinase-3 beta (GSK-3β), with both shared and distinct substrates and functional effects.

In cancer, much focus has been placed on the role of GSK-3β in tumor progression and its modulation of oncogenes (beta-catenin, cyclin D1 and c-Myc), cell cycle regulators (e.g., p27Kip1) and mediators of epithelial-mesenchymal transition (e.g., Zinc finger protein SNAI1, Snail) have been extensively described .[9],[10],[11],[12],[13] More recently, aberrant overexpression of GSK-3β has been shown to promote tumor growth and chemotherapy resistance in various solid tumors including pancreatic, ovarian, colon cancer and glioblastoma[14],[15],[16],[17],[18] through differential effects on pro-survival nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and c-Myc pathways as well on tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and p53-mediated apoptotic mechanisms.[19],[20] GSK-3β is thus a potentially very important therapeutic target in human malignancies.

1.2.1 Effect of GSK-3β Inhibition in Cancer Cells

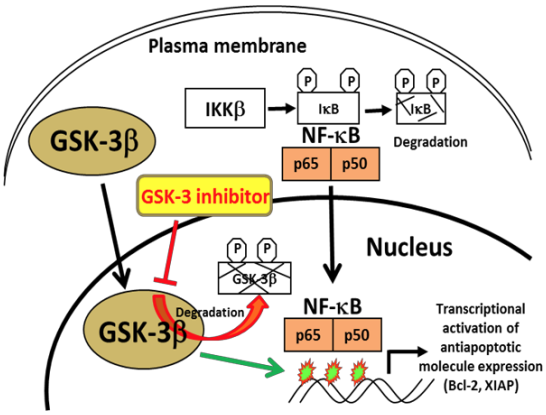
NF-κB is regarded as one of the most important transcription factors and its activation plays an essential role in promoting human cancer progression, metastasis, and chemoresistance.[21],[22] GSK-3β has been demonstrated to have opposing roles in this context, repressing Wnt/beta-catenin signaling on the one hand but maintaining cell

survival and proliferation through the NF-κB pathway on the other.[23] Recent data suggests that GSK-3β positively regulates human cancer cell survival in part through regulation of NF-κB-mediated expression of anti-apoptotic molecules.[24] Disruption of the GSK-3β gene in mice leads to embryonic lethality due to hepatocyte apoptosis and massive liver degeneration, a phenotype that is similar to the disruption of the NF-κB p65 or inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) genes.[25] These findings suggest a link between GSK-3β and the activation of the NF-κB pathway and support GSK-3β as a candidate therapeutic target in human cancer.

Using GSK-3β-deficient mouse embryonic fibroblasts, it was shown that the early steps leading to NF-κB activation following tumor necrosis factor alpha (TNF-α) treatment (degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα) and translocation of NF-κB to the nucleus) were unaffected by the loss of GSK-3β, suggesting that NF-κB is regulated by GSK-3β at the level of the transcriptional complex in the nucleus.[26] Furthermore, nuclear accumulation of GSK-3β was identified selectively in pancreatic, bladder and renal cancer cells, and malignant B-cells but not in normal human cells).[27],[28],[29],[30] Studies demonstrated that only the active form of GSK-3β accumulates in the nucleus of pancreatic cancer cells and that inhibition of GSK-3β activity depletes its nuclear accumulation via proteasome degradation (0).[31]

These studies also revealed an important role of GSK-3β in the regulation of histone modifications, which may contribute to NF-κB p65/p50 binding to promoters and activation of target genes in cancer cells that would lead to increased cancer cell survival.[32] Nuclear GSK-3β may well be the primary effector target for GSK-3 inhibition in cancer cells, leading to depletion of GSK-3β from the nucleus and subsequent inhibition of NF-κB mediated transcription and decreased cancer cell survival (Figure 1).

Figure 1. The Role of GSK-3β in Cancer Cells



Source Ref: [33]

Nuclear GSK-3β positively regulates NF-κB binding to its target gene promoters and NF-κB transcriptional activity in cancer cells. Preclinical results suggest that GSK-3β inhibits hypermethylation of histones and thereby GSK-3β contributes to maintenance of active chromatin at NF-κB target gene promoters, allowing p65 binding and transcriptional activation.[34] Inhibition of GSK-3β resulted in rapid ubiquitin-proteasome degradation of its nuclear pool in cancer cells.[35]
In the clinical setting, the safety and potential efficacy of GSK-3β inhibition was demonstrated in a Phase I dose escalation study of LY2090314, an intravenous competitive inhibitor of GSK-3β, in combination with chemotherapy in various advanced tumors.[36]

1.2.2 Role of GSK-3β in Immune Regulation

The role of GSK-3β in immune regulation has been extensively studied with consequent implications in anti-tumor therapy. Emerging evidence shows that GSK-3β is a central upstream regulator of major co-inhibitory receptors on T cells. First, GSK-3β was found to regulate the transcriptional activation of programmed death-1 (PD-1) on T cells.[37] Subsequent studies showed that pharmacological GSK-3β inhibition leads to reduction of PD-1 expression and increased function of CD8+ cytotoxic T cells in vitro and in vivo.[38],[39] Second, GSK-3β was also found to regulate the expression of the coinhibitory receptor Lymphocyte Activation Gene-3 (LAG-3) on CD4+ and CD8+ T cells. Furthermore, small molecule GSK-3β inhibitors were found to downregulate LAG-3 on CD4+ and CD8+ T cells and enhance tumor clearance. Taken together, these studies highlight the multi-pronged immune regulatory effects of GSK-3β.[40]

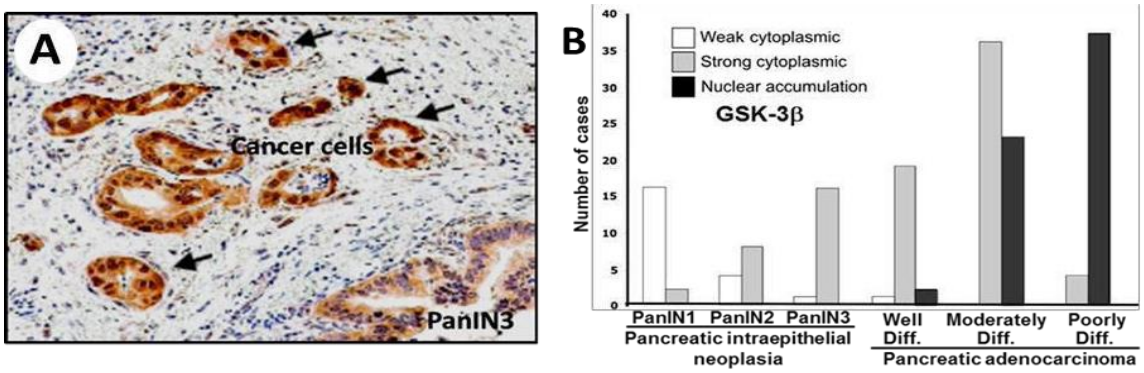
1.3 9-ING-41

9-ING-41 is a small molecule potent selective GSK-3β inhibitor, which has shown broad anti-tumor activity in cell lines and in various patient derived xenografts (PDX) including breast cancer, lymphoma, neuroblastoma, glioblastoma, ovarian cancer, bladder cancer, and pancreatic cancer .[41],[42],[43],[44],[45]It acts through downregulation of NF-κB and decreases the expression NF-κB target genes cyclin D1, Bcl-2, anti-apoptotic protein (XIAP) and B-cell lymphoma-extra-large (Bcl-XL) leading to inhibition of tumor growth in multiple solid tumor cell and lymphoma lines and PDX models. NF-κB is constitutively active in cancer cells and promotes anti-apoptotic molecule expression. NF-κB activation is particularly important in cancer cells that have become chemo- and radioresistant, therefore it is believed that inhibition of GSK-3β may overcome NF-kB-mediated chemoresistance in human cancers.

1.3.1 Preclinical Experience with 9-ING-41 in Pancreatic Tumor Cells

GSK-3β has been established as a novel therapeutic target in human pancreatic cancer.[46],[47],[48] Aberrant nuclear GSK-3β accumulation in pancreatic cancer cell lines and in 62 of 122 (51%) human pancreatic adenocarcinomas (0), with nuclear GSK-3β accumulation significantly correlated to higher grade pancreatic carcinomas.[49] In pancreatic carcinomas, aberrant nuclear GSK-3β is a specific marker of pancreatic cancer cells whereas nuclear GSK-3β was not detectable in acinar or epithelial pancreatic cells and in pancreatic intraepithelial neoplasia (PanIN) lesions (Figure 2).

Figure 2. GSK-3β is Overexpressed and Accumulated in the Nucleus of Pancreatic Cancer Cells

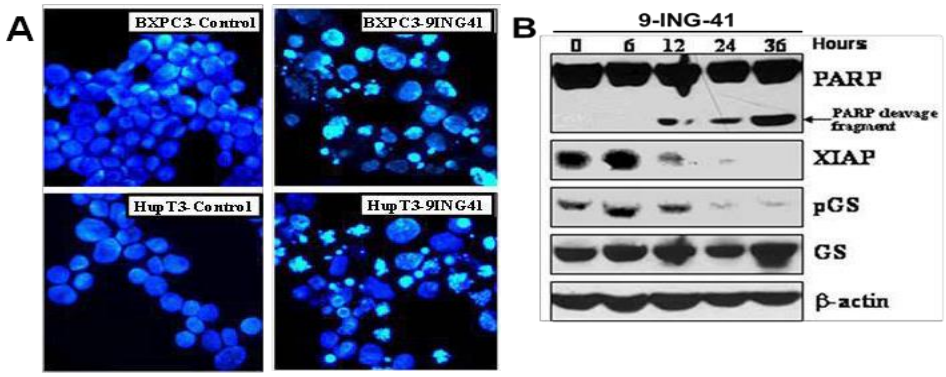


(A) Immunohistochemical analysis of GSK-3β expression and localization in human pancreatic adenocarcinoma. Arrows indicate cancer cells. (B) Nuclear accumulation of GSK-3β is associated with the loss of pancreatic cancer differentiation. Figure represents the distribution of GSK-3β staining patterns in PanIN lesions and pancreatic carcinomas.
Source Ref: [50]

Only the active form of GSK-3β accumulates in the nucleus of pancreatic cancer cells and the inhibition of GSK-3β activity depletes its nuclear accumulation via proteasome degradation, whereas the expression level of cytoplasmic GSK-3β is not changed. *In vivo* studies show that treatment with a commercially available toolkit GSK-3 inhibitor (AR-A014418) suppresses growth of CAPAN2 (Caucasian pancreas adenocarcinoma cell line) pancreatic xenograft tumors in mice. [51] Another *in vivo* study demonstrated that treatment with AR-A014418 suppresses growth of PANC1 (Caucasian pancreatic carcinoma cell line) pancreatic xenograft tumors. Moreover, inhibition of GSK-3β and thus, NF-κB activity, could make pancreatic cancer cells more sensitive to chemotherapeutic agents such as gemcitabine. It has been demonstrated *in vitro* and *in vivo* that inhibition of GSK-3β sensitizes pancreatic cancer cells to gemcitabine . [52]

Unlike the commercially available toolkit GSK-3β inhibitors, which are not amenable for clinical development, 9-ING-41 is potent and possesses attractive drug-like properties that make it a clinical candidate. 9-ING-41 inhibits GSK-3β, as shown by downregulation of phospho-glycogen synthase expression, leading to a decreased expression of B-cell lymphoma-2 (BCL-2) and XIAP, and significant apoptosis in pancreatic cancer cells *in vitro* (Figure 3).

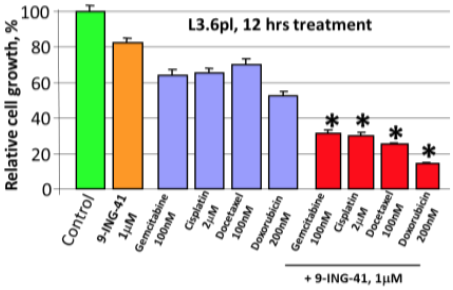
Figure 3. 9-ING-41 Induces Apoptosis in Pancreatic Cancer Cells



(A) Representative Hoechst staining pictures of BXPC3 and HupT3 pancreatic cancer cells treated with 9-ING-41 (5μM) for 36 hours. Fragmented nuclei represent apoptotic cells (B) BXPC3 pancreatic cancer cells were treated with 9-ING-41 (5μM) for 6, 12, 24, and 36 hours as indicated. Whole cell lysates were prepared, separated by SDS-PAGE (50 μg/well), transferred to PVDF membrane, and probed with indicated antibodies. pGS, phosphorylated Glycogen Synthase; GS, Glycogen Synthase. Source Ref: [53]

In the tetrazolium (MTS) proliferation assay, the GI50 (50% growth inhibition) of 9-ING-41 was 1 μM and 0.6 μM for BXPC3 and HupT3 pancreatic cancer cell lines, respectively. With short- term treatment (12 hours), 9-ING-41 significantly enhanced the effect of gemcitabine, cisplatin, docetaxel or doxorubicin in the inhibition of L3.6pl pancreatic cancer cell growth *in vitro* (Figure 4).

Figure 4. 9-ING-41 Potentiates the Antitumor Effect of Standard Agents in Pancreatic Cancer Cells

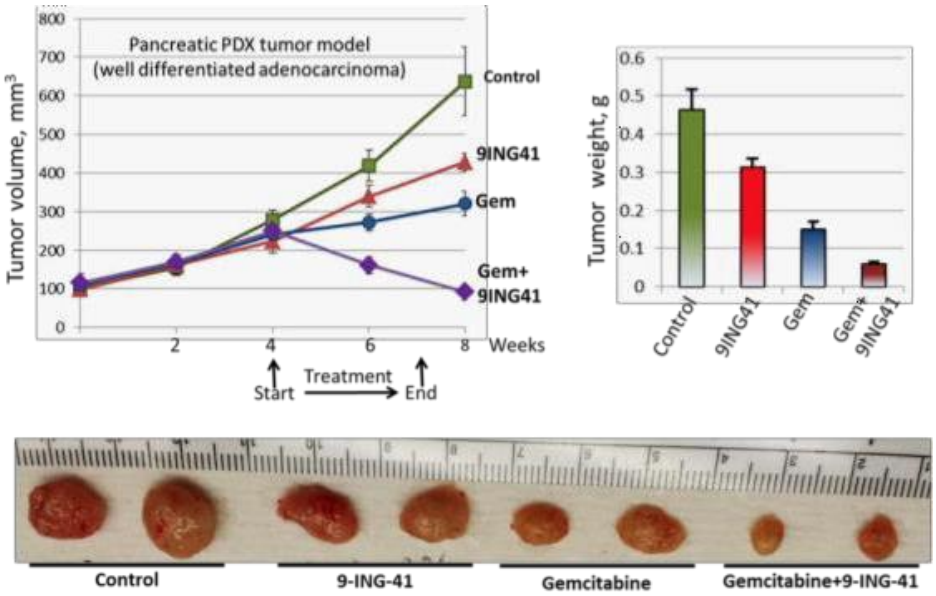


Source Ref: [54]

Pancreatic L3.6pl cancer cells were treated with 9-ING-41 (1 μM), standard cytotoxic agent, or combination of both drugs for 12 hours. After the treatment, drugs were replaced with fresh media and relative cell growth was measured by MTS assay after 96 hours.

Based on these results, it was hypothesized that inhibition of GSK-3β by 9-ING-41 may overcome NF-κB-mediated chemoresistance to conventional chemotherapeutic drugs *in vivo* representing a novel therapeutic strategy for the targeted treatment of human pancreatic cancer. For *in vivo* experiments, subcutaneous and orthotopic pancreatic PDX tumor models by transplantation of freshly resected pancreatic cancer specimens from the patient to immunodeficient mice were developed (Figure 5).

Figure 5. 9-ING-41 Enhances the Antitumor Effect of Gemcitabine in Pancreatic PDX Tumor *In Vivo*



Upper left panel: Points, mean tumor volume; bars, standard error (SE).
Upper right panel: Columns, mean tumor weight; bars, SE.
Source Ref: [55]

Pancreatic PDX tumors were size matched and mice were randomized into four treatment groups: control (30 µL DMSO (dimethyl sulfoxide), daily, Mon-Fri), 9-ING-41 (60 mg/kg dissolved in 30 µL of DMSO, daily, Mon-Fri), gemcitabine (50 mg/kg, twice a week) or a combination of gemcitabine and 9-ING-41 were injected intraperitoneally (i.p.) for 3 weeks as shown in upper left panel of Figure 5. Mice were sacrificed when tumors grew to more than 5 times the original starting volume and the weight of resected tumors was measured as shown in upper right panel (Figure 5). Treatment with 9-ING-41 slowed the growth of pancreatic PDX tumors and led to partial regression of PDX tumors when 9-ING-41 was combined with gemcitabine. [56]

In subsequent work by the Billadeau group, pancreatic cancer cell lines and PDX were treated with 9-ING-41 alone or in combination with chemotherapy. Activation of the DNA damage response pathway and S-phase arrest induced by gemcitabine were assessed in pancreatic tumor cells with pharmacologic inhibition or siRNA depletion of GSK-3 kinases by immunoblotting, flow cytometry and immunofluorescence.[57] 9-ING-41 treatment significantly increased pancreatic tumor cell killing when combined with chemotherapy. 9-ING-41 prevented gemcitabine-induced S-phase arrest suggesting an impact on the ATR-mediated DNA damage response. Both 9-ING-41 and siRNA depletion of GSK-3 kinases impaired the activation of ATR leading to the phosphorylation and activation of Chk1. Mechanistically, depletion or knockdown of GSK-3 kinases resulted in the degradation of the ATR-interacting protein TopBP1, thus limiting the activation of ATR in response to single-strand DNA damage. These data identify a previously unknown role for GSK-3 kinases in the regulation of the TopBP1/ATR/Chk1 DNA damage response pathway and provide a compelling rationale for the inclusion of patients with PDAC in clinical studies of 9-ING-41 alone and in combination with gemcitabine or irinotecan.

