A PHASE 1B STUDY TO DETERMINE THE SAFETY AND TOLERABILITY AND CONFIRM THE DOSE OF CANAKINUMAB AND SPARTALIZUMAB IN COMBINATION WITH NAB-PACLITAXEL AND GEMCITABINE FOR PATIENTS WITH METASTATIC PANCREATIC CANCER

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GLOSSARY AND LIST OF ABBREVIATIONS

AE	Adverse Event
ALK	Anaplastic large cell lymphoma
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine Aminotransferase
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BUN	Blood urea nitrogen
CANTOS	the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study
Ca	Cancer; carcinoma
Ca	Calcium
CAPS	Cryopyrin Associated Periodic Syndromes
CA 19-9	Carbohydrate antigen 19-9
CBC	Complete blood count
CLIA	Clinical Laboratory Improvement Amendments
CR	Complete remission / complete response
CRP	C-reactive protein
CRF/eCRF	Case Report Form/electronic Case Report Forms
CRF	Chronic renal failure
CRO	Clinical Research Organization
CT	Computerized tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte Antigen-4
dL	Deciliter
DSMB	Data and Safety Monitoring Board
ECG	12-lead electrocardiogram (ECG)
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Collection tool
EDTA	Lavender top tubes

FMF	Familial Mediterranean Fever
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle-stimulating hormone
FWA	Federal-wide Assurance
GA	Gemcitabine + nab-paclitaxel
mGPS	modified Glasgow Prognostic Score
GCP	Good Clinical Practice
g	Gram (unit)
Hgb	Hemoglobin
HIDS	Hyperimmunoglobulin D Syndrome
IgG1/κ	Immunoglobulin G1/κ isotype subclass
ICF	Informed Consent Form
ICH GCP	International Conference on Harmonisation - Good Clinical Practice
IL-1	Interleukin-1 cytokine
IL-1α	Interleukin-1α cytokine
IL-1β	Interleukin-1β cytokine
IL-1R	Interleukin-1 Receptor
IL-1Ra	Interleukin-1 Receptor agonist
IL-6	Interleukin-6 cytokine
IB	Investigator Brochure
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LD	Longest diameter
LLN	lower limit of normal
mg	milligram
m^2	meter square
mm	millimeter
MRI	Magnetic Resonance Imaging
MKD	Mevalonate Kinase Deficiency

MMR-D	Mismatch repair deficient state
MDSCs	Myeloid-derived suppressor cells
NCI	National Cancer Institute
NGS	Next-generation sequencing
NIH	National Institutes of Health
ORR	Overall Response Rate
OS	Overall Survival
PanCAN	Pancreatic Cancer Action Network
PD	Progressive disease
PDAC	Pancreatic adenocarcinoma
PET	Positron Emission Tomography
PFS	Progression free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PO	Oral administration/by mouth
PR	Partial Response
PD-1	Programmed cell Death protein-1
PD-L1	Programmed cell Death ligand-1
PD-L2	Programmed cell Death ligand-2
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell / red blood count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SJIA	Systemic Juvenile Idiopathic Arthritis
SD	Stable disease
SOC	Standard of Care
SOP	Standard operating procedures
TLR	Toll-like receptors
TGFβ	Transforming growth factor-β
TRAPS	Tumor Necrosis Factor Receptor Associated Periodic Syndrome

TAMs	Tumor associated microphages
TAN	Tumor associated neutrophils
ULN	Upper limit of normal
WBC	White blood cell count
WCC	White cell count
WOCBP	Women of child-bearing potential

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1.0 INTRODUCTION

1.1 Background

1.1.1 Prevalence and outcomes in pancreatic adenocarcinoma

Pancreatic adenocarcinoma (PDAC) is the third leading cause of cancer death in the United States and is projected to become the fourth leading cause of cancer death by 2020 (Siegal et al. 2020, Amer Cancer Society Facts and Figures 2017). While the incidence and death rates from cancer are declining overall, these rates for pancreatic cancer are on the rise. Pancreatic cancer has the highest incidence-to-mortality ratio of any solid tumour (Bray et al. 2018). An estimated 56,770 people in the US will be diagnosed with pancreatic cancer in 2019, and 45,750 are expected to die from their disease (Howlander et al. 2017).

1.1.2 Prognosis and staging

The majority of patients (52%) are initially diagnosed with advanced disease that is inoperable. Median survival for untreated Stage IV disease (metastatic) is only 4.5 months with 5-year survival for these patients estimated at less than 3% (Amer. Cancer Society Facts and Figures 2017, Howlander et al. 2017, Malvezzi et al. 2013).

For 15 to 20% of newly diagnosed patients, long-term survival can be achieved with treatment by surgical resection followed by adjuvant therapy (Bray et al. 2018). However, recurrence is common, even in cases where optimal resection is achieved. For patients who present with locally advanced disease, treatment consists of chemotherapy with or without radiation. For patients with more advanced disease, including metastatic disease, treatment usually consists of investigational agents, chemotherapy alone, and/or supportive care.

1.1.3 Current treatment landscape

Gemcitabine monotherapy was considered a standard therapy in metastatic disease for many years but provided only a marginal improvement in survival. The addition of erlotinib or capecitabine to gemcitabine have shown small incremental improvements in survival (Moore et al. 2007). More recently, the use of combination therapies such as gemcitabine plus nab-paclitaxel (Von Hoff et al. 2013) and FOLFIRINOX regimen (5-fluouracil, leucovorin, oxaliplatin and irinotecan) (Conroy et al. 2011) have become standard-of-care for patients with PDAC; however, impact on

survival remains modest with median overall survival less than 12 months and the 2-year survival rate less than 7%.

1.1.4 Challenges in pancreatic cancer drug development

Drug development in pancreatic cancer has been challenged by a number of factors hindering pharmaceutical interest in this space. Advanced stage at diagnosis and high patient morbidity are major challenges in improving disease outcomes, specially within this naturally described older patient population.

The desmoplastic tumor microenvironment is known to limit drug penetration and contributes to chemoresistance and, more recently described, immunoresistance (Clinical Dev Success Rates 2006-2015, Mahadevan et al. 2007, Minchinton et al. 2006). Though critical histopathologic aspects of the disease are defined, its molecular underpinnings require further elucidation (Whatcott et al. 2015). Driver mutations in KRAS, p53 and p16 are widely characterized, but large-scale "druggable" targets that effect response remain unknown (Jones et al. 2008). This leads to challenges in identifying rationale and biologically driven therapeutic combinations needed to have a greater impact on patients with advanced disease.

1.2 Study overview

This study combines canakinumab (ACZ885), a high-affinity human anti-interleukin-1β (IL-1β) monoclonal antibody (mAb), and spartalizumab (PDR001), a mAb directed against human Programmed Death-1 (PD-1), with the chemotherapy combination of gemcitabine and nab-paclitaxel. This study will confirm for this 4-drug combination the tolerable doses, the acceptable safety profile, and the dose to be used for a Phase II combination treatment regimen. The description of the two investigational agents and their potential activity in pancreatic cancer are described in **Section 1.3** below.

We hypothesize that blockade of IL-1β and PD-1 will result in alterations in myeloid, lymphoid, and fibroblast subsets within the pancreatic cancer microenvironment. We further predict that circulating monocytes and neutrophils, whose production and mobilization from the bone marrow is augmented in PDAC patients, will decline upon treatment with IL-1β and PD-1 blockade.

This study offers a unique window to collect rich datasets on a small number of patients before and after perturbation of a biological pathway of interest. To this end, we propose to collect pre- and on treatment blood and tumor tissue from trial patients. These samples will be used to expand our knowledge of IL-1β signaling in human PDAC and will generate rich datasets for evaluation of biomarkers of response and understanding of immune regulatory pathways that may contribute to drug resistance. A full description of the samples collected in this study for this analysis is described in **Section 6.0** and is listed in the Schedule of Events Table in **Section 5.0**.

1.3 Overview of IL-1β

IL-1 (interleukin-1) is a pro-inflammatory cytokine secreted by a number of different cells, including monocytes and macrophages. The IL-1 gene family consists of cytokines IL-1α and IL-1β, and the natural receptor antagonist (IL-1Ra). Pro-IL-1α is functionally active and, because of a lack of the leader peptide, it remains in the cytoplasm. Pro-IL-1β is inactive and is secreted after cleavage by a specific intracellular protease abundant in hematopoietic cells. While IL-1β is most commonly found in circulation, detection of IL-1α is rare as it is released only in severe disease states as a consequence of cell death (Dinarello 1996, Garlanda et al 2013).

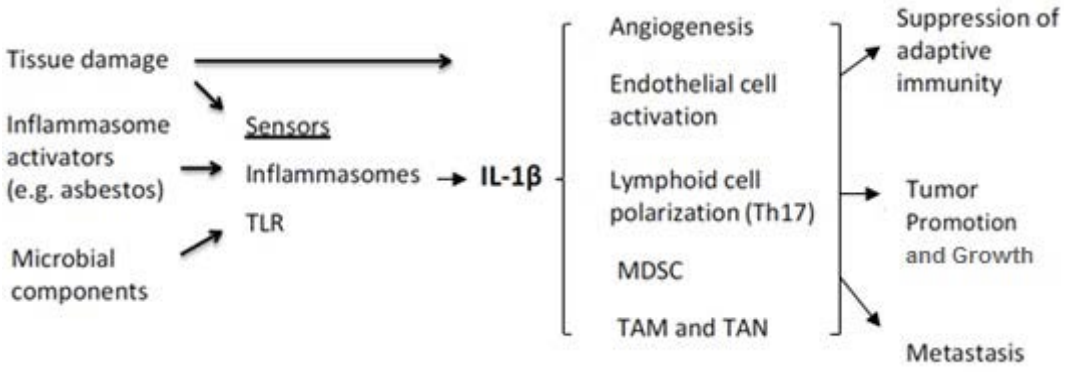
IL-1β binds the IL-1 receptor (IL-1R) inducing a conformational change that allows binding of the accessory protein (IL-1RAcP) to the IL-1β/IL-1R complex. Activated IL-1R, which is found on almost all nucleated cell types, induces intracellular signaling cascade involving MAPK, JNK, ERK and NF-κB that control gene expression of multiple transcription factors, growth factors and cytokines involved in cell functional activation and cell survival responses (Dinarello 1996, Arranz et al 2017). When released as part of inflammatory reaction, IL-1β produces a range of biological effects, including through the induction of other inflammatory mediators such as corticotrophin, platelet factor-4, prostaglandins, IL-6, and IL-8. Circulating IL-1β and IL-6 promote synthesis of C-reactive protein (CRP) in hepatocytes. CRP has a role in clearance of microorganisms and dead cells by the immune system and serves as a sensitive indicator of inflammation and IL-1β secretion. In addition, it is commonly used as a marker of IL-1β inhibition (Ridker 2016). IL-1β modulates hematopoietic stem cell function and contributes to bone marrow regeneration after myeloablation and transplantation. Inhibition of IL-1β signaling reduces bone marrow colony formation *in vivo* and suppresses cell cycle in bone marrow while reducing

numbers of leucocytes and platelets in peripheral blood (Zhang et al 2009). Being a pleiotropic cytokine, IL-1β has roles in other body systems, like bone and cartilage, where it facilitates bone resorption and cartilage destruction (Gowen et al 1983); it promotes vasodilation and leucocytes migration (Koch et al 1992), elevates body core temperature and increases cortisol levels (Garlanda et al 2013), and modulates sensitivity to pain via direct and indirect activation of pain nerve receptors (Sommer and Kress 2004). In addition, IL-1 orchestrates the differentiation and function of innate and adaptive lymphoid cells thus directly contributing to the immune response (Garlanda et al 2013).

1.3.1 IL-1β in cancer

IL-1 expression is elevated in human pancreatic, skin, and other cancers. Patients with IL-1 producing tumors have poor prognosis (Lewis et al 2006). Due to the pleiotropic nature of IL-1, there are several likely mechanisms by which IL-1 promotes tumor growth and metastasis (Figure 1). Preclinical data has demonstrated that IL-1β is involved in all phases of the malignant process, including tumorigenesis, tumor invasiveness, angiogenesis, progression, as well as in activation/suppression of anti-tumor immunity (Apte et al 2006, Becker 2006, Lewis et al 2006, Krelin et al 2007, Zitvogel et al 2013, Wu et al 2016). IL-1β is one of the most abundant and influential cytokines in the tumor microenvironment, and is produced by tumor cells, stromal cellular elements, and infiltrating leukocytes. Furthermore, IL-1β signaling induces a cascade of several pro-metastatic proteins such as matrix metalloproteinases and endothelial adhesion molecules as well as VEGF, transforming growth factor-β (TGFβ), and other chemokines and growth factors thus creating microenvironment that promotes tumor initiation, growth and progression. IL-1β plays major role in later stages of tumor progression by driving angiogenesis, promoting cancer "stemness" and "epithelial to mesenchymal transition" (Mora and Weigert 2016). In addition, IL-1β is capable of suppressing local anti-tumor immunity by promoting the infiltration of immunosuppressive cells into the tumor, including myeloid-derived suppressor cells (MDSCs) and tumor associated microphages (TAMs) (Guo et al 2016).

Figure 1. Involvement of IL-1 in cancer



Based on [Mantovani et al 2018].

Abbreviations: MDSC – myeloid-derived suppressor cells; TAM – tumor-associated macrophages; TAN - tumor-associated neutrophils; TLR – toll-like receptors

1.3.2 IL-1β in pancreatic cancer

IL-1β plays an important role in pancreatic cancer development and progression. High IL-1β concentration in serum and in the tumor correlate with tumor fibrosis, resistance to chemotherapy and poor survival (Maker et al 2011; Zhang et al 2018). In mouse models, IL-1β was shown to promote obesity-induced (a well-established risk factor for pancreatic cancer) pancreatic carcinogenesis and drug resistance (Incio et al 2016). In addition, NLRP3 pathway that controls IL-1β production was shown to support pancreatic cancer progression by increasing population of intratumoral immune-suppressive macrophages and Treg and thus promoting intratumoral immune tolerance (Daley et al 2017). Das et al showed that IL-1β expression is upregulated in patients-derived pancreatic cancer tumors relative to normal pancreatic tissue both in ductal epithelium and in the stroma. This group also showed in the tumor mice model that tumor-derived IL-1β promoted activation of dormant pancreatic stellate cells (important step for carcinogenesis and progression) and induced immunosuppressive tumor microenvironment through increase in immunosuppressive M2 macrophages, MDSC and other cell populations. Elimination of tumor IL-1β signaling was associated with increase in cytotoxic T-cells, attenuation of tumor growth which resulted improved survival of mice (Das et al 2020). All these support the role of IL-1β in pancreatic cancer and identify it as an attractive target for future development.

1.3.3 Anti-IL-1β therapy effect on cancer in CANTOS

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was a randomized, double blind, placebo-controlled phase III trial of 10,061 subjects who were stable after a myocardial infarction (Ridker et al 2017). The study was designed primarily to assess whether canakinumab, a human mAb targeting IL-1β, can prevent recurrent cardiovascular events among men and women who have a persistent proinflammatory response defined by the presence of high-sensitivity CRP (hs-CRP) ≥2 mg/L. Subjects were randomized to three canakinumab doses (50 mg, 150 mg, and 300 mg administered subcutaneously every 3 months), or placebo. The primary endpoint was reducing the risk of recurrent major cardiovascular events. All participants in CANTOS had to be free of previously diagnosed cancer at trial entry, and subjects were followed prospectively for incident AEs (including cancer, except for basal cell carcinoma) for up to 5 years. During the median follow-up of 3.7 years, canakinumab administration was associated with dose-dependent reductions in concentrations of hs-CRP and IL-6 vs placebo. Total cancer mortality (n=196) was lower in the pooled canakinumab group than in the placebo group, the incidence rate of cancer mortality per 100 person-years was 0.64 in the placebo group, 0.55 in the 50 mg group, 0.50 in the 150 mg, and 0.31 in the 300 mg group. The association of canakinumab with a dose-dependent reduction of the incidence cancer mortality rate was prominent with lung cancers. Incidence of fatal non-lung cancers showed a reduction with canakinumab, although the number of these cancers in general was low (Ridker et al 2017). Taken together, these hypothesis-generating data from pre-specified safety analysis of CANTOS suggest the possibility that inhibition of the IL-1β pathway may have a role in the treatment of cancers characterized by an activated IL-1β pathway.