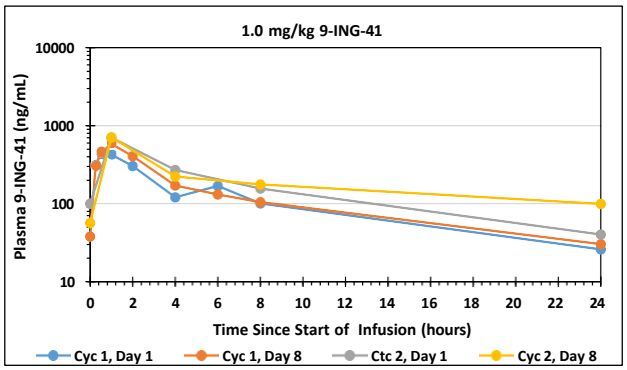
1.3.2 Role of 9-ING-41 as an Immune Modulator

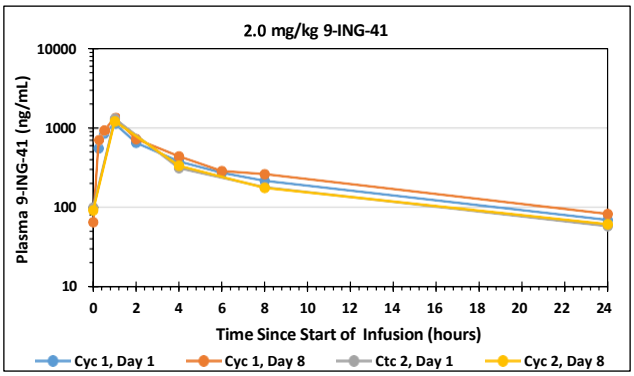
Recent pre-clinical data supports the role of 9-ING-41 as an immune modulator in both in vivo and in vitro tumor models. Melanoma mouse models reveal 9-ING-41 downregulates PD-1 and LAG-3 expression, leading to a synergistic effect when given sequentially or in combination with immune checkpoint inhibitors (Taylor et al. Communication). In both MYC-N amplified and non-amplified cell lines of neuroblastoma, exposure to 9-ING-41 leads to a boost in MHC-1 expression when stimulated with IFNy; and in MYC-N non-amplified lines, a notable increase in PD L1 expression is seen, supporting a combination approach with immune checkpoint blockade (Boes et al. Communication). Moreover, in colorectal cells, 9 ING-41 boosts NK and effector T-cell mediated killing of tumor cells.[58]

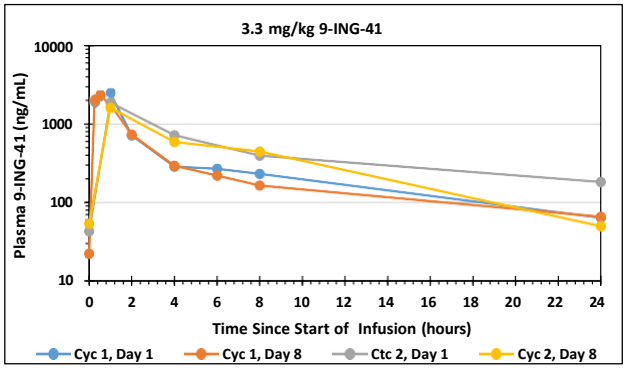
1.3.3 Human Pharmacokinetics of 9-ING-41

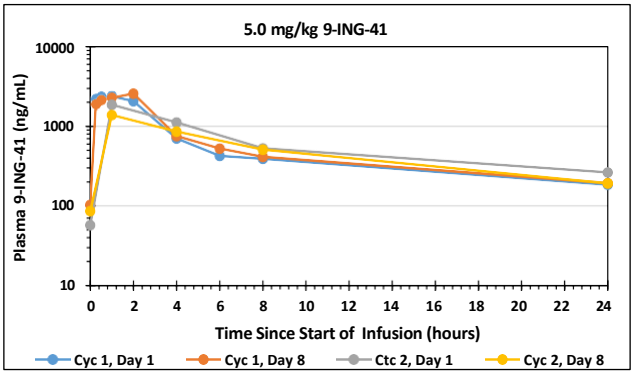
The pharmacokinetics (PK) of 9-ING-41 have been evaluated in cohorts (n=4-7) of patients given 9-ING-41 as IV infusions. Concentrations increased rapidly at all the tested doses, reaching near steady-state levels by 0.25 to 0.5 h into the infusion (Figure 6). Following the end of the infusion, concentrations declined rapidly, decreasing by approximately 30% over the next hour, and approximately 70% by 3 hours post-infusion. The rate of decline in the concentrations slowed after 3 hours post-infusion, dropping just an additional 10% to approximately 20% of the peak concentrations by 7 hours post-infusion. The mean terminal half-lives (over the time interval from 5 to 23 hours post-infusion) ranged from 12 to 20 hours, with no systematic dependence on dose. The systemic exposures, both peak exposure (C_{max}) and total exposure (AUC_{0-72}), were dose proportional (Figure 7), indicating linear pharmacokinetics over the studied dose range. Repeated dosing of 9-ING-41 at 3 to 4 day intervals resulted in similar PK profiles as were observed with the first dose. Based on these data, a sparse sampling protocol has been specified that identifies the minimum and maximum concentrations associated with a dose of 9-ING-41, and obtains an estimate of total exposure (AUC_{0-72}) by taking advantage of the good correlation (R^2 = 0.60,Figure 7) observed between the AUC_{0-72} and the plasma concentration 1 hour after the end of the infusion. This sampling protocol is also anticipated to be able to identify poor metabolizers of 9-ING-41 from the measured pre-dose concentrations in samples collected at the time of the second (and subsequent) dose(s).

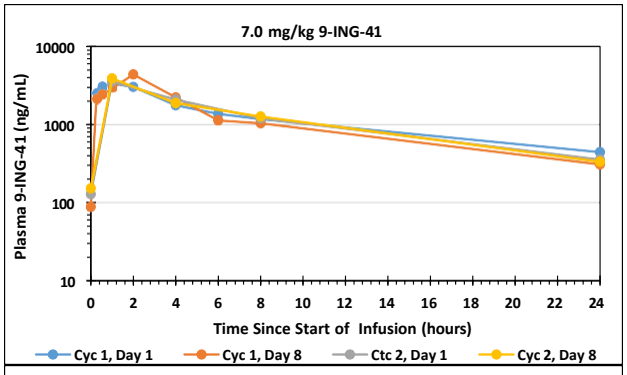
Figure 6. 9-ING-41: Human Dose-proportional Plasma Pharmacokinetics

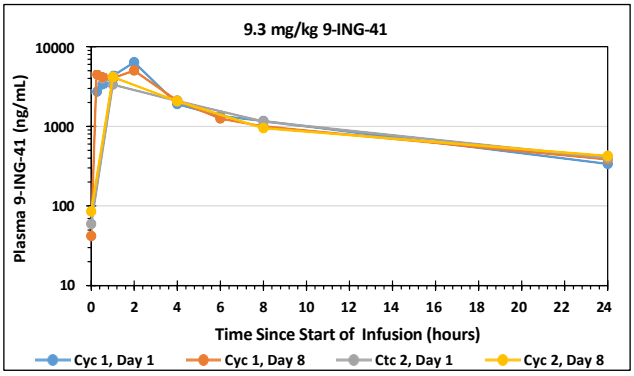












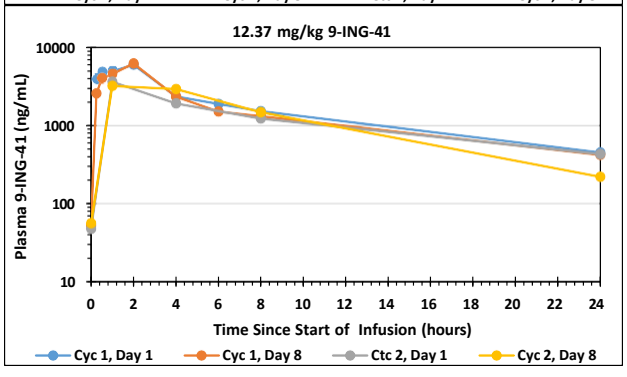
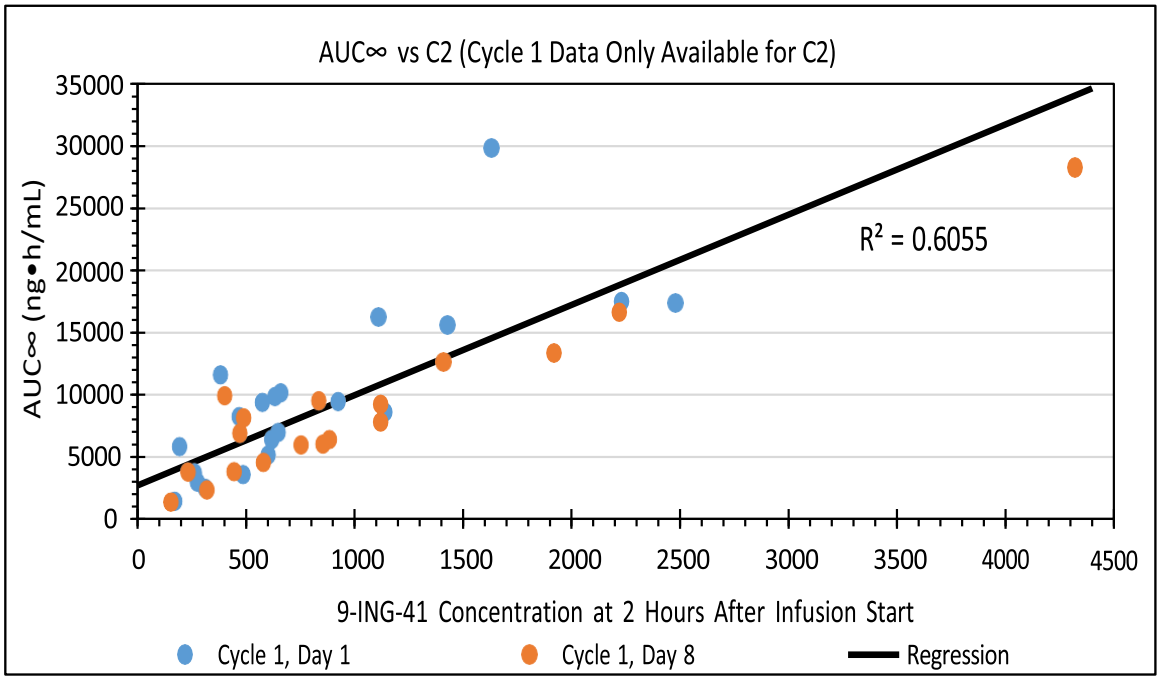


Figure 7. 9-ING-41: Human Dose-proportional Plasma Pharmacokinetics – AUC versus Concentration



1.3.4 Phase 1 Trial of 9 ING-41 (EudraCT# 2018-003739-32 and NCT03678883)

On the 1801 study Part 1 (monotherapy dose escalation), 65 patients with both advanced solid and hematologic malignancies have received 9-ING-41 on a twice weekly IV schedule at eight dose levels: 1.0, 2.0, 3.3, 5, 7, 9.3, 12.4 and 15 mg/kg. No 9-ING-41-attributable SAEs have been observed. The dose of 15 mg/kg has been deemed the RP2D based on the volume of fluid given with this dose.

Over 50% of patients receiving 9-ING-41 have experienced transient visual symptoms, assessed as Grade 1 in 54% and Grade 2 in 3% of patients, respectively. These usually begin approximately one hour into the infusion. Patients report that lights seem brighter and skin tones darker. These symptoms last for approximately one to two hours in most patients but can last for longer. There are no associated, preceding, or delayed visual symptoms. There are no associated vital sign or biochemical abnormalities. No attendant abnormalities have been demonstrable on retinal or general ocular examinations. These episodes tend to attenuate over time and are always completely transient. Some investigators chose to slow the rate of the 9-ING-41 infusion when these visual symptoms occurred, but it is not clear if this had any impact on symptom duration. No specific additional tests or precautions are required if these symptoms occur.

There were also Grades 1 and 2 infusion reactions associated with 9-ING-41 in 8.9% (grade 1) and 3% (grade 2) of patients. Symptoms included but were not limited to: flushing, rash, pruritus, painful chest spasms, nausea, vomiting, dyspnea, tachycardia, dizziness and hypotension. These resolved upon rapid institution of local infusion reaction protocols, usually involving administration of Tylenol, anti-histamines, intravenous fluids and occasionally steroids. Patients who presented with infusion reactions were required to pre-medicate with the same medications upon subsequent infusions.

Two patients currently remain on Part 1 of the study, including one patient with refractory BRAF V600K mutated melanoma with CNS disease in CR after a year, and another patient with ATLL with sustained PR over 15 months. On the 1801 study Part 2 (8 chemotherapy combination regimens), 171 patients with advanced solid tumors have received 9-ING-41 on a twice weekly schedule at doses of 3.3, 5, 7, 9.3, 12.4 and 15 mg/kg combined with carboplatin, doxorubicin, gemcitabine, irinotecan, lomustine, carboplatin plus paclitaxel, carboplatin plus pemetrexed or gemcitabine plus nab-paclitaxel. Patients initially needed to have been previously exposed to that same chemotherapy agent to qualify for study entry, but this was later amended to allow first-line doxorubicin patients. One 9-ING-41 attributable Grade 3 SAE of visual disturbance was observed, but no other clinically significant AEs attributable to the investigational product have been noted in this cohort. The RP2D for all combinations was determined to be 15mg/kg IV. Seven patients still remain on Part 2 of the study, and clinical responses include sustained PRs in PDAC, endometrial cancer and undifferentiated pleomorphic sarcoma, as well as prolonged disease stability in several histologies, including PDAC, appendiceal cancer and mesothelioma.

The data generated on safety and activity on the 1801 study supported its expansion into a Phase 2 signal-seeking gemcitabine/nab-paclitaxel + 9-ING-41 study for first-line advanced PDAC patients. This study is currently in Stage I of a Simon 2-Stage design with disease control rate (CR, PR, or SD for ≥16 weeks) as the primary endpoint.

Of 24 patients enrolled, there are early signs of efficacy in this population, with one confirmed CR (non-centrally reviewed) in a patient with local recurrence after surgical resection and adjuvant gemcitabine-based chemotherapy, one confirmed CR after 4 cycles of SD, 4 PRs and 2 SD ≥16 weeks in an initial cohort of 12 evaluable patients.

Adverse Events with 9-ING-41: Severity (Grade), Number of Patients, and Adverse Event Incidences

Adverse event	Severity	1.0 mg/kg (N=6) n (%)	2.0 mg/kg (N=5) n (%)	3.3 mg/kg (N=7) n (%)	5.0 mg/kg (N=6) n (%)	7.0 mg/kg (N=8) n (%)	9.3 mg/kg (N=10) n (%)	12.4 mg/kg (N=9) n (%)	15.0 mg/kg (N=16) n (%)	Total (N=67) n (%)
Transient Visual impairment	Grade 1	0	0	3 (42.8))	6 (100)	5 (62.5)	8 (80.0)	1 (11.1)	13 (81.2)	36 (53.7)
	Grade 2	0	0	0	0	1 (12.5)	0	1 (11.1)	0	2 (3.0)
Nausea	Grade 1	0	0	0	2 (33.3)	0	2 (20.0)	1 (11.1)	5 (31.3)	10 (14.9)
	Grade 2	0	0	0	0	1 (12.5)	0	0	2 (12.5)	3 (4.5)
Fatigue	Grade 1	0	2 (40.0)	0	0	0	2 (20.0)	0	0	4 (6.0)
	Grade 2	0	0	0	0	3 (37.5)	1 (10.0)	2 (22.2)	4 (25.0)	10 (14.9)
Infusion related reaction	Grade 1	1 (16.7)	0	0	1 (16.7)	2 (25)	0	1 (11.1)	1 (6.3)	6 (8.9)
	Grade 2	0	0	0	0	0	0	1 (11.1)	1 (6.3)	2 (3.0)
Hypotension	Grade 2	0	0	0	0	2 (25.0)	0	0	2 (12.5)	4 (6.0)
Headache	Grade 1	1 (16.7)	0	1 (14.3)	1 (16.7)	1 (12.5)	0	0	1 (6.3)	5 (7.5)
Vomiting	Grade 1	0	0	0	0	1 (12.5)	0	0	2 (12.5)	3 (4.5)
Diarrhea	Grade 1	0	0	1 (14.3)	0	0	0	0	1 (6.3)	2 (3.0)
Accidental exposure to product	Grade 1	0	0	0	0	0	0	0	2 (12.5)	2 (3.0)

1.4 Retifanlimab

1.4.1 Overview

Retifanlimab (also known as INCMGA00012) is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1. Retifanlimab contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1–expressing cells, including T cells, and to sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

In vitro studies with retifanlimab have demonstrated high affinity binding to both recombinant human and cynomolgus monkey PD-1 as well as to PD-1 that is naturally expressed on the cell surface, including on T cells. Consistent with its intended mechanism of action and functional properties, retifanlimab has been shown to inhibit the binding of PD L1 and PD L2 to PD-1, to disrupt the PD-1/PD-L1 inhibitory axis, and to enhance IFN γ secretion in SEB-stimulated human PBMCs with activity comparable to pembrolizumab and nivolumab replicas (generated by MacroGenics, Inc. based on the published sequences of these antibodies). Retifanlimab does not induce ADCC or CDC, mitogenic activity, hemolysis, or cytokine release.

Retifanlimab is currently under development as a therapeutic candidate for the treatment of multiple solid tumors, both as a monotherapy and in combination with other agents.

As of the data cutoff date of 23 SEP 2020, 578 unique participants have been exposed to retifanlimab as monotherapy at doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, 10 mg/kg Q4W, 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W. An additional 96 participants have been exposed to retifanlimab in combination with other anticancer agents (53 participants in combination with epacadostat [INCB024360], 22 participants in combination with parsaclisib [INCB050465], 15 participants in combination with pemigatinib [INCB054828], and 6 participants in combination with INCB001158). The most frequently TEAEs reported for monotherapy studies were fatigue (16.6%), asthenia (15.7%), and diarrhea (14.4%). The most frequently reported immune-related AEs were hypothyroidism (8.1%) and rash (2.4%). The overall safety profile of retifanlimab is as expected for a PD-(L)1 inhibitor.

Retifanlimab has shown meaningful efficacy in platinum-refractory SCAC[59] along with preliminary evidence of clinical activity in multiple other tumor types.[60,61,62]

1.4.2 Justification for retifanlimab dose

Information for 500 mg Q4W(every 28 days) Fixed Dose

Retifanlimab will be administered at 500 mg every 28 days. The selection of this dose was based on modeling of clinical PK data from the first-in-human monotherapy study, INCMGA 0012-101 (NCT03059823), in which 219 participants were treated at doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, and 10 mg/kg Q4W, 375 mg Q3W, 500 mg Q4W and 750 mg Q4W.

A simulation was conducted to investigate the use of weight-based and fixed doses for retifanlimab with the aim of targeting a steady-state trough concentration of approximately 21 µg/mL, which is the median trough

concentration for pembrolizumab 200 mg Q3W.[63] In addition, full PD-1 receptor occupancy was observed on PD 1 expressing CD4+ and CD8+ cells with effects on circulating cytokines that are typical for a PD 1 inhibitor in all dose regimens of Study INCMGA 0012-101. Therefore, the 500 mg Q4W doses was selected as a dose for further development in monotherapy treatments.

Noncompartmental analysis of PK data from 40 participants who received 500 mg Q4W in Study INCMGA 0012-101 demonstrated a C_{trough} value at steady state was 58.7 ± 26.8 mg/L. First dose clearance was 0.302 ± 0.132 L/day. Distribution of retifanlimab was generally limited to the systemic circulation, with a volume of distribution of 6.34 ± 2.49 L. Retifanlimab C_{max} and $AUC_{0-\infty}$ were 168 ± 51.6 mg/L and 1940 ± 795 mg·day/L, respectively after the first dose. Trough serum concentrations of retifanlimab appeared to reach steady state at or before Cycle 6. The accumulation ratio was approximately 1.3 for the Q4W dose regimen. Taken together, retifanlimab showed a PK profile typical of a monoclonal antibody.[64]

1.5 Rationale for Study

Given the role of GSK-3β in immune regulation, the combination of GSK-3β inhibition with PD-1 inhibition may be expected to provide synergistic anti-tumor efficacy. The excellent safety profile of 9-ING-41, along with preclinical and clinical evidence of anti-tumor activity in pancreatic cancer, provides a strong rationale to evaluate the efficacy of 9-ING-41 in combination with a PD-1 inhibitor plus standard chemotherapy (gemcitabine/nab-paclitaxel) as frontline therapy for patients with advanced PDAC.

The PD-1 inhibitor to be used in the present study is retifanlimab, a humanized, hinge-stabilized immunoglobulin G4 (IgG4) monoclonal antibody. *Retifanlimab has shown positive results for the treatment of patients with squamous carcinoma of the anal canal (SCAC) who have progressed after first-line chemotherapy treatment.* In the Phase 2 PODIUM-202 trial, retifanlimab was well-tolerated at a dose of 500 mg administered via IV infusion every 4 weeks (28-day cycle) for up to 2 years.[65] Immune-related AEs of grade 3 or higher occurred in 6.4% of patients and treatment discontinuation due to immune-related AEs occurred in 2.1% of patients. No grade 3 or higher infusion reactions were reported. The most common AEs observed (incidence ≥20%) were fatigue and diarrhea.

1.6 Risk/Benefit Assessment

The combination of 9-ING-41 and retifanlimab with gemcitabine/nab-paclitaxel has not previously been administered to human subjects. In the 1801 study, 9-ING- 41 has been administered in combination with various chemotherapy regimens including gemcitabine/nab-paclitaxel, with one 9-ING-41-related SAE (transient visual change) documented to date. Retifanlimab alone has been well-tolerated when administered for up to 2 years in patients with anal cancer. Overall, based on previous nonclinical and clinical experience, both of these agents appear to have an acceptable safety profile and do not appear to have significant overlapping toxicities. However, it is possible that when they are administered together and in combination with gemcitabine/nab-paclitaxel, more frequent or severe AEs, or new AEs not previously observed with any of these agents administered alone, may occur.

It is not known if administration of 9-ING-41 and retifanlimab will act synergistically to provide increased anti-tumor activity compared to gemcitabine/nab-paclitaxel alone. Subjects in this study should not expect to benefit directly by their participation in the study. The data collected in this study may benefit future cancer patients.

1.6.1 Known Potential Risks

Immediate Risks	More severe or more frequent AEs than expected with gemcitabine/nab-paclitaxel alone, including SAEs or discontinuation due to AEs. Immediate risks also include immunotherapy (retifanlimab) related adverse events including but not limited to immune related hepatitis, pneumonitis, endocrinopathies, colitis, enteritis, mucositis, dermatitis, and nephropathy.
Long-range Risks	Potential long term sequelae of immune related adverse events including but not limited to endocrinopathies, liver dysfunction, respiratory and renal dysfunction.

1.6.2 Known Potential Benefits

Immediate Potential Benefits	Improved response to treatment/disease control.
Long-Range Potential Benefits	Increased PFS and/or OS.

1.6.3 Assessment of Potential Risks and Benefits

Rationale for necessity of exposing participants to risks	The prognosis for patients with advanced PDAC is poor. The rate of disease control with standard chemotherapy is approximately 50%. New treatment options are needed.
Summary of ways risks were minimized in study design	Participants are monitored closely for adverse events/drug reactions. Dose modification and discontinuation guidelines are provided. Supportive care for mitigation of adverse events is described. [Study stopping rules are provided.]
Justification why benefits outweigh risks	The combination of 9-ING-41 and retifanlimab has the potential to increase the anti-tumor response to standard chemotherapy and prolong survival.

Therefore, the potential benefit of this study is judged to outweigh risk and the risk/benefit ratio is in favor of benefit.

1.7 Measures to Minimize Bias: Randomization and Blinding

This is a single-arm, open-label study; therefore, no randomization or blinding procedures will be performed.

2 HYPOTHESIS

Patients with advanced pancreatic cancer previously untreated with systemic agents will have greater responses to standard cytotoxic agents (gemcitabine/nab-paclitaxel) administered in combination with the GSK-3β inhibitor 9-ING-41 plus a PD-1 inhibitor (retifanlimab) compared to historical response rates observed with

gemcitabine/nab-paclitaxel alone because of the potential of GSK-3β inhibition with PD-1 inhibition to provide synergistic anti-tumor efficacy.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

To determine the rate of disease control of the combination of 9-ING-41 and retifanlimab plus gemcitabine/nab-paclitaxel in patients with pancreatic cancer without prior systemic therapy for advanced disease.

3.2 Secondary Objectives

To further assess the efficacy (Overall Response Rate (ORR), median Progression Free Survival (PFS) and median Overall Survival (OS)) of the combination of 9-ING-41 and retifanlimab plus gemcitabine/nab-paclitaxel in patients with advanced pancreatic cancer.

To assess the safety and tolerability of the combination of 9-ING-41 and retifanlimab plus gemcitabine/nab-paclitaxel in patients with advanced pancreatic cancer.

3.3 Exploratory Objectives

To correlate disease control rate with specific molecular and immunologic tumor profile(s).

To correlate disease control rate with cancer antigen (CA) 19-9 levels.

3.4 Primary Endpoints

What is being measured	Measurement/ time frame	Measurement Tool
Disease control rate (DCR)	Stable disease for ≥ 16 weeks, confirmed complete response (CR), or confirmed partial response (PR) during study treatment	Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST[66])

3.5 Secondary Endpoints

What is being measured	Measurement/ time frame	Measurement Tool
Objective response rate (ORR)	Percent of patients with CR or PR	imRECIST
Duration of response (DOR)	Time from documentation of tumor response to disease progression	imRECIST
Progression-free survival (PFS)	Time from study entry until objective tumor progression or death	Survival curve
Overall survival (OS)	Time from study entry to death from any cause	Survival curve

Time to treatment failure (TTF)	Time from study entry to disease progression, or death, whichever occurs first.	Survival curve

3.6 Exploratory Endpoints

What is being measured	Measurement/ time frame	Measurement Tool
Correlation of DCR with specific molecular tumor profiles	Enrollment to EOT	Baseline pre treatment tumor molecular NGS reports through a CLIA certified commercially approved vendors (e.g. UPMC local oncomine panel, Foundation One, Caris, or Tempus)
Correlation of DCR with CA 19-9 levels	Enrollment to EOT	Per standard of care

4 STUDY DESIGN

4.1 Overall Design

This is an open label, single-arm, Simon 2-stage, Phase 2 study of the combination of 9-ING-41 and retifanlimab plus gemcitabine/nab-paclitaxel in patients with pancreatic cancer without prior systemic therapy for advanced disease. The phase 2 trial will be preceded by a safety lead-in of 6-9 patients to determine the recommended phase 2 dose (RP2D).

4.2 Justification for Dose

Based on the results obtained in the 1801 study, 9-ING-41 will be administered at the dose of 9.3 mg/kg twice weekly.

Retifanlimab will be administered at a dose of 500 mg every 4 weeks, which is the dose used for the treatment of patients with locally advanced or metastatic squamous cell carcinoma of the anal canal (SCAC) who have progressed on, or who are refractory to, platinum-based chemotherapy.

Gemcitabine/nab-paclitaxel will be administered at the dose regimen approved for the treatment of patients with advanced pancreatic cancer.

4.3 End of Study Definition

The study will continue until the planned number of patients have been enrolled and treated and all patients have been followed for at least 3 months after the last dose of study drug or until disease progression or death, whichever occurs first, unless the study is stopped due to futility after Stage 1. Patients who discontinue treatment for reasons other than disease progression will be followed for PFS or until patient starts a new anti-cancer treatment, whichever occurs first.

5 PARTICIPANT SELECTION

Patients with pancreatic cancer without prior systemic therapy for advanced disease may be eligible for this trial if they meet all entry criteria.

5.1 Inclusion Criteria

Each potential patient must satisfy all of the following criteria to be enrolled in the study:

- Is able to understand and voluntarily sign a written informed consent and is willing and able to comply with the protocol requirements including scheduled visits, treatment plan, laboratory tests and other study procedures.
- Is aged ≥ 18 years.
- Has pathologically confirmed advanced, recurrent, or metastatic pancreatic cancer AND is previously untreated with systemic agents in the advanced/metastatic setting.
- Must have at least 1 measurable lesion per RECIST v1.1. Lesions that are radiated should not count as target lesions unless there is evidence of growth post radiation on a subsequent scan prior to trial enrollment.
- Must have available archived tumor tissue at study entry; paraffin-embedded tissue block preferred or 10 unstained slides (metastatic tissue preferred to primary tissue) OR if archived tissue is not available, willing to provide a fresh tumor biopsy prior to start of study treatment for tumor comprehensive NGS molecular testing through one of the following vendors: local UPMC oncomine panel (preferred), Foundation One, Caris, or Tempus. Confirmation that archival tissue or fresh tumor tissue is adequate for molecular testing through one of those vendors is needed prior to trial enrolment.
- **Has laboratory function within specified parameters (may be repeated):**
    - Adequate bone marrow function: absolute neutrophil count (ANC) ≥ 1000/mL; hemoglobin ≥ 8.5 g/dL, platelets ≥ 100,000/mL
    - Adequate liver function: transaminases (aspartate aminotransferase/ alanine aminotransferase, AST/ALT) and alkaline phosphatase ≤ 2.5 x ULN (≤ 5 X the upper limit of normal (ULN) in the setting of liver metastasis or infiltration with malignant cells); bilirubin ≤ 1.5 x ULN
    - Adequate renal function: creatinine clearance
    - CrCl > 60 mL/min measured or calculated by Cockcroft-Gault (C-G) equation (estimated glomerular filtration rate [eGFR] can also be used in place of CrCl)
    - Serum amylase and lipase ≤ 1.5 x ULN
    - Eastern Co-operative Oncology Group (ECOG) performance status (PS) 0 – 1 (Appendix A)
    - Has received the final dose of any of the following treatments/ procedures within the specified minimum intervals before first dose of study drug:
        - Focal radiation therapy – 7 days
        - Surgery with general anesthesia – 7 days

- Surgery with local anesthesia – 7 days

- May have received treatment with fluorouracil or gemcitabine as a radiation sensitizer in the adjuvant setting if the treatment was received at least 6 months before study enrollment.
- May have received neoadjuvant chemotherapy with FOLFIRINOX if given at least 6 months before study enrollment.
- May have received prior cytotoxic doses of systemic chemotherapy in the adjuvant setting if given at least 6 months before study enrollment.

- Women of childbearing potential must have a negative baseline blood or urine pregnancy test within 72 hours of first study therapy. Women may be neither breastfeeding nor intending to become pregnant during study participation and must agree to use effective contraceptive methods (hormonal or barrier method of birth control, or true abstinence) for the duration of study participation and in the following **6 months** after discontinuation of study treatment.
- Male patients with partners of childbearing potential must take appropriate precautions to avoid fathering a child from screening until **6 months** after discontinuation of study treatment and use appropriate barrier contraception or true abstinence.
- Must not be receiving any other investigational medicinal product.

5.2 Exclusion Criteria

Participants meeting any of the exclusion criteria listed below at screening will be excluded from study participation.

- Is pregnant or lactating.
- Is known to be hypersensitive to any of the components or metabolites of 9-ING-41 or to the excipients used in its formulation, or known sensitivity to one of the chemotherapeutic agents or to the PD-1 inhibitor.
- History of receiving prior treatment with any anti-PD-1, PD-L1 or PD-L2 agent.
- Has endocrine or acinar pancreatic carcinoma.
- Has not recovered from clinically significant toxicities as a result of prior anticancer therapy, except alopecia, anemia not requiring transfusion support and infertility. Recovery is defined as ≤ Grade 1 or baseline severity per Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (v5.0).
- Has significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, or stroke within 6 months of the first dose of 9-ING-41, or cardiac arrhythmia requiring medical treatment detected at screening.
- Has had a myocardial infarction within 12 weeks of the first dose of 9-ING-41 or has electrocardiogram (ECG) abnormalities that are deemed medically relevant by the investigator or study medical coordinator.
- Has symptomatic rapidly progressive brain metastases or leptomeningeal involvement as assessed by computed tomography (CT) scan or magnetic resonance imaging (MRI). Patients with stable brain metastases or leptomeningeal disease or slowly progressive disease are eligible provided that they have not required new treatments for this disease in a 28-day period before the first dose of study drug, and anticonvulsants and steroids are at a stable dose for a period of 14 days prior to the first dose of study drug.

- Has had major surgery (not including placement of central lines) within 7 days prior to study entry or is planned to have major surgery during the course of the study (major surgery may be defined as any invasive operative procedure in which an extensive resection is performed, e.g., a body cavity is entered, organs are removed, or normal anatomy is altered). In general, if a mesenchymal barrier is opened (pleural cavity, peritoneum, meninges), the surgery is considered major.
- Has any medical and/or social condition that, in the opinion of the investigator would preclude study participation.
- Has received an investigational anti-cancer drug in the 14-day period before the first dose of study drug (or within 5 half-lives if longer) or is currently participating in another interventional clinical trial.
- Has a current malignancy other than pancreatic cancer.
- Known immunodeficiency syndrome or active autoimmune disease or requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (> 10 mg/day of prednisone or equivalent).
    - Physiologic corticosteroid replacement therapy at doses > 10 mg/day of prednisone or equivalent for adrenal or pituitary insufficiency and in the absence of active autoimmune disease is permitted.
    - Participants with asthma that requires intermittent use of bronchodilators, inhaled steroids, or local steroid injections may participate.
    - Participants using topical, ocular, intra-articular, or intranasal steroids (with minimal systemic absorption) may participate.
    - Brief courses of corticosteroids for prophylaxis (eg, contrast dye allergy) or study treatment–related standard premedication are permitted.
- Evidence of interstitial lung disease, history of interstitial lung disease, or active, noninfectious pneumonitis.
- Palliative radiation therapy administered within 1 week of first dose of study treatment or radiation therapy that is > 30 Gy within 6 months of the first dose of study treatment. Note: Participants must have recovered from all radiation-related toxicities, not require corticosteroids for this purpose, and not have had radiation pneumonitis.
- Has received systemic antibiotics ≤ 7 days prior to the first dose of study drug.
- History of organ transplant, including allogeneic stem cell transplantation.
- Known hypersensitivity to another monoclonal antibody that cannot be controlled with standard measures (eg, antihistamines and corticosteroids).
- Known allergy or hypersensitivity to any component of retifanlimab or formulation components.
    - Has received a live vaccine within 28 days of the planned start of study drug.

5.3 Ineligible Patients

Patients who do not meet the study eligibility requirements will be referred back to their treating physicians for additional treatment options.

5.4 Participant Replacement

Participants will not be replaced once treated. Any participant who signs consent but does not receive study treatment may be replaced.

6 CHILD-BEARING POTENTIAL / PREGNANCY

Because the effect of the study treatment is considered possibly teratogenic and has potential risks to the fetus, pregnant females will not be included in the study. However, no female of childbearing potential will be excluded from the study.

An effective form of contraception of the woman's choice will be required during study participation. Participants should not get pregnant, breastfeed, donate sperm or father a child while participating in this study and for **6 months** after the last dose of the study medication.

Women of childbearing potential and male participants must agree to use adequate contraception (hormonal AND barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. If a woman becomes pregnant or suspects she is pregnant while participating in this study or if her male partner is a participant in this study, the treating physician should be informed immediately.

Child-bearing potential is defined as any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has either not undergone a hysterectomy or bilateral oophorectomy or has not been naturally postmenopausal for at least 12 consecutive months.

Participants must agree to use one of the following acceptable forms of birth control.

- Sexual Abstinence
- One barrier method (cervical cap with spermicide plus male condom; diaphragm with spermicide plus male condom) PLUS hormonal method (oral contraceptives, implants, or injections) or an intrauterine device (e.g., Copper-T).

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she should inform her treating physician immediately.

If the partner of a man becomes pregnant or suspects she is pregnant while he is participating in this study, he should inform his treating physician immediately.

Men of child-bearing potential must not father a child or donate sperm while receiving investigational treatment and for **6 months** after their last study treatment.

7 PARTICIPANT REGISTRATION PROCEDURES

7.1 General Guidelines

Eligible participants will be required to be registered through The University of Kansas Cancer Center Clinical Research Office central registration process and registration must occur prior to the initiation of therapy

Issues that would cause treatment delays should be discussed with the Sponsor/Investigator. If a participant does not receive protocol therapy following registration, notify The University of Kansas Cancer Center Clinical Site Management team via email at *KUCC-CTO-IIT@kumc.edu* and update participant's status in the CRIS system.

7.2 Registration Process

The University of Kansas Cancer Center participant registration is accessible for registration Monday through Friday, 8:00 AM to 5:00 PM Central Time. Please allow up to 24 hours for completion of registration.

The registration procedures are as follows:

1. Obtain written informed consent prior to the performance of any study related procedures or assessments. Tests required at screening and performed as part of customary care prior to signing consent, are allowed IF those tests were performed within the timeframe listed in Participant Selection section.
2. Complete appropriate baseline demographic information in CRIS. Print, complete and obtain appropriate signatures for the inclusion/exclusion criteria to document eligibility. Maintain completed documents in participant's research record. Participants must meet all eligibility criteria to be eligible for registration.
3. Use the hyperlink at the bottom of the eligibility criteria or in the CRIS system, complete information and submit to initiate the registration process.
4. Email confirmation of registration will be sent to the person initiating the registration. Registration confirmation should be maintained as part of the participant's research record.

8 PHARMACEUTICAL INFORMATION

For this study, both 9-ING-41 for injection and retifanlimab are considered investigational products. The combination of gemcitabine and nab-paclitaxel (Abraxane) is approved as first-line therapy in patients with advanced pancreatic adenocarcinoma.

8.1 9-ING-41

8.1.1 Overview

9-ING-41 is a GSK-3β inhibitor, which is being evaluated as potential anti-cancer therapy in various solid tumors including pancreatic cancer (See Section with title *Introduction / 9-ING-41*).

8.1.2 Pharmacokinetics and Metabolism

See Section with title, *Introduction / 9-ING-41 / Human Pharmacokinetics of 9-ING-41*. Additional details are provided in the 9-ING-41 Investigator Brochure.

8.1.3 Adverse Effects

Adverse effects are provided in the 9-ING-41 Investigator Brochure.

8.1.4 Pregnancy and Lactation

The teratogenic risk of 9-ING-41 is currently unknown. Patients who are pregnant or lactating are excluded from participation in this study.

Fertile male patients and female patients who are of childbearing potential must agree to use 2 methods of highly effective contraception throughout the study and for at least **90** days after the last dose of investigational product as described in with title, *CHILD-BEARING POTENTIAL / PREGNANCY*.

8.1.5 Drug Interactions

9-ING-41 has a low potential for interaction with the cytochrome P450 metabolic system within the liver.

For FDA designation of drugs with the potential for strong inhibition of CYP2C19, CYP3A4, and CYP1A2 or strong inducers of CYP3A4 please use this URL: *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers*.

8.1.6 Packaging and Labeling Information

9-ING-41 for injection is a light-red to red clear solution of 10 mg/mL 9-ING-41 in an inactive co-solvent mixture of polyethylene glycol 400, ethanol and Tween 80 (polysorbate 80) (PEG400:EtOH:Tween80; 75:17:8).

9-ING-41 for injection is provided as a 27-mL fill (i.e., 2 mL overage) in a 30-mL, clear, USP Type I molded glass vial with Teflon-lined (FluroTec™) gray butyl rubber stopper.