1.3.4 Immunotherapy in pancreatic cancer

Immunotherapy and the use of immune checkpoint inhibitors such as anti-Programmed cell Death protein 1 (PD-1), PD ligand 1 (PDL-1) or cytotoxic T-lymphocyte Antigen 4 (CTLA-4), have been demonstrated to be effective agents for treatment of several key solid tumors. PD-1 is a critical co-inhibitory receptor that is upregulated on T cells upon activation (Freeman et al. 2008). It is also expressed by B cells, NK cells, dendritic cells, and activated monocytes. The ligands for PD-1, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), are expressed by macrophages and monocytes, and can be induced on numerous cell types (T cells, endothelial cells, and tumor cells) during inflammation (Keir et al. 2008). Engagement of PD-1 by its ligands

transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function (Pu et al. 2019). During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-1, to avoid detection by the adaptive immune system (Fox et al. 2011). Blockade of the PD-1 pathway has been shown to lead to both accumulation and increased activity of antitumor effector T cells and reduced numbers of regulatory T cells (Tregs) at the tumor site (Wang et al. 2009; Mangsbo et al. 2010; Mkrtichyan et al. 2011; Rosenblatt et al. 2011). Results of a phase I/II study of pembrolizumab with gemcitabine + nab-paclitaxel in PDAC showed 3 partial responses (27%) and 100% disease control rate among 11 evaluable chemotherapy naive patients with an overall survival of 15 months (Weiss et al. 2018).

Unfortunately, for the majority of patients, single agent immune checkpoint inhibitors have failed to improve survival in PDAC (Brahmer et al. 2012; Royal et al. 2010). A putative explanation is that PDACs have a low mutation burden and have an immune suppressive tumor microenvironment in comparison to other solid cancers, leading to a less immunogenic profile (Biankin et al. 2012). Strategies to overcome this problem include combinations with other checkpoint inhibitors, vaccines, or cytotoxic therapy. Nonetheless, there is a small subgroup of patients with a mismatch repair deficient (MMR-D) state, which represent approximately 1-3% of PDACs (Hu et al. 2018). These patients typically occur in the setting of Lynch syndrome in PDAC, where there is a rationale to use checkpoint inhibitors. These patients present with a significantly higher burden of mutations that may encode proteins recognized by the immune system. This hypothesis was validated in a phase II study of MMR proficient and deficient solid tumors, as significant response to pembrolizumab was seen only in MMR-D patients (Le et al. 2015). Of the 8 patients with metastatic pancreatic cancer enrolled, there were 5 responders (2 complete response, 3 partial response) for an overall response rate of 62%. Median PFS and OS had not been reached (Le et al. 2017). These results have recently led to the FDA approval of pembrolizumab in MMR-D patients with solid tumors agnostic of the specific underlying malignancy (please refer to the Keytruda USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125514Orig1s054lbl.pdf).

Adding chemotherapy to immunotherapy and canakinumab may contribute to increased efficacy of immunotherapy by improving immunogenicity of the tumor by causing tumor cells to emit

"danger" signal, by stimulating anticancer immune effector cells and suppressing immunosuppressive cells (Zitvogel et al. 2013, Zitvogel et al. 2011).

1.3.5 Inflammation in pancreatic cancer and rationale to combine with a IL-1β inhibitor

The presence of stromal desmoplasia is a characteristic of pancreatic cancer that leads to a unique tumor microenvironment that comprises of several cell types that includes fibroblasts that deposit fibronectin and collagen and inflammatory cells and macrophages that releases cytokines. These proinflammatory cytokines such as IL1β and IL-6 have been implicated for the adverse outcomes of pancreatic cancer (Lesina et al. 2011; Ebrahimi et al 2004). This systemic inflammatory response has been associated with a more pronounced symptom burden, including cachexia syndrome, and poorer survival outcomes (Tan CR et.al. 2014). Consequently, elevated levels of CRP, weight loss and low serum albumin concentrations (hypoalbuminemia) are recognized as poor prognostic markers which is thought to be part of the systemic inflammatory response (Salmiheimo A et al 2016). The modified Glasgow Prognostic Score (mGPS) is a risk-stratification tool that evaluates systemic inflammation by incorporating CRP and albumin values into a score to predict clinical outcomes in patients with cancer (McMillan DC. 2013) and is extensively reported in retrospective analyses of pancreatic cancer. Moreover, preclinical models have demonstrated that enhancing IL-1 signaling in pancreatic cancer cells leads to enhanced proliferation of the tumor cells.

It is therefore hypothesized that addition of a IL-1β inhibitor to the combination of inhibitors of immune checkpoint blockade and standard of care chemotherapy would lead to salutary effect on the efficacy of pancreatic cancer by altering the tumor microenvironment as described in **Section 1.3.2** to facilitate the activity of the antitumor immune cells and inhibition of the cancer. Recent preclinical data (Das et al 2020) demonstrated an improved tumor growth suppression when blocking antibodies against IL-1β and PD-1 were combined in the KPC pancreatic cancer mouse model, which is supportive of this hypothesis.

1.4 Overview of canakinumab

Canakinumab (ACZ885) is a high-affinity human anti-interleukin-1β (IL-1β) monoclonal antibody that belongs to the Immunoglobulin G1 (IgG1)/κ isotype subclass. Canakinumab is manufactured in a murine SP2/0 cell line. Currently canakinumab is approved and marketed as Ilaris® in more

than 70 countries for the treatment of IL-1β driven auto-inflammatory diseases: gouty arthritis, Still's disease, Cryopyrin Associated Periodic Syndromes (CAPS), Systemic Juvenile Idiopathic Arthritis (SJIA), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF). For additional details please refer to the canakinumab Investigator's Brochure**.**

1.4.1 Non-clinical experience with canakinumab

Canakinumab neutralizes the bioactivity of human IL-1β by preventing its binding to the IL-1β receptor. Canakinumab specifically binds human IL-1β with a Kd of 40-60 picomolar and has no cross-reactivity with other members of the IL-1 family (e.g. IL-1α IL-1Ra etc). Canakinumab is selective for human and marmoset IL-1β but does not bind to mouse, rat, rabbit, rhesus, or cynomolgus monkey IL-1β. An extensive program of toxicology studies was performed with canakinumab. The marmoset monkey was characterized as an appropriate model to predict human safety. Following IV or SC administration, canakinumab was well tolerated in marmosets at all dose levels without any relevant adverse findings. No anti-drug antibodies were detected. No significant treatment-related effects were observed with respect to male or female fertility in a mouse model using a murine analog of canakinumab. For further details, please refer to the canakinumab Investigator's Brochure.

1.4.2 Clinical experience with canakinumab in cancer

As of June 2019, approximately 13,111 patients were exposed to canakinumab in Novartis-sponsored clinical studies at various doses. Canakinumab is being studied in NSCLC in a number of settings: as single-agent adjuvant therapy (CACZ885T2301), in combination with chemotherapy and immunotherapy in the first line setting (CACZ885U2301 and CPDR001C2101), and in combination with chemotherapy in the second-line treatment setting (CACZ885V2301). These trials are ongoing.

In the open-label safety run-in part of a phase 3 study CACZ885U2301 (CANOPY-1), canakinumab (200 mg SC Q3W) was administered to 30 patients with Stage IIIB/C/IV NSCLC in combination with pembrolizumab and chemotherapy regimens: carboplatin+ pemetrexed (Cohort A; 10 patients), cisplatin+pemetrexed (Cohort B; 11 patients), or carboplatin+paclitaxel (Cohort C; 9 patients). Only 1 dose-limiting toxicity (DLT) was reported with these combinations (in

Cohort C only; hepatitis, considered to be related to pembrolizumab), and 12 SAEs reported in 8 patients, none considered to be related to canakinumab by the investigators. There was no common pattern for SAEs except for infections (two events of pneumonia in two patients, urinary tract infection, lower respiratory tract infection). The dose level review team meeting concluded that the regimen evaluated in all three cohorts in the safety run-in (canakinumab 200 mg Q3W) is tolerable and considered safe to be used in combination with pembrolizumab and chemotherapy in the randomized phase 3 part of the study. The phase 3 part of the study is ongoing.

Study CACZ885T2301 (CANOPY-A) is a phase III randomized double-blind placebo-controlled study exploring canakinumab (200 mg SC every three weeks, up to 18 cycles) as adjuvant therapy in patients with completely resected Stages II-IIIA/IIIB (T>5cmN2) NSCLC. The safety of study treatment in first 56 subjects has been reviewied by DMC that recommended to continue the study.

Study CACZ885T2301 (CANOPY-2) is a phase III randomized double-blind placebo-controlled study exploring canakinumab (200 mg SC every three weeks, up to 18 cycles) evaluating canakinumab (200 mg SC every three weeks) with docetaxel (75 mg/m^2 every three weeks) in patients with metastatic NSCLC previously treated with PD-1 or PD-L1 inhibitors and platinum-based chemotherapy. In the open-label safety run-in part of the study in 8 patients, one DLT of pneumococcoccal pneumonia was reported (considered by the investigator related to combination of canakinumab and docetaxel) in the DLT observation period of the first 42 days of study treatment and 6 SAEs in 3 patients. None of these SAEs were considered related to canakinumab per investigators assessment. The dose level review team concluded that the regimen evaluated in the safety run-in is tolerable and is safe to be used in combination with docetaxel in the randomized phase 3 part of the study. The randomized part of the study is ongoing.

For additional information on studies of canakinumab in patients with oncology indications (including studies in metastatic melanoma, triple-negative breast and colorectal cancer) refer to the last canakinumab Investigator's Brochure. Information on studies exploring canakinumab in combination with PD-1 inhibitor spartalizumab (PDR001) is provided in Section 1.5

1.5 Overview of spartalizumab

Spartalizumab (PDR001) is a mAb directed against human Programmed Death-1 (PD-1). PD-1 is a critical immune-checkpoint receptor that is expressed on CD4 and CD8 T cells upon activation.

Engagement of PD-1 by its ligands, PD-L1 and PD-L2, transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function. During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-1/PD-L1, to avoid detection by the adaptive immune system. Inhibitors of immunological checkpoints, including PD-1 and PD-L1 mAb's, have demonstrated significant antitumor activity in patients with various solid tumors.

1.5.1 Non-clinical experience with spartalizumab

Spartalizumab binds specifically and with high affinity to human PD-1 and enhances IL-2 production in lymphocyte stimulation assays *in vitro.* Spartalizumab does not cross react with rodent PD-1. However, toxicology studies performed in cynomolgus monkeys showed acceptable cross reactivity with monkey PD-1. Repeat administration of spartalizumab to cynomolgus monkeys was tolerated at all doses tested up to 100 mg/kg/week for 5 weeks in the GLP toxicology single-agent study. No drug-related changes in life, mortality, organ weight changes, or macroscopic findings were noted. For further details, please refer to the spartalizumab Investigator's Brochure.

1.5.2 Clinical experience with spartalizumab

As of 26-March-2020, a total of 1702 patients have received spartalizumab in Novartis-sponsored clinical studies as a single agent (562 patients), or in combination with other agents (1140 patients) in multiple tumor types. In these studies spartalizumab was administered every two weeks (Q2W), Q3W or every four weeks (Q4W).

Safety profiles of spartalizumab in clinical studies across different tumor types and regimen/dose groups were similar and consistent with and characteristic of other agents that inhibit the PD-1 receptor. Severe immune-related adverse events (irAEs) were rare and typically manageable with dose interruption and use of immunosuppressive treatment or other supportive therapy as clinically indicated; discontinuations due to irAEs were rare. For additional details on safety of spartalizumab please refer to the spartalizumab Investigator's Brochure**.**

Based on the available PK and safety data, two recommended phase two doses (RP2D) for spartalizumab single-agent have been declared: spartalizumab 400 mg Q4W or 300 mg spartalizumab Q3W.

Clinical experience of administering spartalizumab with chemotherapy or canakinumab include phase I/II studies CPDR001C2101, CPDR001X2103 and CPDR001J2201.

- In CPDR001C2101, spartalizumab (300 mg Q3W) was administered in combination with platinum-based regiments (gemcitabine + cisplatin; pemetrexed + cisplatin; paclitaxel + carboplatin) to patients with advanced and metastatic NSCLC. As of January 2019, a total of 33 adults were treated in this study. The safety profile observed was characterized mostly by toxicities attributed to chemotherapy regimens (e.g. bone marrow suppression, nausea, and asthenia/fatigue). AEs attributed to spartalizumab were manageable and in-line with the existing safety profile of spartalizumab. In addition, the study confirmed spartalizumab recommended dose for subsequent NSCLC trials as 300 mg IV Q3W.
- In CPDR001X2103, spartalizumab was administered to patients with advanced/metastatic colorectal cancer, triple-negative breast cancer or NSCLC in combinations with canakinumab or other immunomodulatory agents or tyrosine kinases inhibitors. One hundred and seven patients were treated with spartalizumab (400 mg Q4W) and canakinumab combination at doses 100 mg (6 patients), 300 mg (13 patients) and 600 mg (88 patients) (all Q8W SC). In the spartalizumab + canakinumab group, 104 patients (97.2 %) had permanently discontinued study treatment, 3 (2.8 %) due to an AE, 93 (86.9 %) due to progression of disease, 5 (4.7 %) due to physician decision and 3 (2.8 %) due to subject/guardian decision. The most frequent AEs (≥20%) in this group regardless of relationship to study drug, were dyspnoea (30.8%), decreased appetite (28.0%), fatigue and nausea (24.3% each) and vomiting (22.4%).
- In CPDR001J2201, spartalizumab was administered to patients with previously treated unresectable or metastatic melanoma in combinations with canakinumab or other immunomodulatory agents or small molecules. As of interim analysis data cutoff date of 07-Oct-2019, 36 patients have been administered spartalizumab 400 mg every 4 weeks and canakinumab 300 mg every 4 weeks. The most frequent AEs (>10%) in the spartalizumab + canakinumab group, regardless of relationship to study drug, were dyspnoea (17.1%), constipation (14.3%), abdominal pain (14.3%), decreased appetite (14.3%), anemia (14.3%), asthenia (14.3%), fatigue (11.4%) and weight decreased (11.4%). Grade >3 AEs reported more than once include anemia (three), fatigue, decreased appetite, tumour pain, lipase and amylase increased (twice each). The most frequent treatment-related AEs,

reported in at least 3 (>8%) subjects include pruritus (8.6%) and eosinophilia (8.6%). Treatment related events were grade >3 gastrointestinal pain, gastroesophageal reflux, lipase increased and peripheral ischaemia (once each). At the interim analysis with a cutoff date of 07-Oct-2019, spartalizumab + canakinumab arm crossed the efficacy futility threshold and will not be further expanded.

For additional details on CPDR001X2103, CPDR001C2101 and CPDR001J2201 please refer to the last edition of the spartalizumab Investigator's Brochure.

1.6 Rationale for the dosing regimen of canakinumab

As described in **Section 1.3.3**, administration of canakinumab (50 mg, 150 mg, and 300 mg SC every three months) in CANTOS resulted in a dose dependent decrease in hs-CRP and was associated with a reduction of lung cancer cumulative incidence and mortality, compared to placebo, in a dose-dependent manner and with no plateau observed at the highest dose administered (300 mg every 3 months), suggesting that higher doses of canakinumab could be associated with a greater decrease in risk of lung cancer incidence rate and mortality (Ridker et al 2017a). Importantly, the median hs-CRP at baseline in subjects who were subsequently diagnosed with cancer was higher compared to those patients who were not diagnosed with cancer (median 6.0 mg/L versus 4.2 mg/L). Moreover, for subjects with higher baseline hs-CRP, the proportion of subjects whose hs-CRP normalized to a post-treatment target level of 2.3 mg/L was less than in subjects with lower baseline hs-CRP. All these suggest that increasing the exposure of canakinumab beyond the maximal dose explored in CANTOS may result in an improved control of inflammation in subjects with higher baseline hs-CRP which may lead to a greater antitumor efficacy of canakinumab. Based on this assumption, a dose of canakinumab 200 mg administered SC every 3 weeks (Q3W), which results in higher steady-state exposure compared to the maximal exposure achieved in CANTOS, was selected for studies exploring anti-tumor effect of canakinumab in NSCLC (Section 1.4.2). In these studies canakinumab is being explored in patients with NSCLC as monotherapy, or in combination with chemotherapy, or with chemotherapy and PD-1 blockers. Rationale for this dose was based on the PK properties of canakinumab, the drug's ability to suppress hs-CRP for at least 1 month across a wide range of doses and indications, efficacy observed in the CANTOS study, safety considerations, and schedule of administration of

a standard of care backbone treatment (i.e. chemotherapy) in NSCLC. Ability of Q3W dosing schedule of canakinumab to suppress hs-CRP for at least 1 month was also demonstrated in two single-dose phase II studies with dose ranges of 0.03 to 10 mg/kg IV ([CACZ885A2213] in diabetes) and 25 to 300 mg SC ([CACZ885H2251] in gouty arthritis).