The route of administration is by IV infusion after diluting 9-ING-41 for injection with 0.9% Sodium Chloride Injection. Dilution must be made into a DEHP-free infusion container/bag; please refer to the Pharmacy Manual for approved infusion supplies. Administration to the patient must be via a DEHP-free, study-approved, giving set; please refer to the Pharmacy Manual for approved giving sets.

9-ING-41 Sample Composition

Component	Amount per Vial*	Function	Quality Standard
9-ING-41	250 mg	active	Manufactured using GMP
Polyethylene Glycol 400	20.06 g	solubilizer	National Formulary (NF)
Ethanol anhydrous	4.55 g	co-solvent	National Formulary (NF)
Polysorbate 80	2.14 g	co-solvent and detergent	United States Pharmacopeia (USP)

* Label claim; total fill includes a 0.756 g overfill for a fill weight of 27.756 g. The amount per vial in this table reflects the expected deliverable dose, and is the label claim of 25 mL containing 250 mg of drug.

8.1.7 Drug Storage and Stability

The investigator, or an approved representative (e.g., pharmacist) will ensure that all 9-ING-41, the investigational product (IP), is stored in a secured area with controlled access and in accordance with applicable regulatory requirements. IP should be stored in original containers and in accordance with the labels.

8.1.8 Preparation/Mixing Instructions

9-ING-41 for injection should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, national, state, or institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

After calculating the dose required for the patient, withdraw the appropriate mL of drug from the vial using sterile technique and add to 0.9% Sodium Chloride Injection in the approved infusion container to produce concentrations specified in the 9-ING-41 Pharmacy Manual.

Upon dilution, infusion contents must equilibrate for 0.25 to 1 hour prior to beginning patient administration. Administer the entire contents of the diluted solution in the infusion container. Complete administration to the patient within 8 hours of making the dilution.

Please reference the recommended infusion rate in the Pharmacy Manual. If the prescribing clinician chooses to amend the volume for infusion, this is permitted within recommended concentrations specified in the Pharmacy Manual.

8.1.9 Administration

9-ING-41 9.3 mg/kg will be administered on Day 1 and 4 of each week of a 28-day cycle. On Day 1 of each cycle, patients will receive 9-ING-41 following administration of gemcitabine/nab-paclitaxel and retifanlimab. On Days 8 and 15 of each cycle, patients will receive 9-ING-41 following administration of gemcitabine/nab-paclitaxel.

The recommended infusion rate is found in the 9-ING-41 Pharmacy Manual. If the prescribing clinician chooses to amend the volume for infusion, this is permitted within recommended concentrations found in the Pharmacy Manual. Infusion may be as an in-patient or as an out-patient according to local resources and the requirements of associated monitoring and concomitant chemotherapy.

Detailed procedures for 9-ING-41 infusion are provided in the Pharmacy Manual. All patients should be weighed within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the dose of 9-ING-41 and concomitant chemotherapy. The decision to recalculate dose(s) according to a change in weight should be in accordance with local practice, however where weight has changed by >10%, dose MUST be recalculated using the most recent weight recorded.

8.1.10 Acquisition and Accountability

9-ING-41 will be supplied for participants by Actuate Therapeutics.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents according to institutional standard operating procedures and policies.

Used drug and remaining unused drug may be destroyed, according to institutional standard operating procedures and policies.

8.2 Retifanlimab (INCMGA00012)

8.2.1 Overview

Retifanlimab is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1. Retifanlimab contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1–expressing cells, including T cells, and to sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

Retifanlimab is an investigational new drug being evaluated for the treatment of patients with solid tumors, both as monotherapy and in combination with other agents.

8.2.2 Pharmacokinetics and Metabolism

See retifanlimab Investigator Brochure.

8.2.3 Adverse Effects

Adverse effects are listed in the Invetgiator's Brochure for retifanlimab.

*Refer to section 11.3.2 to Table B detailing Toxicity Management Guidelines for Immune Related Adverse Events.

See Appendix C for URL to access the following: Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

8.2.4 Pregnancy and Lactation

Standard fertility and early embryonic development, embryo-fetal development and pre- and postnatal development studies have not been conducted with retifanlimab.

Based on its mechanism of action and a literature-based reproductive toxicity assessment, retifanlimab could cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Participants must use contraceptive measures as described in the study protocols and in accordance with CTFG 2020. [67]

NOTE: The CTFG guidance indicates monthly pregnancy testing and use of contraception for 1 to 6 months after final dose.

8.2.5 Drug Interactions

Retifanlimab belongs to the class of IgG antibodies that are administered parenterally and cleared by protein catabolism, extrinsic factors such as food and drug-drug interactions are not anticipated to affect the exposure of retifanlimab. Specifically, drugs that affect cytochrome P450 and other metabolizing enzymes are not expected to interfere with the catabolism of retifanlimab.[68],[69] It is unlikely that retifanlimab would be a victim or a perpetrator of PK drug-drug interactions.[70],[71] Dedicated drug-drug interaction studies of retifanlimab have not been performed.

Retifanlimab is known to increase some proinflammatory cytokine levels. This is a known class effect of checkpoint inhibitory mAbs [72],[73] but is unlikely to modulate CYP enzymes or drug transporters, based on clinical evidence with other agents of this class.[74] It is unlikely that retifanlimab would be a perpetrator of drug-drug interactions, and the potential for clinically significant drug-drug interaction is low.

HIV antiretroviral medications, used according to protocols as appropriate by HIV-positive participants in retifanlimab studies, may be substrates, inhibitors, or inducers of the P-glycoprotein and multidrug-resistant protein transporters and the cytochrome P450 enzyme system. None of the highly active antiretroviral therapies are immunosuppressors.[75] Since retifanlimab is not expected to be a victim or perpetrator of drug transporters or cytochrome P450 enzymes, the potential of drug-drug interaction between antiretroviral drugs and retifanlimab is low.[76] No clinically important differences in the CL of retifanlimab were found in HIV-positive participants taking antiretroviral medications compared to participants who were not HIV-positive.

Glucocorticoid co-administration was explored as a time series covariate in the population pharmacokinetics model. Results show that glucocorticoid co-administration is not a predictor for retifanlimab clearance in the model.

Hormonal contraceptives are metabolized by the cytochrome P450 enzyme system, and retifanlimab is not expected to be a victim or perpetrator of cytochrome P450 enzymes.

Therefore, the potential for pharmacokinetic drug interactions between hormonal contraceptives and retifanlimab is low.[77]

8.2.6 Packaging and Labeling Information

25 mg/mL retifanlimab will be provided in a glass vial for single use. Each vial will be labeled as required per country requirement.

8.2.7 Drug Storage and Stability

Store upright under refrigeration at 2°C-8°C (36°F-46°F), protected from light.

See also retifanlimab pharmacy manual.

8.2.8 Preparation/Mixing Instructions

Prior to Preparation:
Verify that there were no temperature excursions prior to preparing INCMGA00012 for infusion. Deviations from the acceptable temperature range (2°C − 8°C; 36°F − 46°F) since the last documented temperature must be reported immediately and the vials should be placed in temporary quarantine until notified by Incyte.

Before dose preparation, each vial should be inspected visually. If solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or visible particulate matter or discoloration is noted, the vial should not be used. If visible particulate matter, pronounced discoloration, or damage is evident, the vial should be permanently quarantined The study pharmacist or assigned designee should note the time, date and reason for permanently quarantining the vial(s) and a product complaint should be submitted to Incyte as per Section 11. INCMGA00012 was observed to be compatible with the following materials:

- Polyvinylchloride (PVC) with DEHP (di-2-ethylhexyl phthalate)
- PVC (without DEHP)
- Polyolefin (Polyethylene and Polypropylene)
- Polyolefin with polyamide coating
- Ethylene Vinyl Acetate (EVA)
- Polyurethane (PUR)

Study drug administration supplies (ie, IV bags and tubing), should be made only of these materials. The type of infusion components (ie, bags and infusion sets) used for administration should be documented as per institution guidelines.

INCMGA00012 will be prepared by adding the drug product directly to a bag containing 0.9% sodium chloride (normal saline) injection USP or 5% dextrose in water, USP (D5W). Prepared infusion solution will be delivered through an IV administration set including a 0.2 micron low protein binding preferably in-line filter made of polyethersulfone (PES). **The density of liquid formulation is 1.04 g/ml. The final concentration range for INCMGA00012 must be within 0.3 mg/mL to 12 mg/mL in the normal saline IV bag. Institutional guidelines may be followed provided that the drug concentration falls within those parameters.** It is recommended to use 100 mL normal saline IV bags for infusion preparation, however, in case of supply constraints, 250 mL normal saline IV bags may be used if needed.

Infusion Preparation
The total time at room temperature (23-27°C) for the prepared infusion solution should not exceed 6 hours inclusive of infusion time.
***Note**: if necessary, the prepared solution may be stored refrigerated (2-8°C) for up to 24 hours. The refrigerated solution should be allowed to come to room temperature for no more than 30 minutes prior to starting the infusion.*

The preparation of INCMGA00012 with 0.9% sodium chloride injection USP (normal saline) in IV bag is to be performed aseptically by the pharmacy or qualified personnel using the following steps:

1. Confirm the proper dose to be administered.

2. Determine the required drug volume to be administered.
3. Using aseptic technique, prepare the necessary volume of normal saline in the IV bag and label appropriately. The local method for preparing infusion solution is acceptable (ie, gravimetric, volumetric).
4. The vial should be gently inverted to mix the solution. THE VIAL MUST NOT BE SHAKEN; excessive agitation may cause aggregate formation. Before use, parenteral drug products should be inspected visually. If particulate matter or discoloration is noted, the vial should not be used and the vial should be placed in Permanent Quarantine. Incyte should be notified immediately and a product complaint filed.
5. Using aseptic technique, withdraw the required volume from the vial(s). If more than one vial is needed, it is advisable to deliver the study drug to an appropriate single use syringe using a new needle for each vial.
6. Transfer the required volume of INCMGA00012 to the normal saline IV bag. The total infusion volume (normal saline + INCMGA00012) should be rounded to the nearest mL.
7. Gently invert normal saline IV bag to mix the content.
8. THE INFUSION BAG CONTAINING THE DOSE TO BE ADMINISTERED MUST NOT BE SHAKEN; excessive agitation may cause aggregate formation. Before administration the parenteral drug product solution should be inspected visually. The diluted dose solution may contain small translucent to white proteinaceous INCMGA00012 particles. It is acceptable to administer the dose solution with these proteinaceous particles using extension sets with the required sterile, non-pyrogenic, low-protein binding polyethersulfone (PES) 0.2 micron in-line filter. However, if foreign particulate matter or solution discoloration is noted, the final prepared IV solution should not be administered and a product complaint should be submitted as described in Section 10.

See also retifanlimab pharmacy manual.

8.2.9 Administration

Retifanlimab 500 mg will be administered IV (30-minute infusion [-5/+ 15 min]) using an in-line filter on Day 1 of each 28-day cycle. Refer to the Package Insert for additional details of administration.

Retifanlimab will be administered after gemcitabine/nab-paclitaxel and prior to administration of 9-ING-41.

See also retifanlimab pharmacy manual.

8.2.10 Acquisition and Accountability

Retifanlimab will be obtained for participants from Incyte Corporation.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents according to institutional standard operating procedures and policies.

Used drug and remaining unused drug may be destroyed, according to institutional standard operating procedures and policies.

8.3 Gemcitabine/Nab-paclitaxel

8.3.1 Overview

Gemcitabine plus nab-paclitaxel (Abraxane) is a standard of care systemic therapy for advanced, metastatic PDAC.

8.3.2 Pharmacokinetics and metabolism

Refer to package inserts.

8.3.3 Adverse Effects

Common side effects associated with gemcitabine and nab-paclitaxel are indicated in Appendix B.

8.3.4 Pregnancy and Lactation

Refer to package inserts.

8.3.5 Drug Interactions

Refer to package inserts.

8.3.6 Packaging and Labeling Information

Refer to package inserts.

8.3.7 Drug Storage and Stability

Refer to package inserts.

8.3.8 Preparation/Mixing Instructions

Refer to package inserts.

8.3.9 Administration

Nab-paclitaxel 125 mg/m^2 will be administered according to standard of care, IV over 30-40 minutes immediately followed by gemcitabine according to standard of care, 1000 mg/m^2 IV over 30-minutes on Days 1, 8 and 15 of each 28-day cycle. 1-2 days dose administration window would be acceptable.

8.3.10 Acquisition and Accountability

Gemcitabine and nab-paclitaxel will be supplied for participants by the study site.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents according to institutional standard operating procedures and policies.

Used drug and remaining unused drug may be destroyed, according to institutional standard operating procedures and policies.

9 TREATMENT PLAN

The study drugs will be administered within a 28-day cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Adverse Events section. Appropriate dose modifications are described in the Dosing Delays/Dose Modifications section. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

9.1 Treatment Regimen

9.1.1 Safety Lead-in AND Phase II Treatment Regimen

The study treatment regimen is as follows: (1-2 days window)
30- to- 40–minute intravenous (IV) infusion of nab-paclitaxel at a dose of 125 mg per square meter, followed by an infusion of gemcitabine according to the gemcitabine label at a dose of 1000 mg per square meter, on Days 1, 8, and 15 of a 28-day cycle.

- 30-minute (-5/+ 15 min) IV infusion of retifanlimab 500 mg on Day 1 of a 28-day cycle. (retifanlimab will be administered following gemcitabine/nab-paclitaxel.)
- 9-ING-41 administered by IV infusion over 30 minutes to one hour twice weekly (Days 1 and 4 of each week) at a dose of 9.3mg/kg. (On Day 1 of each cycle, 9-ING-41 will be administered following retifanlimab; on Days 8 and 15 of each cycle, 9-ING-41 will be administered following gemcitabine/nab-paclitaxel.)

Agent	Dose	Route	Schedule	Cycle Length
Nab-paclitaxel	125 mg/m^2	IV infusion	Days 1, 8, and 15	28 days
Gemcitabine	1000 mg/m^2	IV infusion	Days 1, 8, and 15	28 days
Retifanlimab	500 mg	IV infusion	Day 1	28 days
9-ING-41	9.3 mg/kg	IV infusion	Twice weekly (Days 1 and 4)	28 days

The safety lead-in will enroll 6-9 patients. The participants enrolled in this study part will receive 9-ING-41 at 9.3mg/kg IV on days 1 and 4 of each week + Retifanlimab at 500mg IV on Day 1 + (gemcitabine at 1000mg/m^2 + Nab-paclitaxel at 125mg/m IV on days 1,8, and 15) (28-day cycles). If ≥ 5/6 participants do not experience Dose limiting toxicities (DLTs) within the DLT window of 28 days, the study will proceed to the phase 2 part. If > 1/6 participants experience DLTs, de-escalation to a lower dose level will follow. Participants enrolled to this lower dose level will receive the drug doses per the dose de-escalation scheme below. Three participants will be enrolled to this dose level. If 0/3 participants do not experience DLTS, the study will proceed to the phase 2 part. The study will be terminated if ≥ 1/3 patients experience DLTs at this lower dose level.

	Phase I Dose De-escalation Scheme			
Dose Level	**Dose of 9-ING-41 (IV) Days 1 & 4 of each week All Cycles (Cycles = 28 days)**	**Dose of Retifanlimab (IV) Day 1 All Cycles**	**Doses of Gemcitabine/Nab-Paclitaxel (IV) Days 1, 8, and 15 All Cycles**	**Number of Participants**
Level 0	9.3 mg/kg	500 mg	1000 mg/m^2 125 mg/m^2	6
Level -1	7 mg/kg	500 mg	1000 mg/m^2 125 mg/m^2	3

9.1.2 Safety Rules Trigger for Enrollment Pause

The PI and study team will review and monitor toxicity and accrual data from this study. Information that raises any questions about participant safety will be addressed with the Data Safety & Monitoring Committee. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research.

If any deaths occur on study that cannot be directly related to disease progression or extraneous causes, we will pause enrollment and the DSMC will review and monitor toxicity from this study to provide guidance regarding whether to continue enrollment or terminate the study.

9.2 Treatment Duration

Patients should complete a minimum of two cycles of study treatment unless criteria for patient withdrawal or discontinuation of treatment are met (see Section with title, *Participant Discontinuation / Withdrawal from the Study*). Study treatment may be continued for as long as the patient does not have progressive disease as defined per imRECIST and/or unacceptable toxicity and as long as the investigator deems that the patient is benefiting from treatment but for a maximum treatment duration of 2 years. Treatment may also be stopped if the patient withdraws consent, or study termination occurs (see Section with title, *Participant Discontinuation / Withdrawal from the Study*).

Participants who discontinue treatment with any drug in the regimen for any reason may continue treatment with the other drugs in the regimen at the investigator's discretion if in participant's best interest.

10 STUDY PROCEDURES AND SCHEDULE

10.1 Screening/Enrollment/Baseline

If the tests required at screening were performed as part of standard of care prior to signing consent for this study, the results from those tests are allowed in this study if the tests were completed within 28 days prior to the start of study treatment.

Within 28 days prior to Day 1 of study treatment the following data will be collected:

- Informed consent
- Complete medical and surgical history, physical examination, including measurement of height, weight, vital signs, and assessment of ECOG performance status
- Laboratory studies: complete blood count (CBC) with differential and platelets, comprehensive metabolic panel (CMP), pancreatic enzymes (amylase and lipase), TSH (Only measure free T3 or free T4 if TSH is abnormal) , and urinalysis
- Electrocardiogram (ECG)
- Routine visual exam at the eye clinic (if not done within the 6 months prior to day 1 of study regimen)
- Pregnancy test (for women of childbearing potential): for female patients of childbearing potential, a blood or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting administration of study treatment—once at the start of screening and once within 72 hours of starting the investigational product. In the case of a positive confirmed pregnancy prior to receipt of 9-ING-41, the patient will be withdrawn from study.
- Archived tumor tissue available at study entry: paraffin-embedded tissue block preferred or 10 unstained slides (metastatic tissue preferred to primary tissue) OR if archived tissue is not available, a fresh tumor biopsy must be obtained prior to start of study treatment. Tumor tissue should be sent as a **standard of care** procedure to one of the CLIA certified lab vendors for comprehensive molecular testing (e.g., UPMC local oncomine panel, Foundation One, Caris, or Tempus). Adequate tissue for molecular testing should be confirmed prior to trial enrolment.
- If not done within the prior 28 days, a positron emission tomography (PET)/CT scan, MRI, and/or CT scan will be performed for radiological evaluation of disease. Bone imaging will be performed as appropriate according to the judgment of the investigator.
- CA19-9 level

10.2 Procedures During Treatment

The following evaluations will be performed at the intervals specified.

- Adverse event occurrence at each visit starting with first dose; physical exam and performance status score (ECOG), each cycle (±5 days within the relevant cycle)
- Vital signs and weight as per Section below with title *History, Physical Exam, Vital Signs, Height and Weight.* Blood pressure to be taken pre- and post-dose of 9-ING-41; other vital signs (temperature, pulse, respiration) to be taken pre-dose and additionally if clinically indicated.
- Complete blood count with differential and platelets prior to Day 1 of every cycle and as clinically indicated
- Comprehensive metabolic panel prior to Day 1 of every cycle and also as clinically indicated

- Serum amylase and lipase prior to Day 1 of every cycle and also as clinically indicated
- TSH (Only measure free T3 or free T4 if TSH is abnormal), prior to day 1 of every cycle and as clinically indicated
- Concomitant medications should be recorded on the CRF (see Section with title *Concomitant Medication and Supportive Care Guidelines*)
- Restaging scans/radiologic evaluations (positron emission tomography (PET)/computed tomography (CT), CT and/or MRI, with or without bone imaging, every 2 cycles.
- CA19-9 levels if elevated at baseline to be followed as per standard of care.
- Pregnancy test (serum) on Day 1 of every cycle if relevant.

10.2.1 History, Physical Exam, Vital Signs, Height and Weight

History of the patient's disease under study, including details of the primary diagnosis and treatment history, will be collected within 4 weeks before the start of treatment. In addition, a history of disease process other than the cancer under study (active or resolved) and concurrent illness will be collected. This will also include prior treatments and any current medical treatments for any condition.

Patients will have a physical examination (PE) to include weight, vital signs (blood pressure, pulse, respiratory rate and temperature), and assessment of ECOG performance status and height prior to the start of treatment and throughout the study as listed in Section with title *Schedule of Events*. Note: height need only be recorded at baseline.

A complete PE will be performed at Screening and at the End of Treatment visit for each patient and will include an assessment of all body systems including neurological examination. (Genitourinary examination is optional). Findings of all PEs should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an AE in the CRF.

Abbreviated PEs should be performed as appropriate, and on an as needed basis for assessment of AEs. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.

Vital signs will include measurements of blood pressure and pulse rate to be recorded in the supine or seated position. On dosing days, blood pressure and pulse rate should be measured prior to administration of the investigational product (pre-dose) and at the end of the infusion.

A blood pressure cuff, which has been properly sized and calibrated, should be used to measure blood pressure. The use of automated devices with valid quality control for measuring blood pressure is acceptable.

10.2.2 Tumor Biopsies

A standard tumor biopsy will be recommended (if feasible) from trial patients at the time of confirmed disease progression. The purpose of these biopsies is to examine the biologic effect of the trial drugs and for longitudinal evaluation of exploratory biomarkers (see Section with title, *EXPLORATORY STUDIES*).

This tumor biopsy tissue, if obtained, will be sent as a **standard of care** procedure to one of the commercially available CLIA certified vendors (UPMC local oncomine panel, Foundation One, Caris, or Tempus) for comprehensive NGS molecular testing.

10.2.3 Laboratory Assessments

The following hematology and blood chemistry parameters will be assessed on Day 1 of every cycle and also as clinically indicated:

Laboratory Tests to be Performed at Local Laboratory*

Hematology	**Chemistry**	**Pancreatic Enzymes**	**Endocrine**
Hemoglobin	ALT	Amylase	TSH (Only measure free T3 or free T4 if TSH is abnormal)
Platelets	AST	Lipase	
WBC	Alk Phos		
% neutrophils	Sodium		
% lymphocytes	Potassium		
%monocytes	Magnesium		
% eosinophils	Chloride		
% basophils	Total calcium		
	Total bilirubin		
	BUN or Urea		
	Creatinine		
	Glucose (nonfasted)		
	Albumin		
	Phosphorus or Phosphate		

***CBC will be monitored per standard of care practice prior to each chemotherapy dose.**

10.3 End of Treatment & Safety follow up Visit

All patients should have a documented End of Treatment visit with associated safety follow up visit monitoring performed within 28 days of the last dose on 9-ING-41 (±5 days).

The visit should incorporate:

- History including concomitant medication usage
- Physical examination to include assessment of all body systems including neurological examination. Genitourinary examination is optional.
- Include weight, vital signs (blood pressure, pulse, respiratory rate and body temperature), and assessment of ECOG performance status
- Hematology
- Blood chemistry
- Pancreatic enzymes
- TSH (Only measure free T3 or free T4 if TSH is abnormal)
- Pregnancy test if clinically indicated as per standard of care
- PET/CT scan if clinically indicated as per standard of care
- MRI and or CT if clinically indicated as per standard of care
- Bone imaging if clinically indicated as per standard of care
- CA19-9 levels as per standard of care
- Safety reporting as per standard CRF (SAEs, non-serious SAEs, exposure to IP whilst pregnant or breast feeding)

10.4 Post-Treatment Follow-Up

Progression free follow up (PFS-FU) and Overall survival follow (OS-FU) up assessments should be completed on all participants unless due to death, lost to follow-up, or the participant specifically has withdrawn consent for follow-up. Discontinuation from treatment does not preclude the need to complete follow-up assessments.

10.5 Pregnancy Follow-Up

Telephone call to check pregnancy status - 6 months after EOT

10.6 Progression Free Survival Follow Up (PFS-FU)

For patients who discontinue study treatment prior to objective disease progression, PFS follow-up is to be performed, in person, every 6-8 weeks for up to 18 months after the last day of study drug, or until objective disease progression or death, whichever occurs first.

The date and regimen of the first subsequent therapy should be recorded in the eCRF if it occurs during PFS-FU.

10.6.1 Overall Survival Follow Up (OS-FU)

For patient who go off treatment due to disease progression, survival follow-up is to be performed every 3 months for up to 18 months after the last day of study drug.

OS-FU may be completed by phone contact. Death information from public sources (e.g. death registry, obituary listing, etc.) can also be used when it is available and verifiable. The date and regimen of the first subsequent therapy should be recorded in the eCRF if it occurs during OS-FU.

10.7 Lost to Follow Up

Institution policy will be followed for participants considered lost to follow up.

10.8 SCHEDULE OF EVENTS

	28-day Cycles																			
	Week																			
	Within 28 days prior to Day 1 of treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	End of Treatment [c]	Safety follow-up [c] (± 5 days)	Pregnancy Follow-up (± 7 days)	Survival follow-up
	Screening Period	Cycle 1 (± 2 days)				Cycle 2 (± 2 days)				Cycle 3 (± 2 days)				Cycles ≥ 4 (± 2 days)						6 months after EOT	
Informed consent	X																				
Nab-paclitaxel plus gemcitabine: Day 1, 8, and 15 of each 28-day cycle		X	X	X		X	X	X		X	X	X		X	X	X					
Dosing of retifanlimab: Day 1 of each 28-day cycle		X				X				X				X							
Dosing of 9-ING-41: Day 1 and Day 4 of each week		XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX				
History (complete history prior to Day 1)	X																	X	X		
Concomitant medications (all visits) & adverse events (only visits after dosing)	X	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	X	X		
ECOG	X				X				X				X				X	X	X		
Vital signs: BP (pre- and post-dose), HR, temp, resp (pre-dose and as clinically indicated)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Height (baseline only) & weight (within 72 hours prior to dosing)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination to be performed as timetabled each cycle (±5 days); collect vitals pre- and post-dose 9-ING-41 and as clinically indicated.	X	X	X	X		X	X	X		X	X	X		X	X	X		X	X		

	28-day Cycles																			
	Week																			
	Within 28 days prior to Day 1 of treatment	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**End of Treatment [c]**	**Safety follow-up [c] (± 5 days)**	**Pregnancy Follow-up (± 7 days)**	**Survival follow-up**
	Screening Period	**Cycle 1 (± 2 days)**				**Cycle 2 (± 2 days)**				**Cycle 3 (± 2 days)**				**Cycles ≥ 4 (± 2 days)**						**6 months after EOT**	
ECG: if abnormal at Screening, follow-up as per standard of care	**X**																				
Routine visual exam @ eye clinic (if not done within 6 months prior to trial enrollment).	**X**																				
Complete blood count with differential and platelets on Day 1 of every cycle and also as clinically indicated[b]	**X**	**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**		
Comprehensive metabolic panel, including magnesium and phosphorus on Day 1 of every cycle and also as clinically indicated[b]	**X**	**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**		
Pancreatic enzymes (amylase and lipase) on Day 1 of every cycle[b]	**X**	**X**				**X**				**X**				**X**				**X**	**X**		
TSH (only measure free T3 and free T4 if TSH is abnormal) on Day 1 of every cycle[b]	**X**	**X**				**X**				**X**				**X**				**X**	**X**		
Urinalysis: dipstick is acceptable; if abnormal at Screening, repeat per standard of care	**X**																				
Pregnancy test of women of child-bearing potential (at start of Screening AND with 72 hours of starting study drug)	**X**	**Day 1 of every cycle**																**X**	**X**		
Standard of care Tumor biopsy or archive tissue sample at Screening	**X**				**X** At time of disease progression																

	28-day Cycles																			
	Week																			
	Within 28 days prior to Day 1 of treatment	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**End of Treatment [c]**	**Safety follow-up [c] (± 5 days)**	**Pregnancy Follow-up (± 7 days)**	**Survival follow-up**
	Screening Period	**Cycle 1 (± 2 days)**				**Cycle 2 (± 2 days)**				**Cycle 3 (± 2 days)**				**Cycles ≥ 4 (± 2 days)**						**6 months after EOT**	
PET/CT scan, MRI and/or CT scan (if not done within 4 weeks prior to Day 1) and thereafter every 2 cycles	**X**								**X**								**X**	**X**	**X**		
Bone imaging at the discretion of the Investigator (at baseline if not done within 4 weeks prior to Day 1) and thereafter per standard of care	**X**																	**X**	**X**		
CA19-9 if elevated at baseline; follow on day 1 of every cycle	**X**	**X**				**X**				**X**				**X**				**X**	**X**		
End of Treatment visit, procedures performed as appropriate																	**X**	**X**	**X**		
Safety Follow-up within 4 weeks of last dose of 9-ING-41 (±5 days)																			**X**		
Patients who discontinue prior to disease progression: PFS follow-up every 6-8 weeks for up to 18 months after last dose or until objective disease progression or death, whichever occurs first																					**X**
Telephone call to check pregnancy status																				**X**	
Survival follow-up every 3 months for up to 18 months after last dose Phone call or medical record review																					**X**

[a] If archived tissue is not available, tumor biopsy tissue, if obtained, will be sent as a **standard of care** procedure to one of the commercially available CLIA certified vendors (UPMC local oncomine panel, Foundation One, Caris, or Tempus) for comprehensive NGS molecular testing.

[b] Approximately 1 tablespoon of blood will be collected each time during the study.

[c] The End of Treatment visit procedures are performed as clinically indicated and per standard of care: pregnancy test, PET/CT scan, MRI and/or CT scan, bone imaging, CA19-9 levels, safety reporting.

10.9 Concomitant Medication and Supportive Care Guidelines

All concomitant treatments, blood products, as well as nondrug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

10.9.1 Supportive Care

Concomitant palliative and supportive treatment(s) considered necessary for the patient's wellbeing may be given at discretion of the investigator or her/his designee assuming there is no known or expected drug-drug interaction.

Anti-emetics
Anti-emetics should be prescribed prophylactically with gemcitabine/nab-paclitaxel according to local recommendations.

Haematopoeitic Growth Factors
Primary prophylactic use of granulocyte colony stimulating factors is permitted during Cycle 1, and they may be used to treat treatment emergent neutropenia as indicated by local guidelines. Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

10.9.2 Prohibited or Restricted Concomitant Medications

Prohibited concomitant medications:

1. Anti-platelet agents and anticoagulants that require INR monitoring, such as warfarin (treatments that do not require INR monitoring, such as low molecular weight heparin and certain factor X inhibitors are permitted)
2. Any other investigational product(s) apart from 9-ING-41 and retifanlimab

10.9.3 Vaccines

COVID-19
COVID-19 vaccination is allowed during the study without restriction.

Influenza
The inactivated seasonal influenza vaccine can be given to participants while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) may be permitted, but must be discussed with the Sponsor/Investigator and may require a study drug washout period prior to and after administration of the vaccine.

10.9.4 DIET

Participants should maintain a normal diet unless modifications are required to manage adverse events such as diarrhea, nausea or vomiting.

11 DOSING DELAYS/DOSE MODIFICATIONS

Toxicity will be assessed according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 (November 27, 2017) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Cancer Institute).

Every effort should be made to administer study treatment at the planned dose and schedule. In the event of significant toxicity, dosing may be interrupted and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom or event.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle

Since 9-ING-41 will be given in combination with retifanlimab plus gemcitabine/nab-paclitaxel, it will be difficult to know with certainty which drug causes which adverse event. On this study, investigators should follow the 3 sets of guidelines; Dosing Modification and Toxicity Management Guidelines for 9-ING-41 and retifanlimab and the standard guidelines for gemcitabine/nab-paclitaxel.

Safety lead-in (Phase I) part of the trial will enroll 6-9 participants per the dose scheme and description detailed in section 15: statistical consideration. Those 6-9 patients will be evaluated for DLT during the first cycle (28 days). Participants who do not complete cycle 1, but did not meet criteria for a DLT will be considered unevaluable and will be replaced. (The safety lead-in phase has been completed.)

Dose Limiting Toxicity Definitions:
Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition.

Adverse events at least possibly attributable to 9-ING-41, retifanlimab, or gemcitabine/nab-paclitaxel or the combination of 9-ING-41, retifanlimab, and gemcitabine/nab-paclitaxel will be used to constitute DLT.

A DLT will be defined as any:

- Any Grade 4AE
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- Any related ≥ Grade 3 non-irAE which is unexpected in severity and/or duration compared to the known safety profiles of 9-ING-41 or retifanlimab or gemcitabine/nab-paclitaxel when used as single agents, and that cannot be managed by dose modification (reduction or interruption) and adequate supportive care, and requires permanent discontinuation of 9-ING-41 and/ or Retifanlimab and/ or gemcitabine/nab-paclitaxel, except for the exclusions listed below.

The definition excludes the following conditions:

• Grade 3 fatigue lasting ≤ 7 days
• Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the participant is asymptomatic
• Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
• Concurrent vitiligo or alopecia of any AE grade
• Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
• Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
• Grade 3 or 4 lymphopenia
• Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
• Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

Note: Tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of enrollment (not the date of therapy).

All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc required for dosing should be performed within 3 days prior to dosing.

Dose modification guidelines for 9-ING-41 are described in the following sections.

Dose delay or discontinuation of retifanlimab are described in the following sections.

Dose modifications of gemcitabine/nab-paclitaxel should be according to prescribing information or site standard of care.

11.1 9-ING-41

11.1.1 9-ING-41 Dose Reduction Steps

Dose reduction steps for 9-ING-41 are shown in the table below.

9-ING-41 Dose Reduction Levels

Dose level	9-ING-41 dose
Starting	9.3 mg/kg
-1	7 mg/kg
-2	5 mg/kg

11.1.2 9-ING-41Dose Modification Guidelines

Each Adverse Event should be attributed to a specific study drug so that dose modifications can be made accordingly. Further clarification can be obtained in consultation with the Sponsor/Investigator. If multiple toxicities are noted, the dose adjustment should be made according to the most severe toxicity guidelines.

11.1.3 9-ING-41 Dose Reduction Criteria

Patients who experience Grade 3/4 9-ING-41-attributable adverse events / toxicity, should have the 9-ING-41 dose reduced by one dose level as described in table above with title *9-ING-41 Dose Reduction Levels*.

For Grade 1/2 9-ING-41-attributable adverse events, dose reduction should be made at the Investigator's discretion.

11.1.4 9-ING-41 Treatment Discontinuation Criteria

9-ING-41 alone, or 9-ING-41 in combination with retifanlimab and chemotherapy should be discontinued permanently for the following:
Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding (aside from minor bleeds ≤ Grade 1) requires discontinuation

Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:

- AST or ALT > 5-10 x ULN for > 2 weeks
- AST or ALT > 10 x ULN
- Total bilirubin > 5 x ULN
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:

- Grade 4 neutropenia < 7 days
- Grade 4 lymphopenia or leukopenia
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

Any treatment-related event that leads to interruption in dosing lasting > 6 weeks from the previous dose requires patient discontinuation, with the following exceptions:

- Dosing interruptions lasting > 6 weeks (e.g. minor surgery) from the previous dose that occur for non-drug- related reasons may be allowed if approved by the Investigator, the Sponsor, and the Data Safety Monitoring Committee (DSMC). Prior to re-initiating treatment in a patient with a dose interruption lasting > 6 weeks, the investigator and the Sponsor must agree to do so. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing interruption.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator or Sponsor, presents a substantial clinical risk to the patient with continued treatment dosing.

11.2 9-ING-41 Guidelines for Restarting 9-ING-41

After Cycle 1 is completed, if a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle. Re-treatment following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:
ANC ≥500/mm^3;
Platelets count ≥50,000/mm^3;
Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator discretion, Grade ≤2 if not considered a safety risk for the patient).

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

9-ING-41 should be delayed for clinically significant CTCAE v5.0 Grade 3/4 toxicity thought to be possibly, probably, or definitely related to study drug; in patients where Grade 2 toxicity is intolerable despite supportive care, treatment may also be delayed or interrupted. Delays to dosing up to and including 28 days beyond planned dosing are at the investigator's discretion.

After resolution to less than or equal to CTCAE v5.0 Grade 2, 9-ING-41 can be restarted at a reduced dose as indicated in table above with title *9-ING-41 Dose Reduction Levels*.. If 9-ING-41 is delayed for more than 28 days, it may be restarted only after discussion between the investigator and the Sponsor.

11.3 Retifanlimab

11.3.1 Management of Suspected Infusion Reactions

The incidence of infusion reactions to retifanlimab in company-sponsored studies is low (2.2%). Infusion or hypersensitivity reactions may be observed with administration of any foreign protein. Premedication with an antipyretic (eg, acetaminophen/paracetamol) and a histamine blocker (eg, diphenhydramine) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy. Routine prophylaxis is not required.

Guidelines for management of suspected infusion reactions are provided in the table below.

Guidelines for management of suspected infusion reactions (Table - A)

Grade	Description[1]	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with an antipyretic (eg, acetaminophen/paracetamol) and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, antihistamines, NSAIDS, antipyretics, narcotics, per institutional preferences). Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. **Subsequent occurrences (after recommended prophylaxis):** Permanently discontinue study treatment.	Premedicate at least 30 minutes before infusion with antihistamines (eg, diphenhydramine 50 mg PO) and an antipyretic (eg, acetaminophen/paracetamol [500-1000 mg PO]). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor. Next infusion should start at 50% of the original infusion rate. If no reaction, rate of infusion can be increase by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.
3 or 4	**Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilatory support indicated.	Stop infusion and initiate appropriate medical therapy (eg, IV fluids, antihistamines NSAIDS, antipyretics, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Permanently discontinue study treatment.

[1] Per NCI CTCAE v5.0, appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study treatment administration.

11.3.2 Procedures for Participants Exhibiting Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as AEs of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.
If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE.