In this study, the backbone regimen of chemotherapy of gemcitabine and nab-paclitaxel is administered as 4-weeks cycles. To align with the dosing regimen of chemotherapy, the every four week regimen of 250 mg canakinumab SC as starting dose was selected. This decision was based on population PK analysis, where a 250 mg Q4W SC dosing schedule resulted in comparable PK at steady state to the 200 mg Q3W SC, the regimen used in NSCLC studies (Table 1-1). This dosing is also supported by a long, 26-days half-life of canakinumab.

Table 1-1: Steady State PK parameters of canakinumab

Dose Regimen	Cmin ug/mL (95% PI)	Cmax ug/mL (95% PI)	AUC0-tau ug*day/mL (95% PI)	Cave ug/mL (95% PI)
200 mg Q3W S.C.	22.44 (9.16, 50.31)	35.21 (16.03, 75.42)	AUC21-24week 625.67 (278.36, 1334.69)	29.79 (13.26, 63.56)
250 mg Q4W S.C.	18.28 (7.50, 43.51)	35.65 (16.31, 76.64)	AUC20-24week 771.81 (348.12, 1705.89)	27.56 (12.43, 60.92)

As described in the canakinumab Investigator's Brochure, safety of canakinumab doses equivalent to or higher than selected for this study dose (250 mg Q4W) has been confirmed in several completed and ongoing studies exploring canakinumab, including in combinations with chemotherapy and/or immunotherapy. In Study CACZ885A2204, canakinumab was given at a dose of 600 mg IV Q4W along with methotrexate. In studies CACZ885G2301 and CACZ885G2301E1 (extension of the former study), canakinumab was administered at a dose of 4 mg/kg up to maximum 300 mg SC Q4W to patients with systemic juvenile idiopathic arthritis for a total median duration of exposure of more than 2 years. As described in **Section 1.4.2**, canakinumab dose of 200 mg SC Q3W is being explored currently as monotherapy or in combination with chemotherapy or chemoimmunotherapy in multiple studies in NSCLC. In a

phase 1b study CADPT01A12101C, 600 mg Q8W canakinumab was adminsitered in combination with spartalizumab and LAG25 to patients with metastatic triple negative breast cancer.

In summary, based on evidence of efficacy from the CANTOS, PK and PD properties of canakinumab and the well-established safety profile of canakinumab at wide dose ranges, a dose of 250 mg SC Q4W has been selected for this study.

1.7 Rationale for the Study Regimen

As described in **Section 1.3.4**, checkpoint inhibitor monotherapy has not demonstrated outstanding efficacy in pancreatic cancer. This is possibly due to the immune suppressive tumor microenvironment with stromal infiltration of myeloid-derived suppressor cells (MDSC), tumor-associated macrophages and/or overall low mutational load. IL-1β plays an important role in pancreatic cancer development and progression via activation of dormant pancreatic stellate cells and increasing population of intratumoral immune-suppressive macrophages M2, Treg and MDSC **(Section 1.3.2)**. Recent preclinical data in pancreas cancer animal models showed improved tumor growth suppression with concurrent blockage of antibodies against IL-1β and PD-1 (Das et al 2020). Similarly, in an animal model of breast cancer, treatment with antibodies against IL-1β caused regression of the tumor due to decrease in intratumoral immunosuppressive macrophages and improvement of antitumor immunity via an increase in dendritic cell function and activated cytotoxic CD8+ lymphocytes (Kaplanov et al 2019). In the same model, where treatment with anti-PD-1 had moderate effect on tumor growth, combination of anti-IL1β and anti-PD-1 abrogated the tumors completely. Combined, this data provide a strong preclinical rationale for a clinical trial investigating a combination of anti-IL1β and anti-PD-1 agents in the treatment of advanced pancreatic cancer.

In this trial, anti-IL-1β antibody canakinumab will be combined with an anti-PD-1 antibody spartalizumab and chemotherapy regimen of gemcitabine and nab-paclitaxel. As described in **Section 1.1.3**, gemcitabine and nab-paclitaxel is a standard treatment regimen for metastatic pancreatic cancer. It is expected, that combining anti-IL1β and anti-PD-1 agents with standard chemotherapy will have more than an additive effect: chemotherapy may increase the amount of neoantigens in the tumor and contribute to improved response to immune checkpoint inhibition. As an evidence, it was shown in preclinical models of pancreatic cancer that combining

gemcitabine with either anti-PD-1 or anti-PD-L1 antibody enhanced tumor infiltration with CD8+ T cells and resulted in complete responses (uncommon in pancreatric cancer models) in the treated animals (Nomi et al 2007). In this trial, approved doses of gemcitabine and nab-paclitaxel will be used **(Section 4.1.1).**

Spartalizumab will be administered at the recommended dose for phase II of 400 mg Q4W (**Section 1.5.2**). As described in **Section 1.5.2,** the combination of chemotherapy and spartalizumab is feasible, with the safety profile mostly attributed to chemotherapy regimens; AEs attributed to spartalizumab were manageable and in-line with the existing safety profile of spartalizumab.

The first dose level explored of canakinumab will be 250 mg Q4W (**Section 1.6**), that is expected to be equivalent to the dose explored in multiple ongoing phase III clinical trials in NSCLC and phase I/II clinical trials in other cancers where no outstanding safety signals as a result of combination with chemotherapy administered in approved doses (and checkpoint inhibitors, where applicable) with canakinumab have been observed, and the combination was feasible and tolerable, no overlapping toxicities were observed (Canakinumab IB).

Canakinumab and spartalizumab are monoclonal antibodies and not metabolized by Cytochrome P450 (CYP450) enzymes or transported by P-glycoprotein (PgP) or related ABC membrane transporters. Therefore, the risk of DDI between canakinumab, spartalizumab and chemotherapy agents is expected to be low. However, as canakinumab is a cytokine modulator, the risk of DDI between canakinumab and chemotherapy agents that are metabolized by CYP enzymes (e.g. paclitaxel) cannot be completely excluded. In addition, when canakinumab was administered together with paclitaxel in the safety run-in of study CACZ885U2301, no additional toxicities or DLT were observed (**Section 1.4.2**). Therefore, the PK of chemotherapy agent that is metabolized by CYP enzymes (nab-paclitaxel) will also be characterized in this study to explore the DDI between canakinumab and spartalizumab and nab-paclitaxel, if any.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Overview

This is an open-label multi-center phase Ib study to confirm the recommended phase II/III dose of canakinumab and spartalizumab in combination with nab-paclitaxel and gemcitabine as first-line therapy for patients with metastatic pancreatic cancer.

Patients will be treated until disease progression, unacceptable toxicity, or until the patient or treating physician decides to stop treatment. Pharmacokinetic (PK) [redacted] samples will be collected at specific time points throughout treatment. Each treatment cycle is 4 weeks.

Please refer to **Table 2-1** below for the summary of the study objectives and endpoints.

Table 2-1: Study Objectives and Endpoint Summary

Objective	Endpoint	Analysis
Primary		Refer to Section 9.4
To confirm the recommended phase II/III dose regimen of canakinumab in combination with spartalizumab, gemcitabine and nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma.	The incidence of dose limiting toxicities (DLT) in the first 56 days (8 weeks) of dosing	
Secondary		Refer to Section 9.5
To determine the safety and tolerability of canakimumab in combination with spartalizumab, nab-paclitaxel and gemcitabine	Safety: Frequency and severity of (S)AEs, laboratory abnormalities, and ECGs Tolerabilty: Frequency of dose interruptions and dose reductions	
To assess the preliminary clinical anti-tumor activity of canakimumab in combination with spartalizumab, nab-paclitaxel and gemcitabine	Objective Response Rate (ORR), Duration of Response (DOR), Time to Response (TTR), Disease Control Rate (DCR), Progression-Free Survival (PFS) per RECIST 1.1 by investigator, and Overall Survival (OS) .	Refer to Section 9.6
To characterize the pharmacokinetics of canakinumab, spartalizumab and chemotherapy agent in combination regimen	PK concentrations and parameters of canakinumab, spartalizumab and chemotherapy	Refer to Section 9.6
[redacted]	[redacted]	[redacted]

2.2 Study Design

This is an open-label multi-center phase Ib study to confirm the recommended phase II/III dose of canakinumab and spartalizumab in combination with nab-paclitaxel and gemcitabine. The study will recruit patients with metastatic pancreatic adenocarcinoma treated in the first line setting. The starting dose level of canakinumab explored will be 250 mg Q4W ("starting dose level"). In case of unacceptable toxicity of the starting dose devel of canakinumab, the dose of canakinumab will be de-escalated to the "-1 dose level" administered as 250 mg Q8W, while other components of the combination stay at the same dose as the starting dose level (See **Table 4-2** in **Section 4.1.5**). Patients will be observed for DLTs for a minimum duration of 56 days (8 weeks). To achieve study objectives and to ensure the adequate number of DLT evaluable patients, the study will recruit approximately ten patients to have at least 6 evaluable patients per dose level of canakinumab. Additional approximately ten patients (to have at least 6 additional evaluable patients) may be enrolled at lower dose level in case a dose de-escalation is necessary.

Dose confirmation will be guided by an adaptive Bayesian logistic regression model (BLRM) based on any DLTs observed for two cycles of treatment (i.e. 56 days, or 8 weeks). The adaptive BLRM will be guided by the Escalation with Overdose Control (EWOC) principle to control the probability of DLT in future patients on the study. BLRM is a well-established and widely used method to estimate the recommended dose for expansion (RDE) or maximal tolerable dose (MTD) in clinical trials in patients with cancer with small sample size. The use of Bayesian response adaptive models for small datasets has been endorsed by academic publications (Babb et al. 1998, Neuenschwander et al. 2008, Neuenschwander et al. 2010, Natanegara et al. 2014), by the European Medicines Agency (Guideline on Clinical Trials in Small Populations, 2007) and it constitutes an important aspect of the FDA's Critical Path Initiative (Clinical Path White Paper, FDA, 2004).

The Bayesian analysis incorporates prior toxicity data of single agent and drugs combinations together with the currently available data to predict the probability of DLT and excessive toxicity of a dose level of interest.

The Bayesian method is be based on a Meta-Analytical-Combined (MAC) approach (Spiegelhalter 2004, Neuenschwander 2016) to combine all historical and concurrent data. Prior toxicity information included in the BLRM model was obtained from three studies with canakinumab as a single agent and combination of canakinumab and spartalizumab (PDR001X2101, ACZ885I2202, PRD001X2103) and from a phase I/II study of nab-paclitaxel + gemcitabine (Von Hoff D, et.al., 2011). Simulation was used to illustrate the recommendation from BLRM under a set of hypothetical scenarios with assumed number of evaulable patients and DLTs (See **Table 9-1**). Full details on the model, prior toxicity information from clinical trials in patients and assessment of DLT probability using the BLRM model are provided in **Section 9.4** and **Appendix B**.

The decisions on a recommended dose will be made by the Investigators and the Sponsor in a Safety Review meeting when at least 6 DLT evaluable patients per dose level will be observed for DLTs for a minimum duration of 56 days (8 weeks). Safety review will be based upon the review of all relevant data available including treatment tolerability and safety information together with the BLRM summaries of DLT probability, PK, PD, and preliminary activity information (if available) at the time of the meeting (**Section 4.1.5).**

3.0 STUDY POPULATION

The study population is treatment naïve metastatic pancreatic ductal adenocarcinoma patients.

3.1 Study Duration

Patients will be treated until disease progression per RECIST 1.1, unacceptable toxicity, or until the patient or treating physician decides to stop treatment.

All patients must be followed for safety up to 150 days after the last dose of spartalizumab or canakinumab, or 30 days after the last dose of the combination chemotherapy, whichever the later.

After the end of safety follow-up, patients will be followed for disease progression if discontinuation of treatment is due to reason other than progression, and for survival (via telephone call or onsite visit if a patient happens to be visiting the site) until the end of study

The study completion is defined as when the last patient has completed the study treatment, safety follow up, and completed survival follow up period up to 1 year from first treatment, whichever is later or in the event of an early study termination decision, the date of that decision.

3.2 Inclusion Criteria

A patient will be eligible to participate in this study if all of the inclusion criteria below are met:

- Age ≥ 18 years at the time of informed consent
- Histologically or cytologically confirmed pancreatic ductal adenocarcinoma (PDAC) (determined by a local laboratory) with metastatic spread of disease (adenosquamous is also allowed).
- Patients must have not received previous anti-cancer therapy for the treatment of metastatic pancreatic ductal adenocarcinoma.
- Patients who received previous neo-/adjuvant systemic therapy for non-metastatic PDAC ≥12 months from the last treatment to study enrollment date are allowed unless this therapy included immunotherapy and/or IL-1 inhibitors.
- Radiographically measurable disease of at least one site by computed tomography (CT) scan (or magnetic resonance imaging, if allergic to CT contrast media) as defined by Response Evaluation Criteria In Solid Tumors (RECIST 1.1). Primary lesion is allowed as long as it is measurable (per RECIST 1.1) and has not been previously irradiated. Imaging results must be obtained within the 28-day screening window.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
- Adequate organ function (laboratory results must be obtained within the 28-day screening window)
    - Absolute neutrophil count ≥ 1500/mm3
    - Hemoglobin ≥ 9 g/dL
    - Platelets ≥ 100,000/mm3
    - Serum creatinine ≤ 1.5 x upper limit normal (ULN), or calculated creatinine clearance ≥ 60 mL/min (Cockcroft Gault)
    - Albumin ≥ 3.0 g/dL

  - Aspartate aminotransferase (AST) serum glutamic oxaloacetic transaminase (SGOT) and/or alanine aminotransferase (ALT) serum glutamic pyruvic transaminase (SGPT) ≤ 3.0 x ULN (≤ 5 x ULN in presence of liver metastasis).
    In patients with elevated ALT or AST, the values must be stable for at least 2 weeks and with no evidence of biliary obstruction on imaging
  - Total bilirubin ≤ 1.5 X ULN
  - INR ≤ 1.5 x ULN
- Consent to provide protocol-mandated tissue and blood samples for diagnostic, PK, and research purposes
- Able to adhere to study visit schedule and other protocol requirements

3.3 Exclusion Criteria

A patient will not be eligible to participate in this study if any of the following criteria below are met:

- Diagnosis of pancreatic neuroendocrine carcinoma or pancreatic acinar cell carcinoma
- Previous immunotherapy (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).
- Known microsatellite instability-high (MSI-H) or mismatch repair-deficient pancreatic cancer
- Prior treatment with canakinumab or drugs of a similar mechanism of action (IL-1 inhibitor).
- History of known hypersensitivity to any of the drugs used in this study or any of their excipients, or patient has contraindication to any of the study drugs as outlined in the local prescribing information (e.g. United States Prescribing Information [USPI])
- Active autoimmune disease that has required systemic treatment in the past 2 years prior to enrollment i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs. Control of the disorder with replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is permitted.

- Patient with suspected or proven immunocompromised state or infections, including:
  - Evidence of active or latent tuberculosis (TB) as determined by locally approved screening methods. If the results of the screening per local treatment guidelines or clinical practice require treatment, then the patient is not eligible.
  - Chronic or active hepatitis B or C
  - Known history of testing positive for Human Immunodeficiency Virus (HIV) infections.
  - Any other medical condition (such as active infection, treated or untreated), which in the opinion of the investigator places the patient at an unacceptable risk for participation in immunomodulatory therapy.