Recommendations for management of specific immune-mediated AEs known to be associated with other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in the table below. Algorithms for evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors and management guidelines for irAEs not detailed elsewhere in the Protocol should follow the ASCO or ESMO Clinical Practice Guidelines.[78],[79]

Toxicity Management Guidelines for Immune-Related AEs (Table - B)

Immune-Related Adverse Event	**Toxicity Grade or Conditions (CTCAE v5.0)**	**Action Taken With** retifanlimab	**AE Management With Corticosteroid and/or Other Supportive Care Therapies**
Pneumonitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue.	
Diarrhea/colitis	Grade 1	No action.	None.
	Grades 2 or 3	Withhold until ≤ Grade 1.	• Consider prompt initiation of standard anti-diarrheal agents. • Administer systemic corticosteroids per local practice followed by taper. • Consider prophylactic antibiotics per local practice. • Consider gastrointestinal consultation and performing endoscopy to rule out colitis.
	Grade 4 or recurrent Grade 3	Permanently discontinue.	
	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	

Immune-Related Adverse Event	**Toxicity Grade or Conditions (CTCAE v5.0)**	**Action Taken With** retifanlimab	**AE Management With Corticosteroid and/or Other Supportive Care Therapies**
AST/ALT elevation and/or increased bilirubin/hepatitis	Grade 3 or 4, or in participants with liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue.	• Administer systemic corticosteroids per local practice followed by taper. • Consider monitoring liver enzymes weekly (or more frequently) until liver enzyme value returns to baseline or is stable.
Endocrinopathies Type 1 diabetes mellitus Hyperglycemia Hyperthyroidism Hypothyroidism Hypophysitis Adrenal insufficiency	Grades 1 and 2	No action.	None.
	Grades 3 and 4 hypothyroidism	No action.	For hypothyroidism, initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.
	Grades 3 or 4	Withhold until ≤ Grade 1. May restart retifanlimab if endocrinopathy has improved to ≤ Grade 2 and is controlled with hormone replacement, if indicated, and steroid taper is complete.	• For Type 1 diabetes mellitus, initiate insulin replacement therapy. • For hyperglycemia, administer antihyperglycemic. • For hyperthyroidism, treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate. • For hypophysitis or adrenal insufficiency, administer corticosteroids and initiate hormonal replacements as clinically indicated.
Nephritis and renal dysfunction	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 3 or 4	Permanently discontinue.	
Rash	Grade 1	No action.	None.
	Grade 2	No action.	Manage with topical steroids with or without drug interruption.
	Grade 3[(1)] or persistent Grade 2 (≥ 2 weeks) or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 4 or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis	Permanently discontinue.	

Immune-Related Adverse Event	**Toxicity Grade or Conditions (CTCAE v5.0)**	**Action Taken With** retifanlimab	**AE Management With Corticosteroid and/or Other Supportive Care Therapies**
Myocarditis	Grade 2	Withhold until ≤ Grade 1.	• Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. • Manage cardiac symptoms according to standard of care and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.
	Grades 3 or 4	Permanently discontinue.	
Important nervous system events (eg, Guillain-Barre syndrome, autoimmune encephalitis, myasthenia gravis, autonomic neuropathy, or transverse myelitis)	Grade 2	Withhold until ≤ Grade 1.	• Neurology consultation is recommended for all neurologic irAEs ≥ Grade 2. • Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. • For Grade 2 transverse myelitis consider permanent discontinuation. • Permanently discontinue for any grade Guillain-Barre Syndrome • Manage symptoms according to standard of care and with guidance from neurology.
	Grades 3 or 4	Permanently discontinue.	
All other irAEs	Grade 3 or intolerable/ persistent Grade 2	Withhold until ≤ Grade 1.	Based on severity of AE, administer corticosteroids.
	Recurrent Grade 3	Consider discontinuation.	
	Grade 4	Permanently discontinue.	

(1) Participants with Grade 3 rash in the absence of desquamation, with no mucosal involvement, not requiring systemic steroids, and resolving or improving to ≤ Grade 1 within 14 days do not have to interrupt retifanlimab.

11.3.3 Treatment Discontinuation Criteria For Retifanlimab

Participants unable to restart study drug treatment ≤ 12 weeks from the start of the treatment delay due to toxicity will be permanently discontinued from study treatment. Treatment breaks of greater than 12 weeks for reasons other than toxicity will be considered on a case by case basis by the study investigator/ sponsor.
Treatment with study drug may continue up to 2 years in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason.

Participant management should follow imRECIST[80], with the decision to treat beyond conventional RECIST progression documented in the study file.

Participants will be evaluated for immune-related AEs for **90 days** after the last dose of study drug or until the start of new anticancer therapy whichever comes first.

11.3.4 Participant Access To Study Agent At Study Closure

Treatment with study drugs may continue for a maximum duration of to 2 years in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason.

11.4 Participant Discontinuation/Withdrawal from the Study

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Participants may be withdrawn from the treatment if any of the following occur:

- Disease progression per imRECIST criteria.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s).
- Participant decides to withdraw from the protocol therapy (follow-up permitted).
- Patient withdraws consent (no follow-up permitted).
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator.
- Major violation of the study protocol (i.e., unable to adhere to study schedule) that in the opinion of the treating investigator, puts the participant at undue risk.
- Discontinuation of the study by UPMC Hillman Cancer Center.
- Confirmed pregnancy.
- Completed overall survival (OS) follow up as per protocol
- Lost to follow-up.
- Death

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the

electronic case report form (eCRF). Alternative care options will be discussed with the participant. Safety monitoring and follow-up assessments should continue as appropriate according to the study schedule, unless the participant has withdrawn consent for study participation. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in CRIS.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Sponsor/Investigator.

12 EXPLORATORY STUDIES

12.1 Exploratory Objectives

If tumor archival tissue is not available, standard of care fresh tumor biopsy (preferably of an accessible metastatic site) should be obtained:
-Tumor core tissue biopsies are required per institutional standard of care for NGS sequencing (ideally 5 cores).
-Tumor tissue biopsies will be collected using standard biopsy needle (core needle of 18 gauge or larger) or be collected by an incisional or excisional tumor biopsy.

**Collected tumor tissue or the available archival tissue will be sent to a CLIA certified commercially available vendors (e.g., UPMC local oncomine panel, Foundation One, Caris, or Tempus) for comprehensive NGS molecular testing as part of standard of care approaches.

Objectives and Type of studies:

1. To explore the genomic alterations correlating with treatment response to the study drug regimen:
   - Comparative analysis of baseline molecular markers between responders and non-responders
   - *Exploratory Markers:* PDL-1 (CPS score), MSI status, tumor mutation burden (TMB), a broad HRD gene panel: ARID1A, ATM, ATRX, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FANCA, FANCC, MRE11A, NBN, PALB2, RAD51C, RAD51D.

2. To explore mechanisms of resistance to the drug combination
   - Comparative analysis of tumor molecular derangements at baseline and at time of disease progression
   - *Exploratory Markers:* molecular alterations per tumor DNA NGS results.

12.2 Sample Preparation, Handling, Storage and Shipment

No research samples will be obtained at baseline or throughout this trial.

The comprehensive tumor molecular testing through commercially available vendors will be done as part of standard of care approaches.

13 SAFETY ASSESSMENT, DOCUMENTATION AND REPORTING

Any adverse events or sserious adverse events experienced by a participant will be collected, documented and reported as outlined throughout this section.

13.1 Definitions

The following definitions of terms apply to this section:

Adverse event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization. The following hospitalizations are NOT considered to be SAEs:
    1. Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the treatment plan are defined as baseline medical conditions and NOT to be considered AEs/SAEs
    2. Visits to the emergency room or other hospital department < 24 hours, that do not result in admission (unless considered an important medical or life-threatening event)
    3. Elective surgery, planned prior to signing consent, and admissions for a planned medical/surgical procedure
    4. Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
    5. Admission for administration of anticancer therapy in the absence of any other

SAEs.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 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 patient or subject 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.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse reaction: any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation

13.2 Eliciting Adverse Event Information

Research subjects will be routinely questioned about AEs at study visits.

13.2.1 Recording Requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should

be classified as a serious adverse event) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

Adverse events will be followed until resolution while the subject remains on-study. Once the subject is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs for 90 days after their last dose of study drug(s).

AEs or abnormal test findings felt to be associated with the investigational drug or study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

13.2.2 Abnormal Test Findings

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.
  Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
- The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.
- The test finding is considered an AE by the Sponsor-Investigator of the IND application.

13.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all AEs (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the first dose of study treatment are fully recorded in the subject's medical records. Source documentation must be available to support all AEs.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an AE. The investigator or sub-investigator (treating physician if applicable) will provide the following for all AEs (both serious and non-serious):

- Event term (as per CTCAE version 5)
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity
- Grade of toxicity
- Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)

- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received concomitant med or other intervention, etc.
- Outcome of event

13.3.1 Grading / Severity

Descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. The following grading scale should be used to assess AE/SAE severity for events not specifically listed in CTCAE version 5.0.

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events (SAEs)

13.3.2 Expectedness

An expected AE is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected AE is an AE not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

13.3.3 Attribution

Attribution is the relationship between an AE or serious AE and the study drugs. Attributions are required for each drug administered as part of the treatment regimen. Attribution will be assigned as follows:

- Definitely Related – The AE is clearly related to the study drug. There is a reasonable causal relationship between study treatment and the AE. The event responds to withdrawal of study treatment (dechallenge) and recurs with rechallenge when clinically feasible.
- Probably Related – The AE is likely related to the study drug. There is a reasonable causal relationship between study treatment and the AE. The event responds to dechallenge.
- Possibly Related – The AE may be related to the study drug. There is a reasonable possibility that study treatment caused the adverse event. The investigator can provide a rationale or evidence to suggest a causal relationship between study treatment and the AE other than just a temporal relationship.
- Unlikely Related– The AE is doubtfully related to the study drug. There is only a temporal relationship to study treatment, but not a reasonable causal relationship between study treatment and the AE.
- Unrelated – The AE is clearly NOT related to the study drug. There is no temporal relationship to study treatment. There is a reasonable causal relationship to another drug product, concurrent disease, or circumstance.

13.3.4 Classification of Outcome

AE outcome describes the status of the AE at the last observation. The Investigator will document the outcome of each AE or SAE using the categories provided below.

Classification	**Definition**
Fatal	Termination of life because of an AE.
Not recovered/not resolved	Participant has not recuperated, or the AE has not improved.
Recovering/resolving	Participant is recuperating or the AE is improving.
Recovered/resolved	Participant has recuperated, the AE resolved, or returned to baseline status / stabilized.
Recovered/resolved with sequelae	AE has resolved, but the participant has been left with symptoms or pathology
Unknown	Not known, not observed, not recorded, or refused.

13.3.5 Action Taken due to AE

The Investigator will provide the action taken regarding study drug in response to the AE. Classifications for each of the potential actions taken are provided below. More than one option may apply to a single

AE/SAE. For example, study drug may be delayed, and the dose reduced in response to an AE. Action related to pembrolizumab and/or VS-6766 will be assessed and recorded separately in the EDC.

Classification	Definition
Dose not changed	No change in administration of study drug
Study drug interrupted	Temporary interruption (termination) in administration of the study drug
Study drug withdrawn	Administration of the study drug terminated (no further dosing)
Not applicable	Determination of a value is not relevant in the current context
Unknown	Not known, not observed, not recorded, or refused

13.4 Serious Adverse Event Reporting

All events meeting the definition of a serious adverse event, which occur after the date of first dose of study treatment and within 90 days of the last dose of study treatment, should be reported according to the departmental SAE checklist and SAE form. The initial SAE form should be sent to the following within 24 hours of the Principal Investigator becoming aware of the event:

1. Anwaar Saeed, MD; at saeeda3@upmc.edu
2. *crssafetysubmissions@upmc.edu*
3. Local Institutional Review Board when reporting requirements are met, per CRS Safety process.
4. Incyte: email – *SafetyReporting@Incyte.com* or fax – (+) 1-866-981-2057

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

13.4.1 Follow-up Reports

All SAEs should be followed to resolution or stabilization. Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form. All follow-up forms must include the date the form is revised and should be submitted to the contacts listed above within 24 hours of the Principal Investigator becoming aware of the new information.

13.4.2 Pregnancy Reporting

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within **6 months** after the last dose, she must inform the investigator immediately and permanently discontinue study treatment. Reporting requirements are the same as for an SAE in above. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male participant becomes pregnant during the male participants participation, or within **6 months** of discontinuing treatment in this study, he must inform the investigator immediately. Reporting requirements are the same as for an SAE above. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

PER INCYTE

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to *SafetyReporting@Incyte.com* or faxed to (+) 1-866-981-2057 within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to *SafetyReporting@Incyte.com* or faxed to (+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

13.5 Review of Safety Information: Sponsor-Investigator Responsibilities

The sponsor-investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

13.6 IND Safety Report

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under Sections 13.6.1 to 13.6.4 below. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

13.6.1 Serious and Unexpected Suspected Adverse Reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to

suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

13.6.2 Findings from Other Studies

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section 13.6.1), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

13.6.3 Findings from Animal or In Vitro Testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

13.6.4 Increased Rate of Occurrence of Serious Suspected Adverse Reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

13.7 Submission of IND Safety Reports

The sponsor must submit each IND safety report in a narrative format or on Form FDA 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a Form FDA 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in

the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

13.7.1 Unexpected Fatal or Life-threatening Suspected Adverse Reaction Reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

13.7.2 Reporting Format or Frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

13.7.3 Investigations of Marketed Drugs

A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements.

13.7.4 Reporting Study Endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under Section 13.8 third bullet of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under Serious and unexpected suspected adverse reaction as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

13.8 Follow-up

- The sponsor must promptly investigate all safety information it receives.
- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under section IND safety reports of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

13.9 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

The principal investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

13.10 Reporting Adverse Events to the Responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) associated with the investigational drug or study treatment(s); 2) serious; and 3) unexpected. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) associated with the investigational drug or study treatment(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

14 MEASUREMENT OF EFFECT

14.1 Antitumor Effect

Tumor assessments may include all known or suspected disease sites as per standard of care. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan for patients with or known/suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases.

Measurements will be obtained at baseline and every 2 cycles thereafter.

Response will be defined as per imRECIST.[81] See Appendix C.

15 STATISTICAL CONSIDERATIONS

This is an open label, single-arm, Simon 2-stage, Phase 2 study of the combination of 9-ING-41, a GSK-3β inhibitor, and retifanlimab, a PD-1 inhibitor, plus gemcitabine/nab-paclitaxel in patients with pancreatic cancer with no prior systemic therapy for advanced disease.

To better define the Recommended phase 2 dose (RP2D) of the trial drug regimen, the phase II trial will be preceded by a safety lead-in of 6-9 patients. Given that published prior trials have already established the safety of the combination of PD-1 inhibitors plus gemcitabine/nab-paclitaxel, and also the safety of the combination of 9-ING-41 plus gemcitabine/nab-paclitaxel, and given the favorable safety profile of 9-ING-41 with no significant overlapping toxicities with either PD-1 inhibitors or chemotherapy, a safety lead-in phase with a dose de-escalation scheme was adopted as an alternative to the classic 3+3 dose escalation design.

The participants enrolled in this study part will receive 9-ING-41 at 9.3mg/kg IV on days 1 and 4 of each week + Retifanlimab at 500mg IV on Day 1 + (gemcitabine at 1000mg/m^2 + Nab-paclitaxel at 125mg/m IV on days 1,8, and 15) (28-day cycles). If ≥ 5/6 participants do not experience Dose limiting toxicities (DLTs) within the DLT window of 28 days, the study will proceed to the phase 2 part. If > 1/6 participants experience DLTs, de-escalation to a lower dose level will follow. Participants enrolled to this lower dose level will receive the drug doses per the dose de-escalation scheme below. Three participants will be enrolled to this dose level. If 0/3 participants do not experience DLTS, the study will proceed to the phase 2 part. The study will be terminated if ≥ 1/3 patients experience DLTs at this lower dose level. The DLTs definition is detailed in section 11 under dose delays/modifications.

	Phase I Dose De-escalation Scheme			
Dose Level	**Dose of 9-ING-41 (IV) Days 1 & 4 of each week All Cycles (Cycles = 28 days)**	**Dose of Retifanlimab (IV) Day 1 All Cycles**	**Doses of Gemcitabine/Nab-Paclitaxel (IV) Days 1, 8, and 15 All Cycles**	**Number of Participants**
Level 0	9.3 mg/kg	500 mg	1000 mg/m^2 125 mg/m^2	6
Level -1	7 mg/kg	500 mg	1000 mg/m^2 125 mg/m^2	3

The safety lead-in phase will be followed by a single arm phase II study to identify whether the regimen of 9-ING-41 plus retifanlimab plus gemcitabine/nab-paclitaxel has a better disease control rate than historic results with gemcitabine/nab-paclitaxel.

The safety lead-in (phase I) patients will be included into the phase 2 size calculation below.

15.1 Sample Size Justification

The primary endpoint is DCR, defined as: stable disease for ≥16 weeks, confirmed CR, or confirmed PR.

A total of 32 patients are planned to be enrolled, with up to 12 patients initially enrolled in Stage 1, and 20 additional patients enrolled in Stage 2 based on outcomes in Stage 1.

The minimum number of responders needed to continue to the next stage, is determined based on the Simon's 2-stage design,[82] with 80% power and one-sided significance level of 0.10. A disease control rate of 70% is hypothesized. A disease control rate of 50% is considered the lower threshold activity (null hypothesis), based on historical data.[83] Based on the design elements specified above, up to 12 patients will be enrolled during Stage 1. If >6 patients achieve disease control, 20 additional patients will be enrolled during Stage 2. Otherwise, enrollment will be terminated. Upon completion of Stage 2, if ≥ 20 of 32 patients achieve disease control, further evaluation may be pursued. If the DCR is 50% or less, the probability of terminating enrollment after Stage 1 is 61%.

15.2 Description of Statistical Methods

As this is an open-label Phase 2 oncology study, descriptive statistics will be utilized for all safety and efficacy parameters. Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP will be finalized before database lock and will describe the analysis populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the study endpoints.

In general, categorical variables will be summarized by frequency distributions (number and percentage of patients), continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, and time-to-event variables will be summarized using Kaplan-Meier methods and figures for the estimated median time.

All analyses, summaries, and listings will be performed using SAS software (Version 9.4 or higher).

15.2.1 Populations for Analysis

Safety Population

The Safety Analysis Population will include all patients who receive at least one dose of 9-ING-41. The Safety Analysis Population will be the primary population for evaluating treatment administration, compliance, and safety in the study.

Efficacy Population
All patients who have received at least two cycles of 9-ING-41 therapy will be considered evaluable for response unless there is definitive evidence of progression or 9-ING-41 related SAE.

15.2.2 Disposition

The number of patients included in each analysis set will be summarized, along with the reason for any exclusions. Patients discontinuing from study treatment and/or withdrawing from study participation the primary reason for discontinuation will be summarized.

15.2.3 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be tabulated. No statistical tests will be performed on these characteristics.

15.2.4 Exposure

The overall duration of study treatment administration and number of cycles initiated will be summarized. For each patient, the cumulative administered doses of 9-ING-41, retifanlimab, gemcitabine, and nab-paclitaxel will be calculated. These data will be further summarized by calculating the mean, standard deviation, median, and range of these values. The number and proportion of patients with 1 or more dose modifications (i.e., dose reduction) of each agent will be tabulated along with the reason for modification.

15.2.5 Safety Analyses

All safety analyses will be performed on the Safety Analysis Population. The safety assessment will be based on the frequency of AEs, on the observation of clinically significant abnormalities of laboratory values, concomitant medication use, vital signs, ECOG performance status and physical examination data in the Safety Analysis Population.

Concomitant medications will be tabulated and summarized by WHO Drug anatomical therapeutic chemical (ATC) and preferred term.

Adverse events will be classified using the standard Medical Dictionary for Regulatory Activities (MedDRA) classification system version 20.0 or higher. Adverse events will be graded by the investigator according to the CTCAE, version 5.0.