  Note: Patients with localized condition unlikely to lead to a systemic infection e.g. chronic nail fungal infection are eligible.
- Allogeneic bone marrow or solid organ transplant
- Treatment with any immune modulating agent in doses with systemic effects e.g.:
  - Systemic treatment with prednisone > 10 mg (or equivalent) for >14 days within 4 weeks prior to the first dose of study treatment.
  - Equivalent dose of methotrexate > 15 mg weekly
  - Patient receiving any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, or tocilizumab).
  - **Note:** Daily glucocorticoid-replacement for conditions such as adrenal or pituitary insufficiency is allowed.
  - **Note:** Topical, inhaled, or local steroid use in doses that are not considered to cause systemic effects are permitted (based on investigator's discretion and consultation with the Medical Monitor if needed).
- Patient has concurrent malignancy other than the disease under investigation, with exception of malignancy that was treated curatively and has not recurred within 2 years prior to the date of screening. Fully resected basal or squamous cell skin cancers, and any carcinoma *in situ* are eligible.
- Uncontrolled or severe cardiac disease (history of unstable angina, myocardial infarction, coronary stenting, or bypass surgery within the prior 6 months), symptomatic congestive

heart failure, serious uncontrolled cardiac arrhythmia [including atrial flutter/fibrillation], requirement for inotropic support or use of devices for cardiac conditions [pacemakers/defibrillators]), uncontrolled hypertension defined by a systolic blood pressure =>160 mg and/or diastolic blood pressure =>100 mg Hg

- Pre-existing peripheral neuropathy > Grade 1 (CTCAE V 5.0)
- Receipt of live vaccines within 3 months prior to the first dose of study treatment or while on active treatment within the trial (examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral vaccine). Seasonal influenza vaccines for injection are generally killed virus vaccines and are permitted. However, intranasal influenza vaccines (e.g. Flu-mist) are live attenuated vaccines and are not permitted.
- Patient has had major surgery within 14 days prior to enrollment
- Patient has symptomatic brain metastases, or brain metastases that require directed therapy (such as focal radiotherapy or surgery). Patients with treated brain metastases have to be neurologically stable and not using systemic steroids for at least 4 weeks prior to the study drug administration.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are willing to use highly effective methods of contraception during treatment with study drugs (canakinumab, spartalizumab, gemcitabine and nab-paclitaxel).
- *Highly effective contraception methods are required while on treatment and for 150 days after stopping spartalizumab.* No contraception is required after treatment with canakinumab is stopped. Contraception use after chemotherapy is stopped should be followed per the local drug label requirements.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had bilateral surgical oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before

taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Note: Women of non-childbearing potential is defined as women who are physiologically and/or anatomically incapable of becoming pregnant, as now further described:

- They are post-menopausal as evidenced by 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate history of vasomotor symptoms).
- They have had bilateral surgical oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

Note: Sexually active male patients and their partners who are women of childbearing potential should follow the contraception recommendations and any other precautionary measures as required by the local prescribing information for the SOC anti-cancer.

- Any significant medical condition, laboratory abnormality or psychiatric condition that would constitute unacceptable safety risks to the patients, contraindicate patient participation in the clinical study, limit the patient's ability to comply with study requirements, or compromise patient's compliance with the protocol and all requirements of the study as stated in the Informed Consent Form. Significant medical conditions include but are not limited to known history or current interstitial lung disease or non-infectious pneumonitis, medical history or current diagnosis of myocarditis, chronic active hepatitis, liver cirrhosis or any other

significant liver disease with moderate to severe hepatic impairment (Child-Pugh B or C), serious non-healing wound/ulcer/bone fracture, uncompensated/symptomatic hypothyroidism, or requirement for hemodialysis or peritoneal dialysis.

- Unwillingness or unable to comply with all requirement of the study as stated in the Informed Consent Form

4.0 STUDY TREATMENT AND DOSE MODIFICATION

4.1 Administration and Dosing

For this study, the investigational drugs (INDs) are spartalizumab (PDR001) and canakinumab (ACZ885). The study treatment is defined as spartalizumab with canakinumab in combination with gemcitabine and nab-paclitaxel. Below are details of the dosing regimen and administration instructions for the four-drug combination. On days of combination therapy canakinumab will be administered first, followed by 30 min observation period. After the end of the observation period, spartalizumab will be administered. After spartalizumab infusion, patient**s** should be closely observed for potential infusion-related reactions for at least 2 hours after the first two spartalizumab infusions (before administration of chemotherapy). The same may apply for the subsequent spartalizumab infusions if medically indicated. Observation for a specific period of time after for the 3rd and subsequent infusions is not necessary (unless medically indicated) but subjects should be provided instructions to notify the study personnel if symptoms of infusion reaction occur after any spartlizumab infusion. Any pre-medication for the chemotherapies should be administered at least 30 minutes after the end of the infusion of spartalizumab (for additional detials see **Section 5.4**).

For the non-investigational drugs (gemcitabine and nab-paclitaxel), prescribing information and local institutional practice are to be followed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the appropriate eCRF page.

4.1.1 Gemcitabine and nab-paclitaxel

Gemcitabine and nab-paclitaxel are FDA approved therapies for metastatic pancreatic cancer and will be supplied or obtained according to local clinical study agreements and in accordance with local guidelines. Additional information may be included on the label as needed or applicable.

The following are recommended parameters for infusion timing and sequence of gemcitabine and nab-paclitaxel, although institutional variation in the administration of the regimen are permitted as long as drug dosing and modification guidelines are followed.

- Nab-paclitaxel is infused at an initial dose of 125 mg/m^2 over 30-40 min on days 1, 8, 15 of each 28-day cycle.
- Gemcitabine is infused at an initial dose of 1000 mg/m^2 over 30 min, immediately after completion of nab-paclitaxel infusion, on days 1, 8, 15 of each 28-day cycle

Doses should be re-adjusted if the patient's BSA changes by +/- ≥10%. If the patient's BSA changes by <10%, no adjustment is necessary unless the site has a standard procedure to adjust doses based upon current BSA according to institutional guidelines.

Specifics on dosing and toxicity modifications for gemcitabine and nab-paclitaxel can be found in their Package Inserts **(Appendix A).**

4.1.2 Canakinumab

Canakinumab is provided as ready-to use pre-filled syringes to be administered by study center personnel. Two strengths of solution for injection will be supplied:

- Canakinumab 50 mg/ 0.5 mL
- Canakinumab 200 mg/ 1.33 mL

The starting dose of canakinumab will be 250 mg, administer subcutaneously (SC) in the abdomen, upper outer thigh or upper outer arm once every 4 weeks. To administer a target dose of canakinumab of 250 mg, two separate subcutaneous injections (one of 200 mg and one of 50 mg) must be administered to the patient at a visit. Pre-medication to prevent injection reaction before the first administration of canakinumab is not recommended. For additional guidance refer to canakinumab (ACZ885) Instructions for Use/ and to the canakinumab Investigators Brochure.

4.1.3 Spartalizumab

Spartalizumab will be supplied in a liquid solution. The starting dose of spartalizumab is 400 mg (prepared by reconstituting four vials with sterile water for injection (SWFI) and diluted in a 5% dextrose infusion bag before use) administered via intravenous infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 4 weeks. Infusion of spartalizumab must take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available during the period of drug administration.

Patients should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever, and vital signs monitored more frequently if clinically indicated, during and for at least 2 hours after the first two spartalizumab infusions (before administration of chemotherapy). Observation for a specified period of time for the 3rd and subsequent infusions is not necessary (unless medically indicated) but subjects should be provided instructions to notify the study personnel if symptoms of infusion reaction occur after any spartalizumab infusion. Patients should not receive pre-medication to prevent infusion reaction before the first infusion of study treatment. If a patient experiences an infusion reaction, he/she may receive premedication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the investigator. Please refer to **Table 4-15** below for additional details. The same may apply for the subsequent spartalizumab infusions if medically indicated.

For additional guidance refer to Spartalizumab (PDR001) Pharmacy Manual and to the spartalizumab Investigator's Brochure**.**

4.1.4 Initial Dosing Schedule

Table 4-1. Initial Dose and Treatment Schedule

Study treatments	**Pharmaceutical form and route of administration**	**Strength**	**Starting Frequency and/or Regimen**	**Dose Administered**
Spartalizumab (PDR001)	Concentrate for solution for IV infusion	4 x 100 mg vials	Day 1 of each 28-day cycle	400 mg

Study treatments	Pharmaceutical form and route of administration	Strength	Starting Frequency and/or Regimen	Dose Administered
Canakinumab (ACZ885)	Solution for s.c. injection in prefilled syringe	200 mg/1.33 mL AND 1 x 50 mg/0.5 mL	Day 1 of each 28-day cycle	250 mg
Gemcitabine	IV		Days 1, 8, 15 of each 28-day cycle	1000 mg/m^2
Nab-paclitaxel	IV		Days 1, 8, 15 of each 28-day cycle	125 mg/m2

4.1.5 Dose Recommendation Guideline for Study Cohort

Approximately ten patients will be enrolled initially to have at least 6 evaluable patients per dose level (additional patients maybe enrolled as needed in order to have 6 evaluable patients). The evaluable criteria are defined in Dose Determining Set (DDS) , and the evaluable patients will be included in the Dose-Determining set. Patients must complete a minimum of 56 days (8 weeks) of dosing of study treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first 56 days of study treatment to be considered evaluable for recommended dose decisions (Please refer to **Section 9.1.3** for further details). Additional approximately ten patients (to have at least 6 additional evaluable patients) may be enrolled at lower dose level in case a dose de-escalation is necessary.

Table 4-1 defines the starting dose level. In case of unaccepatable toxicility of the starting dose devel, the enrollment to the current dose level will be stopped and a lower dose (-1 dose level) will be used. At the -1 dose level, canakinumab is adminstered at 250 mg s.c Q8W while other components of the combination stay the same as the starting dose level. **Table 4-2** below describes the starting dose and the -1 dose level in case the starting dose has unacceptable toxicity.

Table 4-2: Provisional dose levels for the canakimumab with fixed dosage of spartalizumab, Gemcitabine and nab-paclitaxel

Dose level	**Proposed dose** of canakinumab
1 (starting dose)	250 mg s.c. Q4W Canakinumab
*-1**	250 mg s.c Q8W Canakinumab

Spartlizumab: 400 mg s.c. Q4W; Gemcitabine: 1000 mg/m2+ nab-paclitaxel 125 mg/m2 (on day 1, 8, and 15 of every cycle).

**Dose level -1 represents the treatment dose for patients requiring a dose reduction from the starting dose level.*

As the starting dose is the highest provisional dose level, this dose may be declared the recommended dose. This could occur if a minimum of 6 evaluable patients has been treated and deemed evaluable at this dose, and the dose is considered safe by BLRM and it is the dose recommended for patients after the review of all clinical databy investigators and Novartis. At the Dose Confirmation Meeting the Safety Review Team (composed at least of a clinician, patient safety representative and biostatistician) would review all available toxicity information (including adverse events and laboratory abnormalities that are not DLTs) and the available PK information.

The decision on dose tolerability will be based on all relevant data from the ongoing study and a review of safety data from the first 8 weeks. A Bayesian logistic regression model (BLRM) for combinations using the escalation with overdose control (EWOC) criterion to evaluate the risk of DLT will guide the decision. The details of the BLRM are provided in **Section 9.4** and **Appendix B**. The adaptive Bayesian methodology provides an estimate of all dose levels of the combination and incorporates all DLT information at all dose levels for this estimation. To limit the patient exposure to DLT, if 2 or more patients in the starting dose level (or -1 dose level) experienced a DLT, Novartis should be notified and the BLRM will be updated with this new information. Additional patients may be continued into the current dose cohort only if the combination still meets the EWOC criteria and as agreed by Investigators and Novartis personnel.

4.1.5.1 Definitions of Dose Limiting Toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event (AE) or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 8 weeks of study treatment and at least possibly related to

the study drugs. The investigator must notify the sponsor immediately (within 24 hours of the treating physician's knowledge) of any unexpected CTCAE grade ≥ 3 AEs or laboratory abnormalities. NCI CTCAE v5.0 will be used for all grading.

Table 4-3: Criteria for Defining Dose-Limiting Toxicities

TOXICITY	**DLT CRITERIA** (NCI CTCAE v5.0 will be used for grading)
Cardiac	• Grade ≥ 3 cardiac events
Cutaneous reactions	• Grade ≥ 3
Gastrointestinal	• Grade 3 nausea and vomiting for > 3 days despite optimal anti-emetic therapy • Grade 3 diarrhea for > 5 days despite optimal antidiarrheal treatment (which could include steroids) • Grade 4 vomiting or diarrhea
Hematological	• Grade 4 neutropenia for > 7 consecutive days, or grade 4 febrile neutropenia • Grade 4 anemia • Grade 3 thrombocytopenia with clinically significant bleeding (i.e. life threatening and invasive intervention indicated) regardless of duration or requirement for transfusion, or grade 4 thrombocytopenia (<25,000/mm3)
Hepatobiliary	• Grade 4 bilirubin elevation • For patients with normal baseline AST, ALT and bilirubin values: - AST or ALT > 8.0 × ULN; OR - AST or ALT > 5.0 × ULN for more than 2 weeks; OR - AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN without evidence of cholestasis • For patients with abnormal baseline AST or ALT or abnormal baseline bilirubin value: - ALT or AST > 3.0 x baseline value; OR - ALT or AST > 3.0 x baseline (or > 8.0 x ULN), whichever is lower, combined with total bilirubin > 2.0 x baseline and > 2.0 x ULN without evidence of cholestasis
Immune-related toxicities **(except pneumonitis)**	• Grade 3 immune-related toxicities that persist > 14 days with same severity despite treatment with corticosteroids. • Grade 4 immune related toxicities of any duration • Grade ≥ 3 infusion related reaction
Infections	• Grade 4
Hypertension	• Grade 3 hypertension if it persists > 7 days despite optimal anti-hypertensive treatment • Grade 4 hypertension of any duration

Pancreatitis	• Symptomatic serum amylase or lipase elevation, medical intervention required • Grade ≥ 3 pancreatitis
Peripheral neuropathy	• Grade ≥ 3
Pneumonitis	• Grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids • Grade ≥ 3 pneumonitis of any duration
Other AEs	Other clinically significant AEs: • grade ≥ 3 AEs that have not been previously identified for canakinumab or spartalizumab or grade 4 AEs that have not been previously identified for gemcitabine and nab-paclitaxel • grade ≥ 3 AEs that are known to occur with canakinumab or spartalizumab, or grade 4 AEs that are known to occur with gemcitabine and nab-paclitaxel, but cannot be controlled using the recommended product-specific management guidelines (per local prescribing information), or leads to <50% of planned exposure of study medications • Other clinically-significant AEs, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 8 weeks should be considered as DLTs by the Investigators and the sponsor, even if not grade 3 or higher

Events which will NOT be considered as DLT for the purpose of this protocol:

- Clinically insignificant laboratory values ≤ grade 2.
- For electrolyte abnormalities ≥ grade 3, the maximum allowable time limit for correction to ≤ grade 1 is 72 hours.

4.2 Dose Modifications

4.2.1 Dose Modifications of Gemcitabine and Nab-Paclitaxel

Toxicities for gemcitabine and nab-paclitaxel are graded based on Tables 4-4 and 4-5 below (according to CTCAE v5.0). Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Please refer to the gemcitabine and nab-paclitaxel package inserts **(Appendix A)**.

If one or both of the chemotherapy medications are held due to chemotherapy-related toxicity, the other study medications canakinumab and spartalizumab can be given until disease progression per RECIST 1.1, intolerable toxicity, or any other conditions specified in Section 5.4.2.

Doses will be reduced, one level at a time, for hematologic and non-hematological toxicities.

- Two levels of dose modifications are permitted, for each drug, according to the criteria below (**Table 4-4**). If a toxicity requiring dose modification occurs following the second dose reduction of either drug, additional dose reductions are not permitted. However, further treatment should be discussed with the Medical Monitor.
- Dose re-escalation is not permitted.