Analyses of AEs will be based on the principle of treatment emergence. Treatment-emergent AEs (TEAEs) are defined as having onset after study drug dosing or a sign, symptom, or diagnosis that worsens after study drug dosing. All tabulations of AE data will be based on TEAEs.

TEAEs will be summarized based on the number and percentage of patients experiencing the event by system organ class (SOC) and preferred term (PT). The causal relationship between the occurrence of an AE and study intervention will be judged by the Investigator on the basis of his or her clinical judgment. In the event a patient experiences repeat episodes of the same AE, then the event with the highest

severity grade and strongest causal relationship to study intervention will be used for purposes of incidence tabulations.

Tabular summaries will be provided, at a minimum, for:
All TEAEs.
TEAEs by relationship to study drug and maximum severity grade.
TEAEs with action of study drug interrupted or dose reduced.
TEAEs with action of study drug discontinued.
SAEs.

Hematology and serum chemistries will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift. For analytes without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment. Vital signs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range in the same manner described for laboratory values. Frequency statistics will be presented for ECOG performance status.

15.2.6 Efficacy Analyses

Efficacy endpoints are as follows:

Primary Endpoint:

- DCR, defined as: stable disease for ≥ 16 weeks, confirmed CR, or confirmed PR according to imRECIST.

Secondary Endpoints:

- Objective response rate (ORR), defined as the percent of patients with CR or PR according to imRECIST.
- Duration of response (DOR), defined as the time from documentation of tumor response to disease progression according to imRECIST
- Progression-free survival (PFS), defined as the time from study enrolment until objective tumor progression or death
- OS, defined as the time from study entry to death from any cause
- Time to treatment failure (TTF)

Exploratory Endpoints:

- Correlation of DCR with specific molecular tumor profiles
- Correlation of DCR with CA 19-9 levels

The DCR will be summarized along with 95% exact binomial confidence intervals.

Time-to-event analyses (DOR, PFS, TTF, OS) will be performed using Kaplan-Meier methods, and results will be summarized by the 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% CIs.

Descriptive statistics for CA19-9 data will be provided, including the number of observations, mean, standard deviation, median, 25th percentile (first quartile), 75th percentile (third quartile), minimum, and maximum for continuous variables. If this study part proceeds to Stage 2, descriptive analyses will be conducted to examine the relationship(s) between the DCR and CA19-9 levels and specific molecular tumor profiles.

15.3 Interim Analysis

Data will be assessed after Stage 1 to determine whether enrollment should proceed to Stage 2 per rules defined in Section above with title *Sample Size Justification*.

15.4 Study Stopping Rules

Taking into account participant safety considerations, study will be stopped if 30% or greater of the currently enrolled and registered participants experience Grade 3 or greater 9-ING-41 or Retifanlimab related AEs. Thus, based on a Binomial calculator: P (toxicity > 30% data from the trial) > 0.95, the following stopping rules will be implemented:

- > 4 of the first 10 participants experiencing Grade 3 or greater investigational agents related AEs
- > 7 of the first 15 participants experiencing Grade 3 or greater investigational agents related AEs
- > 8 of the first 20 participants experiencing Grade 3 or greater investigational agents related AEs (if more than 20 participants are recruited in the study)

16 REGULATORY REQUIREMENTS AND DATA REPORTING

16.1 Institutional Review Board/Ethics Committee Approval

Before trial initiation this protocol and informed consent form will be submitted for review and approval by the IRB of record for the clinical site. Any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by the IRB. In accordance with FDA 21 CFR 56 of the Code of Federal Regulations the Investigator will forward the Sponsor/Investigator a copy of the IRB approval letter for the initial approval, amendments, informed consent and any informed consent updates.

The Investigator will be responsible for providing the Sponsor/Investigator a list of IRB members including profession and affiliation or a United States Department of Health and Human Services General Assurance number and expiration date. If neither of these is available, the IRB Chairperson must submit a statement indicating the members of the board responsible for the review meet the FDA and other appropriate regulatory requirements. The labeling for all approved trial medications should be submitted to the IRB for information purposes.

16.2 Investigators Protocol Agreement

The Investigator must sign the Protocol Agreement before the study is activated. The original will be forwarded to the Sponsor/Investigator and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed when a protocol amendment is issued.

16.3 Remaining Samples

Any samples remaining after the trial specified analyses will be stored by the collecting institution. This includes the original specimen collected from the participant (blood, tumor tissue) as well as derivatives created from the original specimen (DNA, RNA, blocks or slides).

16.4 Confidentiality

The Investigator and any other personnel involved in the trial shall not disclose or use for any purposes other than for the performance of this trial any data, records or other information disclosed to the Investigator or other trial personnel. Such information shall remain the confidential and proprietary property of the Sponsor/Investigator, the funders, Incyte and Actuate and shall be disclosed only to the Investigator or other designated trial personnel.

Participant confidentiality will be ensured by using assigned site-specific participant ID numbers throughout the trial.

16.5 Publication

The Sponsor/Investigator holds the primary responsibility for publication.

Data
The funders, Incyte and Actuate and their co-development collaborator may use the data generated under the Research Agreement for all purposes, subject to Institutions right to publish.

Publication
The Sponsor/Investigator shall publish the results of the approved study, subject to reasonable delay to allow for filing of patent applications on any inventions (as applicable). Sponsor/Investigator will provide the funders, Incyte and Actuate with the opportunity to review and comment on any publications, prior to submission.

16.6 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the FDA Modernization Act (FDAMA) and the FDA Amendments Act (FDAA) the Sponsor/Investigator of the trial is solely responsible for determining if the trial and results meet the requirement for submission to the Clinical Trials Data Bank, *http://www.clinicaltrials.gov*. Information

posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial location and trial site contact information.

16.7 Data Management

Web-based eCRFs will be used to collect participant data. All eCRFs and resulting data will be developed and maintained in a manner consistent with currently available regulations and guidance pertinent to the use of computerized systems in clinical trials. All users of the eCRF system will be trained prior to the use of the system.

A Risk-Based Monitoring (RBM) approach will be used focusing on critical variables and triggered events and ensuring the eCRF accurately reflects data recorded in source documents.

16.8 Data Monitoring

Data monitoring procedures will be carried out by UPMC Hillman Cancer Center for all participating sites and will be performed on a regular basis to comply with Good Clinical Practice.

The study will be monitored at appropriate intervals, no less than those assigned per The University of Kansas Cancer Center Protocol Review and Monitoring Committee (PRMC) risk level designation, to assure compliance to GCP and to assess the data quality and study integrity.

Interim monitoring visits (IMV) will occur at regular intervals following enrollment/registration of the first study participant with the frequency and duration of each visit depending on recruitment status and participant enrollment/registration.

Review of the case report forms, cross-reference with source documents, review of trial related regulatory documents and logs will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the trial is conducted according to protocol design and regulatory requirements.

The monitor will complete a follow-up letter and provide to the Sponsor/Investigator. The letter will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to ensure compliance. The site will be expected to submit any Corrective and Preventative Action Plan (CAPA) in writing to the Sponsor/Investigator. A copy of the monitoring forms, follow up letter and CAPA will be kept in the site monitor's trial file and will be followed up at the next monitoring session.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data.

17 DATA SAFETY MONITORING PLAN

Investigators/Sub-investigators, regulatory, CRS management, clinical research coordinators, research coordinators, clinical research associates, data managers, and clinic staff meet monthly regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- Serious adverse events
- Subject safety issues
- Recruitment issues
- Accrual
- Protocol deviations
- Unanticipated problems
- Breaches of confidentiality

Minutes from the disease center DSMB meetings are available to those who are unable to participate during the scheduled meeting time.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 5.0. All study treatment associated adverse events that are serious, at least possibly related, and unexpected will be reported to the IRB and the FDA. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

17.1 Serious Adverse Events

Serious adverse events that require expedited reporting will be reviewed by the DSMC Chair or designee who will determine if immediate action is required. If determined to be necessary by the DSMC, all participating sites will be notified of the event and any resulting action within one working day of this determination.

17.2 Review of Serious Adverse Event Rates

Once per month, serious adverse event rates will be monitored by the Cancer Center Quality Assurance team. If any study has 2 or more of the same SAE reported within one month, or more than 6 of the same SAE in 6 months, the DSMC will review summaries of SAEs, and discuss events in detail with the PI. The DSMC chair or designee determines whether further action is required. The Sponsor/Investigator, in collaboration with the DSMC Coordinator ensure that collaborating investigators and IRBs for all participating sites are notified of any resulting action.

17.3 Study Safety and Progress

An overall assessment of toxicities as described in the protocol is reviewed at DSMC meetings. This review enables DSMC committee members to assess whether significant risks are occurring that would warrant study suspension/closure or protocol amendment.

18 DATA HANDLING AND RECORD KEEPING

18.1 Data Collection and Management Responsibilities

Electronic case report forms (eCRFs) will be completed for each participant enrolled and registered on this study. All CRFs will be customized per this study, in order to emphasize completeness and accuracy. The investigatory and trained study staff will enter and edit the data via a secure network with secure identification and password requirements. A complete electronic audit trail will be maintained.

Source documents serve as the evidence of the existence of the participant and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by the Sponsor/Investigator or assigned Clinical Research Manager.

Data captured in the eCRF is to be transcribed from source documents and must be consistent with any discrepancies explained and document. The medical chart and any other clinical worksheets, procedural reports, etc. will be the source documentation of data captured into the study database.

18.2 Protocol Deviations

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. All deviations entered into the data reporting

system must be reported to the DSMC. All deviations will be reported to the IRB per local reporting policy.

18.3 Study Closure

Upon study closure, the Sponsor/Investigator and/or Institution will be required to certify that all safety reporting obligations were met.

18.4 Study Records Retention

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, participant diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or no less than 7 years, per the University of Pittsburgh's requirements.

19 APPENDICES

Appendix A: ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

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

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Appendix B: Mode of Action and Common Side Effects of Gemcitabine and Nab-paclitaxel

Cytotoxic Chemotherapy	**Class (Mode of Action)**	**Very Common (≥ 1/10) Adverse Events**	**Common (≥ 1/100 to < 1/10) Adverse Events**
Gemcitabine	Pyrimidine antimetabolite (inhibition of DNA synthesis and induction of apoptosis)	• Leucopenia • Bone-marrow suppression • Thrombocytopenia • Anaemia • Dyspnoea • Vomiting • Nausea • Elevation of liver transaminases (AST and ALT) and alkaline phosphatase • Allergic skin rash frequently associated with pruritus • Alopecia • Influenza like symptoms • Oedema/peripheral oedema	• Febrile neutropenia • Anorexia • Headache • Insomnia • Somnolence • Cough • Rhinitis • Diarrhoea • Stomatitis and ulceration of the mouth • Constipation • Increased bilirubin • Itching • Sweating • Back pain • Myalgia • Fever • Asthenia • Chills
Paclitaxel protein bound (Abraxane)	Taxane (inhibition of mitotic spindle assembly)	• Neutropenia • Anaemia • Leukopenia • Thrombocytopenia • Lymphopenia • Bone marrow suppression • Anorexia • Peripheral neuropathy • Neuropathy • Hypoaesthesia • Paresthesia • Nausea • Diarrhoea • Vomiting • Constipation • Stomatitis • Alopecia • Rash • Arthralgia • Myalgia • Fatigue • Asthenia • Pyrexia	• Infection • Urinary tract infection • Folliculitis • Upper respiratory tract infection • Candidiasis • Sinusitis • Febrile neutropenia • Dehydration • Decreased appetite • Hypokalaemia • Insomnia • Depression • Anxiety • Peripheral sensory neuropathy • Headache • Dysgeusia • Dizziness • Peripheral motor neuropathy • Ataxia • Sensory disturbance • Somnolence • Increased lacrimation • Blurred vision • Dry eye • Keratoconjunctivitis sicca • Madarosis • Vertigo

Cytotoxic Chemotherapy	Class (Mode of Action)	Very Common (≥ 1/10) Adverse Events	Common (≥ 1/100 to < 1/10) Adverse Events
			• Tachycardia • Arrhythmia • Supraventricular tachycardia • Flushing • Hot flushes • Hypertension
Paclitaxel protein bound (Abraxane) (cont'd)			• Lymphoedema • Interstitial pneumonitis • Dyspnoea • Epistaxis • Pharyngolaryngeal pain • Cough • Rhinitis • Rhinorrhoea • Abdominal pain • Abdominal distension • Upper abdominal pain • Dyspepsia • Gastrooesophageal reflux disease • Oral hypoaesthesia • Nail disorder • Pruritus • Dry skin • Erythema • Nail pigmentation /discolouration • Skin hyperpigmentation • Onycholysis • Nail changes • Pain in extremity • Bone pain • Back pain • Muscle cramps • Limb pain • Peripheral oedema • Mucosal inflammation • Pain • Rigors • Oedema • Weakness • Decreased performance status • Chest pain • Influenza-like illness • Malaise • Lethargy • Hyperpyrexia • Decreased weight • Increased alanine aminotransferase • Increased aspartate aminotransferase

Cytotoxic Chemotherapy	Class (Mode of Action)	Very Common (≥ 1/10) Adverse Events	Common (≥ 1/100 to < 1/10) Adverse Events
			• Decreased haematocrit • Decreased red blood cell count • Increased body temperature • Increased gamma-glutamyltransferase • Increased blood alkaline phosphatase

Source of data - accessed March 2020:
Gemcitabine: Gemcitabine Summary of Product Characteristics https://www.medicines.org.uk/emc/product/3119/smpc
Abraxane: Abraxane Summary of Product Characteristics https://www.medicines.org.uk/emc/product/6438

Appendix C: Protocol Criteria for imRECIST

imRECIST will be used in this study as below:[84]

The article to be used can be found at the following URL:

https://ascopubs.org/doi/full/10.1200/JCO.2017.75.1644

imRECIST follows RECIST v1.1 conventions unless otherwise indicated:

Criterion	imRECIST
Tumor burden	Unidimensional, with other target lesion criteria (number, measurability) per RECIST v1.1
New lesions	New lesions do not categorically define PD Measurable new lesions incorporated into the total tumor burden Nonmeasurable new lesions preclude CR
Nontarget lesions	Nontarget progression does not define PD Can only contribute to defining CR (complete disappearance required)
Radiographic progression	Determined only on the basis of measurable disease ≥20% increase in SLD (RECIST) compared with baseline/nadir Negated by subsequent non-PD assessment ≥4 weeks from the date first documented (lack of confirmation) Best response may occur after any number of PD assessments

CR, complete response; imRECIST, immune-modified RECIST; PD, progression disease; RECIST, Response Evaluation Criteria in Solid Tumors; SLD, sum of longest diameters
Source ref: Hodi 2018

imRECIST timepoint response definitions:

% Change in Sum of Diameters[a]	Non-target Lesion Response Assessment	Overall imRECIST Timepoint Response
-100% from baseline[b]	CR	CR
-100% from baseline[b]	Non-CR or not all evaluated	PR
≤ -30% from baseline	Any	PR
> -30% to < +20%	Any	SD
Not all evaluated	Any	NE
≥ +20% from nadir SLD	Any	PD

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLD, sum of the longest diameter.

[a] Percent change in sum of the diameters (including measurable new lesions when present).

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm in order to meet the definition of CR.

Source Ref: Hodi 2018

20 LITERATURE REFERENCES

[1] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703. doi: 10.1056/NEJMoa1304369.

[2] American Cancer Society. Key Statistics for Pancreatic Cancer. 2021a [Available from: *https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html*

[3] American Cancer Society. Survival Rates for Pancreatic Cancer. 2021b [Available from: *https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging/survival-rates.html*

[4] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86. doi: 10.1002/ijc.29210. Epub 2014 Oct 9.

[5] National Comprehensive Cancer Network (NCCN). Pancreatic adenocarcinoma (Version 1.2021 [Available from: *https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf*

[6] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. New England Journal of Medicine. 2011;364(19):1817-25. doi: 10.1056/NEJMoa1011923.

[7] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703. doi: 10.1056/NEJMoa1304369.

[8] Woodgett JR. Molecular cloning and expression of glycogen synthase kinase-3/factor A. EMBO J. 1990;9(8):2431-8.

[9] Doble BW, Patel S, Wood GA, Kockeritz LK, Woodgett JR. Functional redundancy of GSK-3alpha and GSK-3beta in Wnt/beta-catenin signaling shown by using an allelic series of embryonic stem cell lines. Dev Cell. 2007;12(6):957-71. doi: 10.1016/j.devcel.2007.04.001.

[10] Gregory MA, Qi Y, Hann SR. Phosphorylation by glycogen synthase kinase-3 controls c-myc proteolysis and subnuclear localization. J Biol Chem. 2003;278(51):51606-12. doi: 10.1074/jbc.M310722200.

[11] An J, Yang DY, Xu QZ, Zhang SM, Huo YY, Shang ZF, et al. DNA-dependent protein kinase catalytic subunit modulates the stability of c-Myc oncoprotein. Mol Cancer. 2008;7:32. doi: 10.1186/1476-4598-7-32.

[12] Lin SY, Xia W, Wang JC, Kwong KY, Spohn B, Wen Y, Pestell RG, Hung MC. Beta-catenin, a novel prognostic marker for breast cancer: its roles in cyclin D1 expression and cancer progression. Proc Natl Acad Sci U S A. 2000;97(8):4262-6. doi: 10.1073/pnas.060025397.

[13] Wang R, Wang Y, Liu N, Ren C, Jiang C, Zhang K, et al. FBW7 regulates endothelial functions by targeting KLF2 for ubiquitination and degradation. Cell Res. 2013;23(6):803-19. doi: 10.1038/cr.2013.42.

[14] Ougolkov AV, Fernandez-Zapico ME, Savoy DN, Urrutia RA, Billadeau DD. Glycogen synthase kinase-3beta participates in nuclear factor kappaB-mediated gene transcription and cell survival in pancreatic cancer cells. Cancer Res. 2005;65(6):2076-81. doi: 10.1158/0008-5472.CAN-04-3642.

[15] Fu Y, Hu D, Qiu J, Xie X, Ye F, Lu WG. Overexpression of glycogen synthase kinase-3 in ovarian carcinoma cells with acquired paclitaxel resistance. Int J Gynecol Cancer. 2011;21(3):439-44. doi: 10.1097/IGC.0b013e31820d7366.

[16] Shakoori A, Ougolkov A, Yu ZW, Zhang B, Modarressi MH, Billadeau DD, et al. Deregulated GSK3beta activity in colorectal cancer: its association with tumor cell survival and proliferation. Biochem Biophys Res Commun. 2005;334(4):1365-73. doi: 10.1016/j.bbrc.2005.07.041.

[17] Mai W, Kawakami K, Shakoori A, Kyo S, Miyashita K, Yokoi K, et al. Deregulated GSK3{beta} sustains gastrointestinal cancer cells survival by modulating human telomerase reverse transcriptase and telomerase. Clin Cancer Res. 2009;15(22):6810-9. doi: 10.1158/1078-0432.CCR-09-0973.

[18] Miyashita K, Nakada M, Shakoori A, Ishigaki Y, Shimasaki T, Motoo Y, Kawakami K, Minamoto T. An emerging strategy for cancer treatment targeting aberrant glycogen synthase kinase 3 beta. Anticancer Agents Med Chem. 2009;9(10):1114-22.