Table 4-4. Dose Modifications of nab-paclitaxel and Gemcitabine

Dose Level	nab-paclitaxel Dose (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
First dose reduction	100	800
Second dose reduction	75	600

If chemotherapy treatment is held for > 3 consecutive weeks for a toxicity thought to be related to gemcitabine and nab-paclitaxel, patients should permanently discontinue both gemcitabine and nab-paclitaxel. However, if a patient is clinically benefitting at the end of a 3-week hold, treating physicians may contact the Medical Monitor to potentially extend chemotherapy treatment.

Patients who discontinue study treatment should proceed with further clinical treatment at the discretion of the treating physician. After the discontinuation of treatment, all patients will continue to remain on study and will be followed for survival, subsequent treatment regimens, and outcome assessment.

In all situations where toxicity justifies discontinuation of an agent, only the individual offending agent should be removed from the regimen and treatment should continue otherwise per protocol.

Determination regarding the need for dose modifications of gemcitabine and/or nab-paclitaxel should be made based on the following guidelines. Questions regarding adverse reactions, dose modifications, or toxicity management should be directed to the Medical Monitor.

Table 4-5. Dose Modifications of nab-paclitaxel and Gemcitabine for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	nab-paclitaxel Dose	Gemcitabine Dose
Day 1	≥ 1,500	AND	≥ 100,000	Treat on time at current dose levels	
	< 1,500	OR	< 100,000	Delay doses until recovery	
Day 8	≥ 1,000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 to < 1,000	OR	≥ 50,000 to < 75,000	Reduce by one dose level	
	< 500	OR	< 50,000	Withhold doses	
Day 15: If Day 8 doses were given without modification:					
Day 15	≥ 1,000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 to < 1,000	OR	≥ 50,000 to < 75,000	Reduce by one dose level from Day 8	
	< 500	OR	< 50,000	Withhold doses	
Day 15: If Day 8 doses were reduced:					
Day 15	≥ 1,000	AND	≥ 75,000	Treat with same doses as Day 8	
	≥ 500 to < 1,000	OR	≥ 50,000 to < 75,000	Reduce by one dose level from dose of Day 8	
	< 500	OR	< 50,000	Withhold doses	
Day 15: If Day 8 doses were withheld:					
Day 15	≥ 1,000	AND	≥ 75,000	Reduce by one dose level from dose of Day 8	
	≥ 500 to < 1,000	OR	≥ 50,000 to < 75,000	Reduce by two dose levels from dose of Day 8	
	< 500	OR	< 50,000	Withhold doses	

The use of granulocyte colony stimulating factors is permitted per institutional/national guidelines for the treatment or neutropenic fever or infections or in the prevention of febrile neutropenia.

Prophylactic use of granulocyte colony stimulating factors is permitted for high risk patients. If hematologic toxicity is restricted to platelet counts alone, dose modification of gemcitabine and nab-paclitaxel could be considered after discussion with the Medical Monitor.

Other hematologic toxicities do not require dose modification. However, red blood cell transfusions should be considered for hemoglobin < 7 g/dL or significant symptoms of anemia or per institutional guidelines.

Table 4-6. Dose Modifications of nab-paclitaxel and Gemcitabine for Other Clinically Significant Non-Hematologic* Toxicities

Adverse Drug Reaction	nab-paclitaxel Dose	Gemcitabine Dose
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC is ≥ 1500/mm^3; resume at next lower dose level for both agents	
Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improvement to ≤ Grade 1; Resume at next lower dose level	Treat with same dose
Cutaneous Toxicity Grade 2 or 3	Reduce doses to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; Resume at next lower dose level	

For all other of ≥ Grade 3 non-hematologic toxicities (*except nausea, vomiting, alopecia and pulmonary embolism):

- Withhold dose of either or both agent(s) until improvement to ≤ Grade 1
- Resume at next lower dose level

4.2.2 Dose modification and dose interruption of spartalizumab and canakinumab

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions are permitted in order to allow the patient to continue the study treatment. Dose interruption for spartalizumab and canakinumab includes delaying or withholding the treatment for any reason as well as an interruption of treatment during an infusion. For dose modifications of canakinumab

please see **Section 4.2.3** and **Tables 4-6 and 4-7** below. For dose modifications of spartalizumab please see **Sections 4.2.4 and 4.2.5** below.

If canakinumab is interrupted for more than 12 weeks or a subject misses more than two doses of canakinumab due to canakinumab-related toxicities (whichever is longer), canakinumab must be permanently discontinued. If the chemotherapy drugs need to be interrupted due to chemotherapy-related toxicity, canakinumab and spartalizumab can be continued if a patient is clinically benefitting from the treatment until disease progression per RECIST 1.1, intolerable toxicity, or any other conditions specified in **Section 5.4.2**.

If spartalizumab and chemotherapy drugs are permanently discontinued due to toxicity, the investigator can continue canakinumab until disease progression per RECIST 1.1 or any other conditions for treatment discontinuation as defined **Section 5.4.2**, whichever is earlier.

4.2.3 Dose Modification Guidelines for Canakinumab

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions are permitted in order to allow patients to continue the study treatment. There are no canakinumab dose reductions allowed. However, if required, dose regimen modification by adjusting the interval between doses can be allowed (from Q4W to Q8W).

Table 4-7. Criteria for Dose Interruption and Re-Initiation of Canakinumab for Adverse Events at least possibly related to canakinumab treatment

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab**
General guidance for adverse drug reaction (to be followed whenever no other specific guidance is described in this table)	
Grade 1/ Grade 2	Maintain dose level
Grade 3	Interrupt dose until resolved to ≤ grade 2, then increase canakinumab dosing interval[a]
Grade 4	Permanently discontinue canakinumab
Exceptions to the above general guidance[b]	
Infections	

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab**
Grade 2	Maintain dose level. For an infection that requires medical intervention, if it persists for >14 days despite appropriate treatment, then interrupt dose until infection resolves to <grade 2; then resume treatment and maintain dose
Grade 3	Omit dose until resolved to <grade 2, then maintain dose and schedule
Neutropenia (ANC)	
Grade 2	Interrupt until ≤ grade 1, then maintain dose
Grade 3	Interrupt until resolved to ≤ grade 1, then: • For subjects receiving chemotherapy, maintain canakinumab dosing interval, only delay canakinumab dose to match chemotherapy dosing • After permanent discontinuation of chemotherapy, increase canakinumab dosing interval[a]
Grade 4	• If ≤7 consecutive days, omit dose until resolved to ≤ grade 1, then maintain dose and schedule • If >7 consecutive days, permanently discontinue canakinumab
Febrile neutropenia	
Grade 3	Omit dose until resolved, then maintain dose and schedule
Grade 4	Permanently discontinue canakinumab
Thrombocytopenia	
Grade 3	Interrupt dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 - increase canakinumab dosing interval[a] • With clinically significant bleeding (i.e. life threatening or invasive intervention indicated) - increase canakinumab dosing interval[a]
Serum creatinine	
Grade 2	• Maintain dose level; monitor other renal functions (e.g. creatinine clearance, glomerular filtration rate/GFR, blood urea nitrogen/BUN, urinalysis). • If elevated creatinine level persists at grade 2 for >14 days despite appropriate management for other underlying contributing factors, interrupt the dose until resolved to <grade 2 or baseline, then resume treatment and increase dosing interval of canakinumab
Grade 3	• 1st occurrence: Omit dose until resolved to ≤ grade 1 or baseline, then maintain dose and schedule • 2nd occurrence: Permanently discontinue treatment
Isolated total bilirubin elevation*	
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation (e.g. disease progression [imaging]). Treat alternative causes according to local institutional guidelines
Grade 2: > 1.5 - 3.0 x ULN	• Maintain treatment. • Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ grade 1 or to baseline • If isolated bilirubin remains stable at grade 2, continue treatment with canakinumab at the same dosing interval

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab**
Grade 3: >3.0 – 10 ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, monitor LFTs weekly until resolution to ≤ grade 1 or to baseline. If resolved in ≤ 14 days, maintain dose regimen; if not resolved in 14 days, permanently discontinue canakinumab. (Please see foot-note regarding alternative cause/s of bilirubin elevation).
Grade 4: > 10 x ULN	See footnote* - otherwise permanently discontinue treatment If alternative cause/s is identified and managed, and bilirubin resolves to ≤ grade 1 or to baseline, resume canakinumab at the same dose regimen.
* An isolated bilirubin elevation is not typical for DILI. Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation should therefore, be ruled out before basing dose modification decisions on bilirubin values alone.	
Isolated AST or ALT elevation	
Grade 1, 2	May continue canakinumab treatment
Grade 3: >5 - 20 x ULN* **With normal baseline:**	
AST or ALT >5.0 – 10.0 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to grade ≤1 or to baseline. If resolved in ≤ 14 days, maintain dose level; if resolved in > 14 days, reduce by 1 dose level.
AST or ALT >10.0 – 20.0 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to grade ≤1 or to baseline. Then reduce by 1 dose level.
With abnormal baseline ALT/AST (up to grade 2: ≤ 5.0 ULN):	
ALT/AST > 2.0 x baseline AND > 5.0 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to baseline. If resolved in ≤ 14 days, maintain dose level; if resolved in > 14 days, reduce by 1 dose level
ALT/AST > 3.0 x baseline AND >10 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor weekly until resolved to baseline, then reduce by 1 dose level
Grade 4: >20 x ULN*	Permanently discontinue treatment
Combined elevations of AST or ALT and total bilirubin	
With normal baseline LFTs:	
Grade 2 ALT/AST (>3.0 x ULN) with bilirubin > 2.0 x ULN (unless Gilbert's syndrome)	Interrupt study treatment. Assess if case is true DILI.* • **If DILI confirmed** - Permanently discontinue. • **If Not DILI** – interrupt treatment. Treat the identified cause according to institutional guidelines. Repeat LFTs within 48-72 hours, then monitor weekly, till enzyme levels resolve to ≤Grade 1 or Baseline.
With abnormal baseline LFTs:	
ALT or AST >3.0 x baseline	After recovery, re-administration of study treatment could be considered only if Investigator assesses benefit to outweigh the risk. Any decision

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab**
OR ALT or AST >8.0 x ULN [which ever is lower) combined with total bilirubin >2.0 x baseline AND >2.0 x ULN	regarding re-administration of study drug/s and dose regimen should be discussed with the Sponsor.
* For additional information on follow-up of potential drug induced liver injury cases, refer to section 4.3.2	
Pancreatitis	
Grade 3	Permanently discontinue canakinumab
Hypertension	
Grade 3	• Interrupt dose until resolved ≤ grade 1, if resolved within ≤7 days then maintain dose level • if it persists > 7 days despite optimal anti-hypertensive treatment - then increase canakinumab dosing interval
Diarrhea - institute appropriate anti-diarrheal treatment and follow general guidelines	
Rash/photosensitivity - initiate/institute appropriate skin toxicity therapy (such as antihistamines and/or topical corticosteroids) and follow general guidelines.	
Grade 3	Omit dose until resolved to grade ≤1 • if resolved ≤7 days – increase canakinumab dosing interval • if resolved >7 days despite optimal therapy – permanently discontinue canakinumab
Steven Johnson Syndrome, Toxic epidermal necrolysis	
• Permanently discontinue canakinumab	
Tuberculosis or reactivation of hepatitis	
• Permanently discontinue canakinumab	
Asymptomatic laboratory abnormalities-	
• If clinically significant, follow general guidelines	
DILI – drug-induced liver injury; LFTs- Liver function Tests [a] Canakinumab dosing interval can be increased from Q4W to Q8W. [b] If relatedness to canakinumab can be excluded with certainty and there is no risk for the patient, the dose modification for canakinumab is not mandatory	

4.2.4 Dose modification and Dose Interruption for spartalizumab

The following sections address the specific instructions for mandatory and recommended dose modifications and recommended management for adverse events considered suspected to be related to spartalizumab. These modifications/interruptions must be recorded on the Dosage Administration Record CRF.

4.2.4.1 General dose modification instructions for spartalizumab

No dose reductions of spartalizumab are allowed. Dose interruption for spartalizumab includes delaying or withholding the treatment for any reason as well as an interruption of treatment. All dose interruptions and the reason for the dose interruption must be documented in the eCRF. Overall, patients with AEs suspected to be related to spartalizumab including those of potential immune-mediated etiology (irAE) may need to interrupt or permanently discontinue study treatment as outlined in **Section 4.2.5** below.

4.2.5 Dose modification and Management Requirements for Potential Immune-Mediated Adverse Events (irAEs)

Adverse events of a potential immune-mediated etiology (irAE) can be associated with spartalizumab treatment. Investigators must be vigilant and carefully identify AEs that may be suggestive of potential irAEs as their appearance may be sub-clinical and early diagnosis is critical for its adequate management and resolution. Collaboration with disease-specific subspecialties is encouraged; corticosteroids are the mainstay of treatment for most irAEs.

An irAE may be of low grade and self-limited, most frequently involving the GI tract (e.g. diarrhea/colitis), skin (e.g. rashes, pruritus), liver (e.g. hepatitis), lung (e.g. pneumonitis), kidneys (e.g. nephritis) and endocrine systems (e.g. hypothyroidism, hyperthyroidism, type I diabetes, hypophysitis including hypopituitarism and adrenal insufficiency). Other immune-mediated AEs may rarely include the nervous system (e.g. encephalitis, Guillain-Barre syndrome, myasthenia gravis), eye (e.g. uveitis, vision changes), musculo-skeletal system (e.g. myositis, arthritis), pancreas (e.g. pancreatitis), cardio-vascular system (e.g. vasculitis, myocarditis) or blood system (e.g. anemia, cytopenias), and severe skin reactions such as toxic epidermal necrolysis (TEN) or Steven Johnson syndrome (SJS). Furthermore, complications in patients with bone marrow or solid organ transplant have been reported (e.g. organ rejection, severe graft-versus-host disease). However, nearly all organs can be affected by immune-mediated toxicities. irAEs often occur relatively early (mostly within weeks to 3 months after treatment initiation), however, may develop at any time during treatment (even after several months), and may also occur after the treatment discontinuation.

Serological, immunological and histological assessments should be performed as deemed appropriate by the investigator, to verify the potential immune-related nature of the AE, and exclude a neoplastic, infectious or metabolic origin of the AE.

Severe grade or persistent lower grade irAEs typically require interrupting or permanently discontinuing treatment and administration of systemic steroids, and sometimes other immunosuppressive medications (i.e. tumor necrosis factor alpha (TNFα) antagonists, mycophenolate or tacrolimus, etc.). Early recognition and work-up of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immunosuppressants. Some events like endocrinopathies may require life-long hormonal replacement.

Tapering of steroids should not be too rapid (i.e. >4 weeks) to avoid recurrence or worsening of irAEs. The management of irAEs may further include initiation of antibiotics for prophylaxis against opportunistic infections.

Patients should be instructed to return to the study site as soon as possible (instead of waiting for their next scheduled visit) if they experience symptoms consistent with an irAE. Patients who experience a new or worsening irAE should be contacted and/or evaluated by the study site more frequently.

Based on clinical experience and published guidelines on the management of irAEs in patients treated with immune checkpoint inhibitors (Brahmer et al, 2018, Haanen et al, 2017, NCCN 2018), instructions have been developed how to manage irAEs that may occur in patients receiving spartalizumab with canakinumab. Dose modification requirements and AE management guidelines for the potential irAEs are provided in the following tables: diarrhea/colitis (**Table 4-8)**, hepatitis (liver laboratory alterations) (**Table 4-9),** skin toxicity (**Table 4-10)**, nephritis (**Table 4-11)**, pneumonitis **(Table 4-12**), endocrinopathies (**Table 4-13),** and other potential immune-related AEs (**Table 4-14)**. In addition, guidance for management of spartalizumab infusion-related reactions is provided in (**Table 4-15**).

Investigators are encouraged to contact the Medical Monitor/ Sponsor as needed to discuss cases that warrant separate discussion outside of the scope of the current instructions.

The dosing modification requirements are mandatory or recommended depending on AE, however, the AE management guidelines are recommendations and can be modified according to the local practices.

Table 4-8. Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related diarrhea/colitis at least possibly related to spartalizumab treatment

Diarrhea and/or Colitis		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
Grade 1 diarrhea: < 4 stools per day over baseline Grade 1 colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Symptomatic treatment (hydration, diet) • Monitor closely	May continue treatment (recommendation)
Grade 2 diarrhea: 4-6 stools per day over baseline Grade 2 colitis: abdominal pain; mucus or blood in stool	• Consult with GI specialist • Stool evaluation, imaging and endoscopy as clinically indicated • Symptomatic treatment (hydration, diet) • Commence steroids (0.5-1 mg/kg/d prednisone or IV equivalent) until recovery to grade 1, particularly in case of persisting/worsening symptoms, ulcerations or bleeding seen on endoscopy, or blood in stool. If no improvement within few days, manage as per Grade 3. • Slowly taper steroids once symptoms improve to Grade 1 (i.e. over 4-6 weeks)	• Interrupt treatment until diarrhea/colitis recover to grade ≤1 or baseline
Grade 3 diarrhea: increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care ADL Grade 3 colitis: severe abdominal pain; peritoneal signs	• Consider hospitalization; rule out bowel perforation and initiate IV hydration as needed • Consultation with GI specialist; consider endoscopy and biopsy • In addition to symptomatic treatment, initiate treatment with IV steroids (1 to 2 mg/kg/d of methylprednisolone or equivalent) • Consider antibiotics as appropriate	• Interrupt treatment until diarrhea/colitis recover to grade ≤1 or baseline

Diarrhea and/or Colitis		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
	• If no improvement in 2-3 days: consider initiating infliximab 5 mg/kg and continue steroids. (infliximab is contraindicated in patients with sepsis/perforation) • Slowly taper steroids once symptoms improve to grade 1 (4 to 6 weeks) • If symptoms worsen during steroid reduction, re-escalate as needed followed by more prolonged taper and consider infliximab	
Grade 4 diarrhea or colitis: life-threatening consequences; urgent intervention indicated	Same as for grade 3	Permanently discontinue treatment

Table 4-9. Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related liver laboratory alterations at least possibly related to spartalizumab treatment

Abnormal liver function tests		
Severity	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Isolated AST and/or ALT elevation		
With normal AST and ALT at baseline:		
Grade 3: AST or ALT (>5.0 – 20.0) x ULN: AST or ALT >5.0 – 10.0 x ULN	Start oral prednisolone 1 mg/kg	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to grade ≤1 or to baseline; then resume same dose
AST or ALT >10.0 – 20.0 x ULN	Start I.V. (methyl) prednisolone 1-2 mg/kg	Permanently discontinue study treatment. Monitor LFTs within 48-72 hours, then monitor LFTs weekly until recovery to grade ≤1 or to baseline.
Grade 4: AST or ALT (>20 x ULN)	Start I.V. (methyl) prednisolone 2 mg/kg	Permanently discontinue treatment

Abnormal liver function tests		
Severity	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Isolated AST and/or ALT elevation		
With abnormal ALT/AST (up to grade 2 - ≤ 5.0 x ULN) at baseline:		
ALT/AST > 2.0 x baseline AND > 5.0 x ULN	If rising ALT/AST when re-checked, start oral prednisolone 1 mg/kg	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to baseline; then resume same dose.
ALT/AST > 3.0 x baseline AND >10 x ULN	Start oral prednisone/ prednisolone 1-2 mg/kg	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor weekly until resolved to baseline, then resume same dose.
AST or ALT >20 x ULN (grade 4)	Start I.V. (methyl) prednisolone 1-2 mg/kg	Permanently discontinue treatment.
Concomitant elevation of AST and/or ALT and total bilirubin		
With normal AST/ALT and bilirubin at baseline:		
Grade 2 ALT and/or AST elevation (>3.0 x ULN) with bilirubin > 2.0 x ULN (unless Gilbert's syndrome)	Start I.V. (methyl) prednisolone 1-2 mg/kg	Interrupt treatment. Assess if case is drug induced liver injury (DILI) - • If DILI confirmed, permanently discontinue study treatment. For additional information on follow-up of potential drug induced liver injury cases, refer to section 4.3.2. If no DILI confirmed, interrupt treatment, treat the identified cause according to institutional guidelines. Repeat LFTs within 48-72 hours, then monitor weekly, till enzyme levels resolve to ≤grade 1 or baseline. After recovery, re-administration of study treatment could be considered only if Investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drugs and dose regimen should be discussed with the Medical Monitor.
With abnormal ALT/AST at baseline:		
ALT or AST >3.0 x baseline OR ALT or AST >8.0 x ULN [whichever is lower] combined with total bilirubin >2.0 x baseline AND >2.0 x ULN	Start oral prednisone/ prednisolone 1-2 mg/kg[f]	Same as above

Isolated total bilirubin elevation	
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (e.g. by testing ALP) or alternative causes of bilirubin elevation (e.g. disease progression [imaging]). Treat alternative causes according to institutional guidelines
Grade 2 (>1.5 - 3.0 ULN)	Maintain treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ grade 1 or to baseline. If isolated bilirubin remains stable at Grade 2, continue treatment with spartalizumab at the same dose regimen.
Grade 3 (>3.0 – 10 ULN)	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline.
Grade 4 (> 10 x ULN)	See footnote*- otherwise discontinue treatment

Foot note: an isolated bilirubin elevation is not typical for DILI. Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation should therefore, be ruled out before basing dose modification decisions on bilirubin values alone.

Table 4-10. Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related skin events at least possibly related to spartalizumab treatment

Skin Events		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
Grade 1 (e.g. rash, pruritus)	• Initiate prophylactic and symptomatic treatment • Consider mild/moderate potency topical steroids or urea containing creams in combination with oral antipruritics • Reassess after 2 weeks	May continue treatment (recommendation)
Grade 2 (e.g. rash, pruritus)	• Consider initiating systemic steroids (e.g. oral prednisolone 0.5-1mg/kg daily). • In addition, treat with topical emollients, oral antihistamines, and medium/high-potency topical steroids • If symptoms persist or recur consider skin biopsy	• Consider dose interruption (recommendation) • In case of bullous dermatitis, acute generalized exanthematous pustulosis or DRESS, interrupt spartalizumab until recovery to grade ≤1 or baseline (mandatory)
Grade 3 (e.g. rash, pruritus and other severe cutaneous adverse reactions, bullous dermatitis)	• Consult with dermatologist and consider skin biopsy. • Initiate systemic steroids (1 mg/kg/d prednisone or IV equivalent); consider increasing if no improvement • High-potency topical steroids • Topical emollients, oral antihistamines as indicated • Consider GABA agonists or aprepitant in case of severe pruritus	• Interrupt treatment until recovery to grade ≤1 or baseline • For patients with severe cutaneous adverse reaction or bullous dermatitis, risk/benefit before resuming treatment should be carefully considered.
Grade 4: life-threatening	• Urgent dermatologic consultation and additional measures as per local guidelines	Permanently discontinue treatment
Stevens-Johnson syndrome, toxic epidermal necrolysis	• Hospitalization and urgent dermatology consultation • Institute supportive care immediately as per institutional guidelines	Permanently discontinue treatment

Table 4-11. Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related nephritis at least possibly related to spartalizumab treatment

Nephritis		
Creatinine increased	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
Creatinine >ULN to ≤1.5x ULN; >1 to ≤1.5x baseline	• Monitor creatinine weekly • Rule-out other causes (e.g. fluids, medications, IV contrast) • Promote hydration and consider cessation of nephrotoxic drugs	May continue treatment (recommendation)
Creatinine >1.5 to ≤3 x ULN; >1.5 to ≤3 x baseline	• Monitor creatinine every 2 to 3 days and consult with nephrologist • Rule-out other causes (e.g. fluids, medications, IV contrast) • Initiate 0.5 to 1 mg/kg/d prednisone or equivalents if other causes are ruled-out • If worsening or no improvement: 1 to 2 mg/kg/d prednisone or equivalents • Promote hydration and cessation of nephrotoxic drugs • Consider renal biopsy	Interrupt treatment until serum creatinine recovers to ≤ grade 1 or baseline.
Creatinine >3.0 ULN	• Monitor creatinine every 1 to 2 days and consider hospitalization • Consult with nephrologist and consider renal biopsy • Start 1 to 2 mg/kg/d prednisone or equivalents • Once event improves to grade ≤1, slowly taper steroids over at least 4-6 weeks	Permanently discontinue treatment

Table 4-12. Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related pneumonitis at least possibly related to spartalizumab treatment

Pneumonitis		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
Grade 1: asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Confirm diagnosis by appropriate investigations (CT scan) and rule out other causes e.g. infection. • Chest imaging/CT scan; repeat imaging in 3-4 weeks or as clinically indicated • Monitor symptoms every 2-3 days; clinical evaluation and laboratory work-up for infection: pulse oximetry • Consultation with pulmonologist recommended	Consider treatment interruption (recommendation)
Grade 2: symptomatic; medical intervention indicated; limits instrumental ADLs	• Chest imaging/CT scan; repeat imaging in 3-4 weeks or as clinically indicated • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection, pulse oximetry • Consult pulmonologist • Pulmonary function tests • Bronchoscopy with biopsy and/or BAL to rule out infection and/or disease progression/lung infiltration • Initiate steroids (1 to 2 mg/kg/d prednisone or equivalent) • Consider empirical antibiotics • If no improvement within 2-3 days, or worsening, treat as grade 3	• Interrupt treatment until recovery to grade ≤1 or baseline • Permanently discontinue treatment in case of recurring grade 2 pneumonitis
Grade 3: severe symptoms; limits self-care ADLs; oxygen indicated Grade 4: life- threatening respiratory compromise; urgent intervention required (e.g. tracheotomy or intubation)	• Same as grade 2; in addition: • Hospitalization and pulmonary and infectious disease consultation • Methylprednisolone (1-2 mg/kg/d or equivalent) until symptoms improve to Grade ≤1, then slow taper over ≥4-6 weeks • If no improvement within 48 hours, consider infliximab and/or other immune-suppressive therapy, or IVIG as per local guidelines • Consider empiric antibiotic therapy	Permanently discontinue treatment

Table 4-13. Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related endocrine events at least possibly related to spartalizumab treatment

Endocrine events		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
Grade 1: e.g. asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated	• Consider endocrinologist consult • If hypophysitis is suspected, consider pituitary gland imaging (MRIs with gadolinium and sellar cuts); evaluate hormone levels as clinically indicated • Repeat labs in 1 to 3 weeks/MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan • If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated	May continue treatment (recommendation)
Grade 2: moderately symptomatic endocrinopathy (e.g., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism), or minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	• Endocrinology consultation • Rule out infection/sepsis and other alternative causes with appropriate cultures/imaging • Evaluate hormone levels (e.g. ACTH, cortisol, FSH/FH, TSH, free T4, testosterone/estrogen), metabolic panel (e.g. Na, K, CO2, glucose), and imaging (e.g. brain MRI) as clinically indicated • Initiate hormone replacement therapy as appropriate • Consider steroids (methylprednisolone 1 to 2 mg/kg/d or equivalent) in case of severe hypophysitis or thyrotoxicosis • Consider beta-blocker in case of severe hyperthyroidism • Consider hospitalization (e.g. in case of severe	• Interrupt treatment until recovery to mild or no symptoms, and controlled with hormone replacement therapy. Hypothyroidism may be managed with replacement therapy without treatment interruption (unless life-threatening) (recommendation) • Permanently discontinue spartalizumab for life-threatening endocrinopathies (i.e. hyperthyroidism, adrenal insufficiency, hypophysitis) or recurring severe/life-threatening events not controlled by hormone replacement therapy.

Endocrine events		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
	adrenal insufficiency/crisis), fluid replacement, and other supportive measures as clinically indicated	
Autoimmune diabetes (grade 3 hyperglycemia, or symptomatic hyperglycemia) Autoimmune diabetes (grade 4 hyperglycemia, or life-threatening complications)	• Initiate anti-glycemic therapy (i.e. insulin) as medically indicated and monitor glucose levels regularly until metabolic control is achieved • Evaluate for ketoacidosis as medically indicated • Consultation with endocrinologist • Consider hospitalization (e.g. in case of ketoacidosis)	• Interrupt treatment until recovery to grade 1 or baseline • Permanently discontinue treatment in case of recurring severe/life-threatening events not controlled by anti-glycemic therapy.

Table 4-14. Mandatory dose modification requirements and recommended clinical management guidelines for "other" potential immune-related AEs at least possibly related to spartalizumab treatment

Other (e.g. autoimmune neuropathy, demyelinating polyneuropathy, Guillain-Barre syndrome, myasthenia gravis-like syndrome, encephalitis, non-infectious myocarditis, pericarditis, pancreatitis, grade 3 fatigue with rapid onset in absence of disease progression, etc.)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
Grade 1: mild	• Provide symptomatic treatment evaluate/monitor adequately	May continue treatment (recommendation)
Grade 2: moderate	• Ensure adequate evaluation to confirm etiology or exclude other causes • Provide symptomatic treatment • Systemic corticosteroids may be indicated • Consider biopsy or additional tests for confirmation of diagnosis • A specialist should be consulted	Consider interruption of treatment until recovery to ≤ grade 1 or baseline (recommendation)
Grade 3: severe	• Initiate systemic corticosteroids (prednisone at a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate • Monitor closely and consult with a specialist	• Interrupt treatment until recovery to ≤ grade 1 or baseline. • May restart treatment at the same dose and schedule taking into account the risks and benefits
Grade 4: life-threatening	• Hospitalization and consult with specialist	Permanently discontinue treatment

Other (e.g. autoimmune neuropathy, demyelinating polyneuropathy, Guillain-Barre syndrome, myasthenia gravis-like syndrome, encephalitis, non-infectious myocarditis, pericarditis, pancreatitis, grade 3 fatigue with rapid onset in absence of disease progression, etc.)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
	• Initiate systemic corticosteroids (prednisone a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate	
Encephalitis or aseptic meningitis	• Rule out infectious or other causes of moderate to severe neurologic deterioration, and consult with specialist. • If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents.	Permanently discontinue treatment
Guillain-Barre, neuropathy (motor, sensory or autonomic) OR , or transverse myelitis (grade 3: severe symptoms; limiting self-care and ADL)	• Hospitalization and consult with specialist	Permanently discontinue treatment
Myasthenia gravis	• Consult with specialist • Consider pyridostigmine and systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d; other therapies as appropriate (e.g. IVIG) • Hospitalization in case of severe cases	Grade 2: Interrupt treatment until recovery to ≤ grade 1 or baseline Grade ≥3: Permanently discontinue treatment
Myocarditis grade ≥2 or cardiac event grade ≥3	• Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d • Consult with specialist; hospitalization as indicated	Permanently discontinue treatment
Pancreatitis/serum amylase/lipase increase Grade ≥2	• Evaluate for pancreatitis (clinical assessment, abdominal imaging and/or MRCP as appropriate) • Initiate steroids in case of ≥ grade 2 acute pancreatitis • Treatment may be continued in case of asymptomatic, isolated enzyme elevations without evidence for pancreatitis	Grade 2: interrupt treatment until recovery to ≤ grade 1 or baseline Grade≥3: permanently discontinue treatment
Autoimmune hemolytic anemia, hemolytic uremic syndrome, or acquired hemophilia, grade ≥3	• Consult with specialist • Consider systemic corticosteroids and other therapies as appropriate (e.g. transfusion) per local institutional guidelines	• Permanently discontinue treatment

Other (e.g. autoimmune neuropathy, demyelinating polyneuropathy, Guillain-Barre syndrome, myasthenia gravis-like syndrome, encephalitis, non-infectious myocarditis, pericarditis, pancreatitis, grade 3 fatigue with rapid onset in absence of disease progression, etc.)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
Ocular events	• Consult with ophthalmologist	• Grade 2: interrupt treatment until recovery to ≤ grade 1 or baseline • Grade 3 and 4: permanently discontinue treatment

Table 4-15. Mandatory dose modification requirements and recommended clinical management guidelines for potential infusion-related reactions or injection site reaction at least possibly related to spartalizumab treatment

Infusion reaction		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
Grade 1: mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs/pulse oximetry as medically indicated until patient is deemed medically stable • Consider slowing infusion rate until recovery of symptoms	May continue treatment (recommendation)
Grade 2: requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• Additional medical therapy as per local institutional guidelines that may include : o IV fluids o Antihistamines o NSAIDS, acetaminophen o Narcotics o Oxygen and corticosteroids as indicated • Increase monitoring of vital signs/pulse oximetry as medically indicated until patient is deemed medically stable • If symptoms resolve, the infusion may be restarted at 50% of the original infusion rate • Pre-medicate patients approximately 1.5 hours prior to next infusion with: o Diphenhydramine (50 mg PO or equivalent)	• Stop infusion and keep line open • Permanently discontinue treatment in case of recurring infusion reaction despite adequate premedication and prolonged infusion/slow infusion rate

Infusion reaction		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements (unless specified otherwise)**
	○ Acetaminophen (500-1000 mg PO or equivalent) ○ Or as per local institutional guidelines	
Grade 3: prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: life-threatening; pressor or ventilatory support indicated	• Stop Infusion • Additional medical therapy as per local institutional guidelines that may include: ○ IV fluids ○ Antihistamines ○ NSAIDS, acetaminophen ○ Narcotics ○ Oxygen ○ Corticosteroids ○ Epinephrine • Close monitoring of vital signs, pulse oximetry and ECG as medically indicated until the patient is deemed medically stable • Hospitalization as indicated	Permanently discontinue treatment

4.2.5.1 Guidance for Corticosteroids Tapering for Management of Immune-Related AEs

Consultation with disease-specific experts is recommended. Steroids should be tapered slowly and based on response/recovery of clinical symptoms. Consider complete tapering over a period of at least 4 weeks (sometime 6-8 weeks or longer) to present recurrent irAEs. Slower tapering or re-escalation of corticosteroids therapy may be needed if the adverse event is not showing improvement. Once corticosteroid tapering is achieved at a level of 10 mg of prednisone/day (or equivalent) or less, spartalizumab can be restarted as indicated in the dose modification tables.