[19] Liao X, Zhang L, Thrasher JB, Du J, Li B. Glycogen synthase kinase-3beta suppression eliminates tumor necrosis factor-related apoptosis-inducing ligand resistance in prostate cancer. Mol Cancer Ther. 2003;2(11):1215-22.

[20] Tan J, Zhuang L, Leong HS, Iyer NG, Liu ET, Yu Q. Pharmacologic modulation of glycogen synthase kinase-3beta promotes p53-dependent apoptosis through a direct Bax-mediated mitochondrial pathway in colorectal cancer cells. Cancer Res. 2005;65(19):9012-20. doi: 10.1158/0008-5472.CAN-05-1226.

[21] Aggarwal BB. Nuclear factor-kappaB: the enemy within. Cancer Cell. 2004;6(3):203-8. doi: 10.1016/j.ccr.2004.09.003.

[22] Tas SW, Vervoordeldonk MJ, Tak PP. Gene therapy targeting nuclear factor-kappaB: towards clinical application in inflammatory diseases and cancer. Curr Gene Ther. 2009;9(3):160-70.

[23] Shakoori A, Ougolkov A, Yu ZW, Zhang B, Modarressi MH, Billadeau DD, et al. Deregulated GSK3beta activity in colorectal cancer: its association with tumor cell survival and proliferation. Biochem Biophys Res Commun. 2005;334(4):1365-73. doi: 10.1016/j.bbrc.2005.07.041.

[24] Bilim V, Ougolkov A, Yuuki K, Naito S, Kawazoe H, Muto A, et al. Glycogen synthase kinase-3: a new therapeutic target in renal cell carcinoma. Br J Cancer. 2009;101(12):2005-14. doi: 10.1038/sj.bjc.6605437.

[25] Hoeflich KP, Luo J, Rubie EA, Tsao MS, Jin O, Woodgett JR. Requirement for glycogen synthase kinase-3beta in cell survival and NF-kappaB activation. Nature. 2000;406(6791):86-90. doi: 10.1038/35017574.

[26] Hoeflich KP, Luo J, Rubie EA, Tsao MS, Jin O, Woodgett JR. Requirement for glycogen synthase kinase-3beta in cell survival and NF-kappaB activation. Nature. 2000;406(6791):86-90. doi: 10.1038/35017574

[27] Bilim V, Ougolkov A, Yuuki K, Naito S, Kawazoe H, Muto A, et al. Glycogen synthase kinase-3: a new therapeutic target in renal cell carcinoma. Br J Cancer. 2009;101(12):2005-14. doi: 10.1038/sj.bjc.6605437.

[28] Naito S, Bilim V, Yuuki K, Ugolkov A, Motoyama T, Nagaoka A, Kato T, Tomita Y. Glycogen synthase kinase-3beta: a prognostic marker and a potential therapeutic target in human bladder cancer. Clin Cancer Res. 2010;16(21):5124-32. doi: 10.1158/1078-0432.CCR-10-0275.

[29] Ougolkov AV, Billadeau DD. Targeting GSK-3: a promising approach for cancer therapy? Future Oncol. 2006a;2(1):91-100. doi: 10.2217/14796694.2.1.91.

[30] Ougolkov AV, Bone ND, Fernandez-Zapico ME, Kay NE, Billadeau DD. Inhibition of glycogen synthase kinase-3 activity leads to epigenetic silencing of nuclear factor kappaB target genes and induction of apoptosis in chronic lymphocytic leukemia B cells. Blood. 2007;110(2):735-42. doi: 10.1182/blood-2006-12-060947.

[31] Ougolkov AV, Billadeau DD. Targeting GSK-3: a promising approach for cancer therapy? Future Oncol. 2006a;2(1):91-100. doi: 10.2217/14796694.2.1.91.

[32] Ougolkov AV, Bone ND, Fernandez-Zapico ME, Kay NE, Billadeau DD. Inhibition of glycogen synthase kinase-3 activity leads to epigenetic silencing of nuclear factor kappaB target genes and induction of apoptosis in chronic lymphocytic leukemia B cells. Blood. 2007;110(2):735-42. doi: 10.1182/blood-2006-12-060947.

[33] Ougolkov AV, Billadeau DD. Targeting GSK-3: a promising approach for cancer therapy? Future Oncol. 2006a;2(1):91-100. doi: 10.2217/14796694.2.1.91.

[34] Ougolkov AV, Bone ND, Fernandez-Zapico ME, Kay NE, Billadeau DD. Inhibition of glycogen synthase kinase-3 activity leads to epigenetic silencing of nuclear factor kappaB target genes and induction of apoptosis in chronic lymphocytic leukemia B cells. Blood. 2007;110(2):735-42. doi: 10.1182/blood-2006-12-060947.

[35] Ougolkov AV, Fernandez-Zapico ME, Bilim VN, Smyrk TC, Chari ST, Billadeau DD. Aberrant nuclear accumulation of glycogen synthase kinase-3beta in human pancreatic cancer: association with kinase activity and tumor dedifferentiation. Clin Cancer Res. 2006b;12(17):5074-81.

[36] Gray JE, Infante JR, Brail LH, Simon GR, Cooksey JF, Jones SF, et al. A first-in-human phase I dose-escalation, pharmacokinetic, and pharmacodynamic evaluation of intravenous LY2090314, a glycogen synthase kinase 3 inhibitor, administered in combination with pemetrexed and carboplatin. Invest New Drugs. 2015;33(6):1187-96. doi: 10.007/s10637-015-0278-7. Epub 2015 Sep 25.

[37] Taylor A, Rudd CE. Glycogen synthase kinase 3 inactivation compensates for the lack of CD28 in the priming of CD8+ cytotoxic T-cells: Implications for anti-PD-1 immunotherapy. Frontiers in Immunology. 2017;8(DEC).

[38] Taylor A, Harker JA, Chanthong K, Stevenson PG, Zuniga EI, Rudd CE. Glycogen synthase kinase 3 inactivation drives T-bet-mediated downregulation of co-receptor PD-1 to enhance CD8+ cytolytic T cell responses. Immunity. 2016;44(2):274-86.

[39] Taylor A, Rothstein D, Rudd CE. Small-molecule inhibition of PD-1 transcription is an effective alternative to antibody blockade in cancer therapy. Cancer Res. 2018;78(3):706-17. doi: 10.1158/0008-5472.CAN-17-0491. Epub 2017 Oct 20.

[40] Rudd CE, Chanthong K, Taylor A. Small molecule inhibition of GSK-3 specifically inhibits the transcription of inhibitory co-receptor LAG-3 for enhanced anti-tumor immunity. Cell Rep. 2020;30(7):2075-82.e4. doi: 10.1016/j.celrep.2020.01.076

[41] Ugolkov A, Gaisina I, Zhang JS, Billadeau DD, White K, Kozikowski A, et al. GSK-3 inhibition overcomes chemoresistance in human breast cancer. Cancer Lett. 2016;380(2):384-92. doi: 10.1016/j.canlet.2016.07.006.

[42] Ugolkov A, Qiang W, Bondarenko G, Procissi D, Gaisina I, James CD, et al. Combination treatment with the GSK-3 inhibitor 9-ING-41 and CCNU cures orthotopic chemoresistant glioblastoma in patient-derived xenograft models. Transl Oncol. 2017;10(4):669-78. doi: 10.1016/j.tranon.2017.06.003.

[43] Ugolkov AV, Bondarenko GI, Dubrovskyi O, Berbegall AP, Navarro S, Noguera R, et al. 9-ING-41, a small-molecule glycogen synthase kinase-3 inhibitor, is active in neuroblastoma. Anticancer Drugs. 2018;29(8):717-24. doi: 10.1097/CAD.0000000000000652.

[44] Kuroki H, Anraku T, Kazama A, Bilim V, Tasaki M, Schmitt D, et al. 9-ING-41, a small molecule inhibitor of GSK-3beta, potentiates the effects of anticancer therapeutics in bladder cancer. Sci Rep. 2019;9(1):19977. doi: 10.1038/s41598-019-56461-4.

[45] Hilliard TS, Gaisina IN, Muehlbauer AG, Gaisin AM, Gallier F, Burdette JE. Glycogen synthase kinase 3beta inhibitors induce apoptosis in ovarian cancer cells and inhibit in-vivo tumor growth. Anticancer Drugs. 2011;22(10):978-85. doi: 10.1097/CAD.0b013e32834ac8fc.

[46] Bilim V, Ougolkov A, Yuuki K, Naito S, Kawazoe H, Muto A, et al. Glycogen synthase kinase-3: a new therapeutic target in renal cell carcinoma. Br J Cancer. 2009;101(12):2005-14. doi: 10.1038/sj.bjc.6605437.

[47] Gaisina IN, Gallier F, Ougolkov AV, Kim KH, Kurome T, Guo S, et al. From a natural product lead to the identification of potent and selective benzofuran-3-yl-(indol-3-yl)maleimides as glycogen synthase kinase 3beta inhibitors that suppress proliferation and survival of pancreatic cancer cells. J Med Chem. 2009;52(7). doi: 10.1021/jm801317h.

[48] Ougolkov AV, Billadeau DD. Targeting GSK-3: a promising approach for cancer therapy? Future Oncol. 2006a;2(1):91-100. doi: 10.2217/14796694.2.1.91.

[49] Ougolkov AV, Fernandez-Zapico ME, Bilim VN, Smyrk TC, Chari ST, Billadeau DD. Aberrant nuclear accumulation of glycogen synthase kinase-3beta in human pancreatic cancer: association with kinase activity and tumor dedifferentiation. Clin Cancer Res. 2006b;12(17):5074-81.

[50] Ougolkov AV, Fernandez-Zapico ME, Bilim VN, Smyrk TC, Chari ST, Billadeau DD. Aberrant nuclear accumulation of glycogen synthase kinase-3beta in human pancreatic cancer: association with kinase activity and tumor dedifferentiation. Clin Cancer Res. 2006b;12(17):5074-81.

[51] Ougolkov AV, Billadeau DD. Targeting GSK-3: a promising approach for cancer therapy? Future Oncol. 2006a;2(1):91-100. doi: 10.2217/14796694.2.1.91.

[52] Shimasaki T, Kitano A, Motoo Y, Minamoto T. Aberrant glycogen synthase kinase 3beta in the development of pancreatic cancer. J Carcinog. 2012;11:15. doi: 10.4103/1477-3163.100866.
Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1-10.

[53] Gaisina IN, Gallier F, Ougolkov AV, Kim KH, Kurome T, Guo S, et al. From a natural product lead to the identification of potent and selective benzofuran-3-yl-(indol-3-yl)maleimides as glycogen synthase kinase 3beta inhibitors that suppress proliferation and survival of pancreatic cancer cells. J Med Chem. 2009;52(7). doi: 10.1021/jm801317h.

[54] Ougolkov AV, Fernandez-Zapico ME, Savoy DN, Urrutia RA, Billadeau DD. Glycogen synthase kinase-3beta participates in nuclear factor kappaB-mediated gene transcription and cell survival in pancreatic cancer cells. Cancer Res. 2005;65(6):2076-81. doi: 10.1158/0008-5472.CAN-04-3642.

[55] Ougolkov AV, Fernandez-Zapico ME, Savoy DN, Urrutia RA, Billadeau DD. Glycogen synthase kinase-3beta participates in nuclear factor kappaB-mediated gene transcription and cell survival in pancreatic cancer cells. Cancer Res. 2005;65(6):2076-81. doi: 10.1158/0008-5472.CAN-04-3642.

[56] Ougolkov AV, Fernandez-Zapico ME, Savoy DN, Urrutia RA, Billadeau DD. Glycogen synthase kinase-3beta participates in nuclear factor kappaB-mediated gene transcription and cell survival in pancreatic cancer cells. Cancer Res. 2005;65(6):2076-81. doi: 10.1158/0008-5472.CAN-04-3642.

[57] Ding L, Madamsetty VS, Kiers S, Alekhina O, Ugolkov A, Dube J, et al. Glycogen synthase kinase-3 inhibition sensitizes pancreatic cancer cells to chemotherapy by abrogating the TopBP1/ATR-mediated DNA damage response. Clin Cancer Res. 2019;25(21):6452-62. doi: 10.1158/078-0432.CCR-19-799. Epub 2019 Sep 18.

[58] El-Deiry, WS. GSK3β inhibition by small molecule 9-ING-41 decreases VEGF and other cytokines, and boosts NK and T cell-mediated killing of colorectal tumor cells. To be presented at: American Association for Cancer Research (AACR) Annual Meeting, 2021.

[59] Rao S, Capdevila J, Gilbert D, et al. POD1UM-202: Phase II study of retifanlimab in patients (pts) with squamous carcinoma of the anal canal (SCAC) who progressed following platinum-based chemotherapy. *Annals of Oncology*. 2020;31(suppl 4):S1142-S1215. doi: 10.1016/annonc/annonc325

[60] Mehnert J, Joshua A, Lakhani N, et al. First-in-human Phase 1 study of INCMGA00012 in patients with advanced solid tumors: interim results of the cohort expansion phase. Abstract P669 presented at: The Society for Immunotherapy of Cancer; November 7-11, 2018; Washington, DC.

[61] Grignani G, et al. POD1UM-201: A Phase 2 Study of Retifanlimab(INCMGA00012) in Locally Advanced or Metastatic Merkel Cell Carcinoma. Abstract P1089 Presented at ESMO Virtual Congress 2020.

[62] Berton D, et al. A phase 1 study of retifanlimab (INCMGA00012), a PD-1 inhibitor, in patients with advanced solid tumors: Preliminary results in recurrent MSI-high or dMMR endometrial cancer (POD1UM-101). Abstract 586 Presented at Society for Immunotherapy of Cancer, 35th Annual Meeting, November 9–14, 2020.

[63] Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer 2017;5:43.

[64] Centanni M, Moes DJAR, Trocóniz IF, Ciccolini J, van Hasselt JGC. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. Clin Pharmacokinet 2019;58:835-857. (Referenced in Incyte Corporation. Clinical Study Protocol Information for INCMGA00012/Retifanlimab dated June 08 2021).

[65] Rao S, Capdevila J, Gilbert D, et al. POD1UM-202: Phase II study of retifanlimab in patients (pts) with squamous carcinoma of the anal canal (SCAC) who progressed following platinum-based chemotherapy. *Annals of Oncology*. 2020;31(suppl 4):S1142-S1215. doi: 10.1016/annonc/annonc325

[66] Hodi FS, Ballinger M, Lyons B, Soria J-C, Nishino M, Tabernero J, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): Refining guidelines to assess the clinical benefit of cancer immunotherapy. Journal of Clinical Oncology. 2018;36(9):850-858.

[67] Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. Version 1.1 dated 09-21-2020. URL: *https://legemiddelverket.no/Documents/Godkjenning/Klinisk%20utpr%C3%B8ving/2014_09_HMA_CTFG_Contraception_guidance%20Version%201.1.pdf* . Accessed 05-24-2021.

[68] Food and Drug Administration. Guidance for Industry: Drug-Drug Interaction Assessment for Therapeutic Proteins. August 2020.

[69] Sheng J, Srivastava S, Sanghavi K, et al. Clinical pharmacology considerations for the development of immune checkpoint inhibitors. J Clin Pharmacol 2017;57 Suppl 10:S26-S42.

[70] Food and Drug Administration. Guidance for Industry: Drug-Drug Interaction Assessment for Therapeutic Proteins. August 2020.

[71] European Medicines Agency. Guideline on the investigation of drug interactions. CPMP/EWP/560/95/Rev. 1 Corr. 2. 2012.

[72] Feun LG, Li YY, Wu C, et al. Phase 2 study of pembrolizumab and circulating biomarkers to predict anticancer response in advanced, unresectable hepatocellular carcinoma. *Cancer* 2019;125(20):3603-3614.

[73] Matsuo N, Azuma K, Hattori S, et al. Association between soluble immune mediators and tumor responses in patients with nonsmall cell lung cancer treated with anti-PD-1 inhibitor. Int J Cancer 2019;144(5):1170-1179.

[74] Sheng J, Srivastava S, Sanghavi K, et al. Clinical pharmacology considerations for the development of immune checkpoint inhibitors. J Clin Pharmacol 2017;57 Suppl 10:S26-S42.

[75] Izzedine H, Launay-Vacher V, Baumelou A, Deray G. Antiretroviral and immunosuppressive drug-drug interactions: an update. Kidney Int 2004;66(2):532-541.

[76] Food and Drug Administration. Guidance for Industry: Drug-Drug Interaction Assessment for Therapeutic Proteins. August 2020.

[77] Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. Version 1.1 dated 09-21-2020. URL: *https://legemiddelverket.no/Documents/Godkjenning/Klinisk%20utpr%C3%B8ving/2014_09_HMA_CTFG_Contraception_guidance%20Version%201.1.pdf* . Accessed 05-24-2021.

[78] Brahmer J, Lacchetti C, Schneider B, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714-1768.

[79] Haanen J, Carbonnel F, Robert C, et al. Management of Toxicities From Immunotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. (2017) 28 (suppl 4): iv119–iv142
URL: *https://www.esmo.org/guidelines/supportive-and-palliative-care/toxicities-from-immunotherapy* . Accessed 05-24-2021.

[80] Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143-e152.

[81] Hodi FS, Ballinger M, Lyons B, Soria J-C, Nishino M, Tabernero J, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): Refining guidelines to assess the clinical benefit of cancer immunotherapy. Journal of Clinical Oncology. 2018;36(9):850-858.

[82] Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1-10.

[83] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703. doi: 10.1056/NEJMoa1304369.

[84] Hodi FS, Ballinger M, Lyons B, Soria J-C, Nishino M, Tabernero J, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): Refining guidelines to assess the clinical benefit of cancer immunotherapy. Journal of Clinical Oncology. 2018;36(9):850-858.

2023-02-04 PSP v2 template_22-194

Final Audit Report 2023-10-24

Created:	2023-10-24
By:	Mina Decola (decolam@upmc.edu)
Status:	Signed
Transaction ID:	CBJCHBCAABAAB-hxuQ9j2jr5k_G6RMjLYLCJbtVWdsRY

"2023-02-04 PSP v2 template_22-194" History

Document created by Mina Decola (decolam@upmc.edu)
2023-10-24 - 2:46:40 PM GMT- IP address: 128.147.28.12

Document emailed to saeeda3@upmc.edu for signature
2023-10-24 - 2:48:19 PM GMT

Email viewed by saeeda3@upmc.edu
2023-10-24 - 2:48:25 PM GMT- IP address: 4.154.11.187

saeeda3@upmc.edu authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2023-10-24 - 3:13:06 PM GMT

Signer saeeda3@upmc.edu entered name at signing as Anwaar Saeed
2023-10-24 - 3:13:56 PM GMT- IP address: 128.147.28.11

saeeda3@upmc.edu authenticated with Adobe Acrobat Sign.
Challenge: The user completed the signing ceremony by clicking on 'Click to Sign' button.
2023-10-24 - 3:13:56 PM GMT

Document e-signed by Anwaar Saeed (saeeda3@upmc.edu)
Signing reason: I approve this agreement.
Signature Date: 2023-10-24 - 3:13:58 PM GMT - Time Source: server- IP address: 128.147.28.11

Agreement completed.
2023-10-24 - 3:13:58 PM GMT