4.2.6 Permanent discontinuation of spartalizumab

In general, spartalizumab must be permanently discontinued in case of:

- Any grade 4 (life-threatening) adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy)

- Persistent grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to ≤ grade 1 within 12 weeks
- Inability to reduce the dose of steroids (for the management of irAE) to 10 mg/day or less of prednisone or equivalent within 12 weeks*
- Any severe or grade 3 recurring adverse event that is at least possibly related to spartalizumab

  *The 12 week timeframe will begin from the time the irAE reaches a grade that leads to spartalizumab interruption.

4.3 Follow-up for toxicities

4.3.1 Follow-up of Immune-Related AEs

The emergence of Immune-Related AE (irAE) may be anticipated based on the mechanism of action of immunomodulatory therapies. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator to verify the immune-related nature of the AE and to exclude alternative explanations. Recommendations have been developed to assist investigators in assessing and managing the most frequently occurring irAEs.

Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 30 days, and subsequently at approximately 30-day intervals (or more frequently if required by institutional practices, or if clinically indicated), until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

If an AE is suspected to be immune-related the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. All patients must be followed-up for irAEs for 150 days following the last dose of spartalizumab . If SAEs suspected to be related to study medication occur beyond Day 150, information should also be collected.

4.3.2 Follow-up of Potential Drug-Induced Liver Injury (DILI) Cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potentially severe DILI (including immune-related DILI), and should be considered

as clinically important events and should be assessed appropriately to establish diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value (please see **Table 5-1**); patients meeting any of the following criteria will require further follow-up and assessments as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 3.0 x baseline] or 8.0x ULN, whichever is lower, combined with [TBIL > 2.0 x baseline AND > 2.0 x ULN]

NOTE: As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before the diagnosis of DILI is confirmed.

A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, GLDH, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion with CT, MRI, duplex sonography.

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out if LFTs are caused by cholestasis (defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis).

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

Table 4-16 provides guidance on specific clinical and diagnostic assessments to be (OR which can be) performed to rule out possible alternative causes of the observed LFT abnormalities.

Table 4-16. Guidance for specific clinical and diagnostic assessments

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, γGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatitis	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Ceruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon patients medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Obtain PK sample to determine exposure to study drug and metabolites.

Following appropriate causality assessments, as outlined above, the causality of the drug is estimated as "probable" i.e. >50% likely, if it appears greater than all other causes combined. The term "drug-induced" indicates *probably caused* by the drug, not by something else, and only such a case can be considered DILI case and should be reported as an SAE.

4.3.3 Follow-up for Infections

Patients should be followed closely for any signs or symptoms of infection and receive prompt appropriate treatment for any suspected infection.

4.4 Concomitant Medications

A detailed list of a patient's current medications will be gathered at consent and assessed against the list of concerning or prohibited concomitant medications listed below, as appropriate. Any required medication adjustments or wash outs will be documented on an individual basis. Once on study, newly prescribed concomitant medications will be added and similarly reviewed to ensure patient safety and compliance.

4.4.1 Permitted Concomitant Therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed except those prohibited in **Section 4.4.3** and **Appendix A** (Package Inserts for gemcitabine and nab-paclitaxel).

- Medications to prevent or treat nausea or vomiting
- Anti-diarrheal medications (e.g. loperamide) for patients who develop diarrhea
- Pain medication to allow the patient to be as comfortable as possible
- Treatment with bisphosphonates or denosumab for pre-existing, painful bone/liver metastases, and limited-field palliative radiotherapy or surgery is permitted. Patients requiring initiation of such treatment during the course of the study must be evaluated for disease progression; radiotherapy like any concomitant medication must be listed on the CRF. Spartalizumab should be held for ≥1 week prior to radiotherapy or surgery, and be resumed ≥2 weeks after radiation or surgery, provided the patient has recovered from radiation or surgery related toxicity. Caution is advised for radiation that include lung tissue or heart.
- Immunosuppressive agents to treat suspected irAEs
- Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents as per local or published guidelines are permitted at least > 2 weeks before the **start** of study treatment; in case of anemia, thrombocytopenia or neutropenia, potential immune-mediated etiology should be ruled out before administration of these agents
- Nutritional support or appetite stimulants (e.g. megestrol)
- Oxygen therapy and blood products or transfusions
- Inactivated vaccines
- The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

4.4.2 Permitted concomitant therapy requiring caution and/or action

If a patient is using erythropoiesis stimulating agents (ESAs) prior to enrollment (at least > 2 weeks before start of study treatment), he/she may continue the treatment.

Anticoagulation and anti-aggregation agents are permitted if the patients are already at stable doses for > 2 weeks at time of first dose and International Normalized Ratio (INR) should be monitored as clinically indicated per investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor sample according to the institutional guidelines.

In cases of isolated brain progression or other local progression, patients may receive palliative radiotherapy or surgery. In addition, localized, palliative radiotherapy for pre-existing bone/liver metastases is permitted. Spartalizumab should be held for ≥1 week prior to radiotherapy or surgery. Spartalizumab may be resumed ≥2 weeks after radiation or surgery, provided the patient has recovered from radiation or surgery related toxicity. If palliative radiotherapy or surgery is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be assessed and documented (Patients must not continue study treatment beyond disease progression per RECIST 1.1 [see Section 5.4.1]).

Since the metabolism of nab-paclitaxel is catalyzed by CYP2C8 and CYP3A4, caution should be exercised when administering paclitaxel/nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

Cytochrome P450 (CYP450) enzymes are suppressed by increased levels of cytokines (e.g.,IL-1) during chronic inflammation. CYP450 expression may be normalized when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index. Caution should be exercised when administering these agents concomitantly with canakinumab. Given the potential DDI via cytokine modulation by canakinumab, subjects who are on warfarin or warfarin-like treatment with narrow therapeutic index, should have their international normalized ratio (INR) measured locally and warfarin or warfarin-like treatment dose adjusted accordingly within one month from starting study treatment.

4.4.3 Prohibited concomitant therapy

There are no prohibited or required concomitant medications for combination of gemcitabine and nab-paclitaxel. Other antineoplastic agents or investigational drugs, other than what is specified in this protocol, are prohibited.

Over the course of this study, additional medications may be required to manage aspects of the disease state of the patients, including side effects from study treatments or disease recurrence. Supportive care, including but not limited to antiemetic medications, may be administered at the discretion of the Investigator, consistent with institutional guidelines.

For information regarding other drugs that may interact with either nab-paclitaxel or gemcitabine and affect their metabolism, pharmacokinetics, or excretion, see the nab-paclitaxel and gemcitabine package inserts (refer to Prescribing Information), **Appendix A.**

Treatment with the following agents is not permitted within ≤ 2 weeks prior start of study treatment:

- hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), or
- thrombopoietin mimetics, or
- erythroid stimulating agents.

If erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained. In addition, hematopoietic colony-stimulating growth factors and thrombopoietin mimetics may be used to treat treatment emergent cytopenias during the course of the study.

During the course of the study, patients must not receive other additional investigational drugs, devices, chemotherapy, or any other therapies that may be active against cancer or modulate the immune responses. However, limited-volume palliative radiotherapy may be allowed as concomitant therapy. Such local therapies administered during the study treatment must be documented. Additionally, no other therapeutic systemic antineoplastic agents and no immunosuppressive medication may be administered while on this study unless given for the management of immune toxicity or circumstances where there is further discussion with the Medical Monitor .

4.4.3.1 Prohibited concomitant therapy for spartalizumab

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for use as pre-medication for chemotherapy (when needed), the treatment of infusion reaction, irAEs, treatment for brain metastasis, and for prophylaxis against imaging contrast dye allergy or replacement-dose steroids in the setting of adrenal insufficiency (providing this is < 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as COPD requiring treatment for ≤ 3 weeks. If systemic corticosteroids are required for the control of infusion reactions or irAEs, it must be tapered and be at non-immunosuppressive doses (<10 mg/day of prednisone or equivalent) before the next administration of study treatment. If the dose of prednisone or equivalent cannot be reduced to less than 10 mg/day within 12 weeks from irAE cause delay dosing then spartalizumab must be discontinued.

The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed.

There are no spartalizumab-specific prohibited therapies during the post-treatment follow-up period.

4.4.3.2 Prohibited concomitant therapy for canakinumab

Due to the potential risk of serious infections and increased risk of neutropenia, caution should be excised when administering canakinumab in combination with immuno-suppressive medications.

The use of below is not allowed after the start of study treatment and for at least 130 days after discontinuation of canakinumab unless medically indicated for the management of immune related AEs or other serious conditions. In these cases patients should be closely monitored for infection and the dose modification guidelines should be followed.

- Any systemic antiretroviral agents and / or any biologic drugs targeting the immune system (e.g. TNF-alpha blockers, anakinra, rituximab, abatacept, tocilizumab)
- **Live vaccines.** All immunizations should be completed at least 3 months prior to initiating canakinumab. Patients should discontinue canakinumab if administered any live vaccine during the course of the study. Inactivated vaccines are allowed.

4.5 Overdose

Overdose, as defined for this protocol, refers to the medications included in the therapeutic regimens to which patients are randomized (the agents being given to treat pancreatic cancer). On a per dose basis, an overdose is defined as 10% over the protocol-specified dose given to a patient, regardless of any associated AEs or sequelae. On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol-required schedule or frequency. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF.

4.6 Investigational Product Accountability and Disposal

Investigational product (IP) should be disposed of in accordance with institutional/regional requirements. Disposition should be recorded on the investigational drug accountability forms. The Investigator, or designee, shall record the dispensing of IP to patients in the IP accountability record. The IP record will be made available to authorized sponsor-designated monitoring personnel, for the purpose of accounting for the IP supply.

Inspections of the IP supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to the sponsor designee and a plan for resolution will be documented.

Investigational product will not be loaned or dispensed by the Investigator to another Investigator or site.

4.7 Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the patient's eCRF and source documents. The Investigator or designee is responsible for the accountability for all study-specific IP either administered or in their custody during the course of the study.

5.0 STUDY ASSESSMENTS

All patients will undergo uniform assessments and procedures defined below in **Section 5.1**. For ease of review, the procedures are described below: 1) Screening/ Baseline, 2) Study Treatment Assessments, 3) End of Treatment, 4) As Needed Assessments, 5) Safety Follow-Up, 6) Post Treatment Efficacy Follow Up, and 7) Survival Follow-Up.

5.1 Study Schedule

Table 5-1. Schedule of Events

Protocol Activity	Screening	Treatment Period							End of Treatment[12] (+/- 7 days)	Safety Follow-Up (F/U) (+/- 7 days)					Post-treatment Efficacy Follow Up (F/U)[17]	Survival Follow-Up (F/U) (every 3 months)
	Days -28 to -1	Cycle 1			Cycle 2			Day 1 Cycle 3 and beyond		30 day safety F/U	60 day safety F/U	90 day safety F/U	120 day safety F/U	150 day safety F/U		
Visit Window	N/A	± 3 Days			± 2 Days			± 2 Days							± 7 days	± 14 days
Days	-28	1	8	15	1	8	15									
Informed Consent	X[1] (Treatment ICF)															
Inclusion/Exclusion Criteria Confirmation	X															
Tumor Treatment History (medications, surgery, radiation)	X															
Demographics	X															
Medical History/Family History/ Current Medical Conditions	X															
Tuberculosis Status[2]	X	If Clinically Indicated														
Hepatitis Status	X	If Clinically Indicated														
Vital Signs (BP, Temperature and HR)	X	X	X		X			X	X	X						
Physical Examination	X	X			X			X	X	X						
Neuropathy Assessment	X	X			X			X	X	X						
12-lead ECG	X	If Clinically Indicated														
Adverse Events Evaluation	X	X	X	X	X	X	X	X	X	X[3]	X[3]	X[3]	X[3]	X[3]		
Serious Adverse Events Evaluation	X	X	X	X	X	X	X	X	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Pharmacokinetics (PK) of spartalizumab and canakinumab, [redacted]		X	X	X	X			X	X							
Concomitant Medication[6,7]	X	X			X			X	X	X	X	X	X	X		
ECOG Performance Status	X	X			X			X	X	X						
Height	X															
Weight	X	X			X			X	X	X					X	

Table 5-1: Schedule of Events (Continued)

Protocol Activity	Screening	Treatment Period							End of Treatment[12] (+/- 7 days)	Safety Follow-Up (F/U) (+/- 7 days)					Post-treatment Efficacy Follow Up (F/U)[17]	Survival Follow-Up (F/U) (every 3 months)
	Days -28 to -1	Cycle 1			Cycle 2			Day 1 Cycle 3 and Beyond		30 day safety F/U	60 day safety F/U	90 day safety F/U	120 day safety F/U	150 day safety F/U		
Visit Window	N/A	± 3 Days			± 2 Days			± 2 Days	± 2 Days						± 7 days	± 14 days
Days		1	8	15	1	8	15									
Laboratory																
Complete Blood Count with Differential	X	X		X	X		X	X	X	X						
Electrolytes, BUN, Creatinine, Glucose, Calcium, Uric Acid, SGOT/AST, SGPT/ALT, Alk Phos, Total Bilirubin, etc.	X	X		X	X		X	X	X	X						
Thyroid Panel (T3, T4, and TSH)	X	X			X			X[8]	X	X						
PT/INR/APTT[18]	X							X								
Pregnancy Test (Serum) (WOCBP)	X								X	X						
Pregnancy Test, (Urine) (WOCBP)		X			X			X			X	X	X	X		
Urinalysis	X	X			X			X	X	X				X	X	
HIV	X[10]	If Clinically Indicated														
HBV sAG	X[11]															
HCV Ab or HCV RNA (only if there is an active infection)	X[11]															
Study Treatment Administration																
Canakinumab		X			X			X								
Spartalizumab		X			X			X								
Gemcitabine[19]		X	X	X	X	X	X	X								
Nab-paclitaxel[19]		X	X	X	X	X	X	X								
Follow-Up																
Survival follow-up																X
Anti-neoplastic therapies since discontinuation of study treatment										X	X	X	X		X	X

Table 5-1: Schedule of Events (Continued)

Protocol Activity	Screening	Treatment Period							End of Treatment[12] (+/- 7 days)	Safety Follow-Up (F/U) (+/- 7 days)					Post-treatment Efficacy Follow Up (F/U)[17]	Survival Follow-Up (F/U) (every 3 months)
	Days -28 to -1	Cycle 1			Cycle 2			Day 1 Cycle 3 and Beyond		30 day safety F/U	60 day safety F/U	90 day safety F/U	120 day safety F/U	150 day safety F/U		
Visit Window	N/A	± 3 Days			± 2 Days			± 2 Days	± 2 Days						± 7 days	± 14 days
Days		1	8	15	1	8	15									
Biomarker/ Sample Collection																
CA19-9[9]	X				X			X	X						X	
[redacted]																
Tumor Assessment																
CT (or MRI if Contrast Allergy) of the Chest, Abdomen and Pelvis with Oral and IV Contrast	X							X[14]	X						X (If appropriate)	
Brain CT or MRI[15]		If Clinically Indicated														
Whole body bone Scan		If Clinically Indicated														
Localized bone CT, MRI or X-ray[16]		If Clinically Indicated														
RECIST 1.1 Tumor Evaluation/Response Assessment	X							X[14]	X						X	

Table 5-1: Schedule of Events (Continued)

Footnotes:

A cycle is at defined as 4 weeks

1 Treatment ICF must be signed by patient prior to the initiation of treatment

2 Tuberculosis screening is performed per local and institutional guidelines

3 Only study treatment-related AEs will be reported after the start of new anti-cancer therapy and until the end of the Safety Follow-Up period;

4 Only study treatment-related SAEs will be reported after the end of safety f/u or after the start of new anti-cancer therapy, whichever is the earliest, until the end of survival f/u; After the Safety Follow-up Period, and in the post-treatment efficacy follow-up period, report only treatment-related SAEs until the start of a new anti-neoplastic therapy;

5 The specific Pharmacokinetic and [redacted] blood collection for canakinumab, spartalizumab, gemcitabine and nab-paclitaxel is outlined in **Section 5.6** below. Blood draws for canakinumab and spartalizumab will be performed on Days 1,8, and 15 of Cycle 1, and Day 1 of Cycles 2-5 (pre-dose); Blood draws for gemcitabine and nab-paclitaxel will be performed on Day 1 of Cycles 1 and 2 (pre-dose);

6 Concomitant medications should be recorded from 28 days prior to starting study treatment (during screening period) until end of safety follow up or start of new antineoplastic medications, whichever is sooner. *After starting a new antineoplastic medication, only report medications related to study treatment-related AEs/SAEs*

7 Concomitant medications must be collected at any visit when AEs are collected; No need to report conmeds after the end of safety f/u or at the start of new anti-cancer therapy;

8 Thyroid panel should be performed on Day 1 of the first two cycles, and Day 1 of every second cycle (cycles 4,6, etc.)

9 CA 19-9 should be evaluated every 4 weeks from C1D1 of treatment (every Cycle)

10 HIV testing during screening period to be conducted only if there is a known history of HIV documented in clinical notes or if patient is currently receiving treatment for HIV. HIV testing is not required in the absence of clinical suspicion (i.e. this test is NOT mandatory).

11 HBV/HCV during screening period to be conducted only if there is an active infection of HBV and/or HCV. Patients who have tested positive for antibody (due to exposure) with no history of active infection do not need a HBV/HCV test during screening period

12 Procedures completed within 14 days of last study treatment can be used for End of Treatment values when appropriate; Reason for stopping treatment will be recorded in EDC;

13 [redacted]

14 CT or MRI of chest, abdomen, pelvis, and Tumor evaluation per RECIST 1.1 is performed Every 8 weeks (every 2 cycles) starting from C1D1 of study treatment.

15 If brain lesions are documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis.

16 Only for lesions on whole body scan that are not visible on the chest, abdomen and pelvis scans. If bone lesions were documented at screening, follow same schedule as CT/MRI of the chest, abdomen, and pelvis.

17 Post Treatment Efficacy Follow-up visit is for those patients who discontinue treatment due to reasons other than disease progression, and therefore could have these assessments performed to show possible disease progression during the follow-up period. The frequency of assessment for patients in post-treatment efficacy follow-up is the same as during the treatment period.

18 This test will only occur prior to the two biopsies on the Screening/ Day 1 visit and the Cycle 3 Day 1 treatment (after 8 weeks of treatment).

19 Gemcitabine and nab-paclitaxel will be administered on days 1, 8, and 15 of each 28-day cycle.

5.2 Baseline Procedures

Patients will have the following procedures conducted within 28 days of Day 1 of Study treatment. Questions regarding eligibility should be directed to the Medical Monitor or his/her authorized designee.

The following procedures will be performed within 28 days prior to Cycle 1 Day 1 treatment (Baseline):

- Informed consent
- Medical History, Family History, Demographics, and Cancer History (including specifically previous PDAC treatments)
- Tuberculosis Status Assessment
- Hepatitis Status Assessment
- Vital signs (including blood pressure, temperature, and heart rate)
- Physical examination (including height and weight)
- Clinical assessment of neuropathy performed according to local practice
- 12-lead electrocardiogram (ECG)
- Adverse Event and Serious Adverse Event assessment
- List of prior and concomitant medications going back over the last 6 months
- ECOG Performance Status (see **Table 5-2** below)
- Laboratory blood tests (collected and assessed locally)
    - Complete blood count (CBC) with differential (absolute), including but not limited to:
        - Red blood cell (RBC) count
        - Hemoglobin
        - Hematocrit
        - Differential White blood cell (WBC) count
        - Absolute neutrophil count (ANC)
        - Platelet count
    - Chemistry panel including, but not limited to:
        - Sodium
        - Potassium

  - Calcium
  - Chloride
  - Uric Acid
  - Blood urea nitrogen (BUN)
  - Creatinine
  - Glucose
  - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT)
  - Alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)
  - LDH
  - Serum Lipase
  - Alkaline phosphatase
  - Bilirubin (total and direct)

- Coagulation tests including (only performed prior to the two biopsies per patient—please see Section 5.7 below (As Needed Assessments)):
  - Prothrombin time (PT) and international normalized ratio (INR)
  - Partial thromboplastin time (PTT)
- Thyroid Panel (free T3, free T4, and TSH)
- Pregnancy test (serum) is required for WOCBP and will be performed within 14 days of Day 1 of study treatment.
- Urinalysis
- CA 19-9 (as defined by local practice)
- HIV test (if there is a known history of HIV in clinical notes or if patient is currently receiving treatment for HIV; HIV testing is not required in the absence of clinical suspicion (this is NOT mandatory));
- Laboratory Assessments for active viral infections: Hepatitis B surface antigen (HBV sAG) and Hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA)
- [redacted]
- [redacted]

- Computerized tomography (CT) scans (with PO and IV contrast) of the chest, abdomen, and pelvis. In the case of CT contrast agent allergy, Magnetic Resonance Imaging (MRI) of the abdomen and pelvis (with IV contrast) along with CT scan of the chest is acceptable. Scans will be reviewed and interpreted at each site per standard a protocol detailed in the Study Manual/ Imaging Guidelines.
  - Response assessment/tumor evaluation
  - Patients with historical tumor scans evaluable per RECIST 1.1 performed ≤ 28 days prior to Day 1 of study treatment need not repeat scans for the purposes of screening unless progression is suspected.

Note: the imaging modality chosen at baseline should remain the same throughout the duration of this study.

- Confirmation that patient has met all inclusion and exclusion criteria

Table 5-2: ECOG Performance Status*

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 house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; 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.

5.3 Treatment Procedures

All patients will have the following procedures performed prior to receiving any study treatment, unless otherwise specified below. For all visits, an administrative window of ± 2 business days is permitted. Treatment or visit delays for public holidays or weather conditions do not constitute protocol violations.

The following procedures will be performed at Day 1 of every cycle, prior to any study treatment administration, unless otherwise specified below:

- Vital signs (including blood pressure, temperature, and heart rate) (also performed on Day 8 of Cycle 1 only);
- Physical examination;
- Clinical assessment of neuropathy performed according to local practice;
- Adverse Event and Serious Adverse Event assessment (performed on Days 1,8, and 15 of every treatment cycle)
- Pharmacokinetics (PK) and [redacted] blood draws performed on Days 1, 8, and 15 of Cycle 1, and Day 1 of Cycles 2-5 (pre-dose); (See **Section 5.6** below for details on specific days and times for PK and [redacted] draws)
- New concomitant medications since last visit;
- ECOG Performance Status (see **Table 5-2** above)
- Weight
- Laboratory blood test (collected and assessed locally)
    - Complete blood count (CBC) with differential (absolute) to be performed on Days 1 and 15 of Cycles 1 and 2, and Day 1 only of Cycle 3 and thereafter, including but not limited to:
        - Red blood cell (RBC) count
        - Hemoglobin
        - Hematocrit
        - Differential White blood cell (WBC) count
        - Absolute neutrophil count (ANC)
        - Platelet count
    - Chemistry panel to be performed on Days 1 and 15 of Cycles 1 and 2, and Day 1 only of Cycle 3 and thereafter including, but not limited to:
        - Sodium
        - Potassium
        - Calcium
        - Chloride

  - Uric Acid
  - Blood urea nitrogen (BUN)
  - Creatinine
  - Glucose
  - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT)
  - Alanine aminotransferase (ALT/SGPT)
  - Alkaline phosphatase
  - LDH
  - Serum Lipase
  - Bilirubin (total and direct)
- Thyroid Panel (free T3, free T4, and TSH)
- Pregnancy test (urine) is required for WOCBP
- Urinalysis
- CA 19-9 (as defined by local practice) (to be performed on Day 1 Cycle 1 and every cycle thereafter (every 4 weeks))
- [redacted]

5.4 Study Treatments

Please also refer to **Section 4.0** for complete study drug administration information, and for dose modification and toxicity information.

Canakinumab

Canakinumab is provided as ready-to use pre-filled syringes to be administered by study center personnel. Two strengths of solution for injection will be supplied:

- Canakinumab 50 mg/ 0.5 mL
- Canakinumab 200 mg/ 1.33 mL

The starting dose of canakinumab will be 250 mg, administer subcutaneously (SC) in the abdomen, upper outer thigh or upper outer arm once every 4 weeks (on Day 1 of each treatment cycle). To administer a target dose of canakinumab of 250 mg, two separate subcutaneous injections must be administered to the patient at a visit and should not be injected in the same site (e.g. if first injection was done in the thigh, the second injection should be done in the opposite thigh). Alternate injection sites should be used throughout the study.

If this initial dose level (DL1) of 250 mg Q4W is not tolerated, the next reduced dose level -1 (DL -1) will be explored. DL -1 aims to reduce canakinumab exposure by increasing the dosing interval of 250 mg dose from Q4W to Q8W without change in actual dose strength.

For additional guidance refer to canakinumab (ACZ885) Instructions for Use/Pharmacy Manual and to the canakinumab Investigator's Brochure.

Spartalizumab

Spartalizumab will be supplied in a liquid solution. The starting dose of spartalizumab is 400 mg (prepared by reconstituting four vials with sterile water for injection (SWFI) and diluted in a 5% dextrose infusion bag before use) administered via intravenous infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 4 weeks (on Day 1 of every cycle). For additional guidance refer to spartalizumab Instructions for Use/Pharmacy Manual and to the spartalizumab Investigator's Brochure.

On days of combination therapy canakinumab will be injected first followed by 30 min observation period and then by spartalizumab infusion. After spartalizumab infusion, patients should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever, and vital signs monitored more frequently if clinically indicated, during and for at least 2 hours after the first two spartalizumab infusions (before administration of chemotherapy). The same may apply for the subsequent spartalizumab infusions if medically indicated.

Gemcitabine/Nab-paclitaxel

- Nab-paclitaxel is infused at an initial dose of 125 mg/m^2 over 30-40 min on days 1, 8, 15 of each 28-day cycle.
- Gemcitabine is infused at an initial dose of 1000 mg/m^2 over 30 min, immediately after completion of nab-paclitaxel infusion, on days 1, 8, 15 of each 28-day cycle

If one of the chemotherapy medications is held, the other study medications may be given.

Doses should be re-adjusted if the patient's BSA changes by +/- ≥10%. If the patient's BSA changes by <10%, no adjustment is necessary unless the site has a standard procedure to adjust doses based upon current BSA according to institutional guidelines.

On days of combination therapy, chemotherapy will be administered at least 30 minutes after the end of spartalizumab infusion. Any pre-medication for the chemotherapies, if required, should be administered at least 30 minutes after the end of the infusion of spartalizumab.
Specifics on dosing and toxicity modifications for gemcitabine and nab-paclitaxel can be found in their Package Inserts **(Appendix A).**

5.4.1 Study Treatment Beyond Disease Progression

Patients will not continue study treatment beyond PD per RECIST 1.1, since progression prior to response has not been reported in pancreatic cancer treated with immunotherapy and was associated with grade 3/4 AEs when treatment continued beyond progression (Parseghian et al 2018). Therefore, the overall risk-benefit for continuing the study treatment beyond disease progression is considered as not favorable.

5.4.2 Study Treatment Duration

Patients will continue to receive study treatment until one of the following events occur:

- disease progression per RECIST 1.1 is radiologically documented by investigator assessment;
- unacceptable toxicity that precludes further treatment;
- treatment is discontinued at the discretion of the investigator;
- patient withdrawal of consent;

- pregnancy;
- patient is lost to follow-up;
- death

If study chemotherapy drugs are permanently discontinued because of chemotherapy-related intolerable toxicities, the investigator can continue spartalizumab with canakinumab until RECIST 1.1 disease progression as per investigator assessment, as long as:

- The patient is continuing to benefit from investigational drug treatment as assessed by the investigator, **and**
- The patient is tolerating the treatment and clearly understands the risks associated with continuing treatment with canakinumab.

If spartalizumab and/or canakinumab have been discontinued because of treatment-related toxicity, treatment with chemotherapy may continue as long as the patient is continuing to benefit from chemotherapy continuation as assessed by the investigator.

5.5 End of Treatment Procedures

All the procedures outlined below need to be completed within 14 days of last dose of study treatment, or otherwise repeated.

- Vital signs (including blood pressure, temperature, and heart rate);
- Physical examination;
- Clinical assessment of neuropathy performed according to local practice;
- Adverse Event and Serious Adverse Event assessment;
- New concomitant medications since last visit;
- ECOG Performance Status (see **Table 5-2** below);
- Pharmacokinetics (PK) and [redacted] blood draws performed during the End of Treatment Visit; (See **Section 5.6** below for details on specific days and times for PK and [redacted] draws)
- Weight;
- Laboratory blood test (collected and assessed locally);
    - Complete blood count (CBC) with differential (absolute), including but not limited to:

- Red blood cell (RBC) count
- Hemoglobin
- Hematocrit
- Differential White blood cell (WBC) count
- Absolute neutrophil count (ANC)
- Platelet count

- Chemistry panel including, but not limited to:
  - Sodium
  - Potassium
  - Calcium
  - Chloride
  - Uric Acid
  - Blood urea nitrogen (BUN)
  - Creatinine
  - Glucose
  - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT)
  - Alanine aminotransferase (ALT/SGPT)
  - Alkaline phosphatase
  - LDH
  - Serum Lipase
  - Bilirubin (total and direct)
- Thyroid Panel (free T3, free T4, and TSH)
- Pregnancy test (Serum) is required for WOCBP
- Urinalysis
- CA 19-9 (as defined by local practice);
- [redacted]

5.6 Pharmacokinetic (PK) and [redacted] Blood Draw Schedules

Time points of blood sample collection for canakinumab pharmacokinetic (PK) and [redacted] blood samples are outlined in **Table 5-3**. Time points of blood sample collection for spartalizumab pharmacokinetic (PK) and [redacted] blood samples are outlined in **Table 5-4**. On days and time points where blood [redacted] PK samples are to be drawn, the PK sample must be drawn first. If patients experience a SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK [redacted] blood sample should be obtained as close as possible to the event occurrence. Time points of blood sample collection for gemcitabine and nab-paclitaxel PK are outlined in **Table 5-5** and **Table 5-6** respectively. All PK [redacted] samples collected will be sent to Novartis. Please see the Laboratory Manual for details.

Table 5-3: Pharmacokinetic [redacted] Blood Collection Log for Canakinumab

Cycle	Day	Scheduled Time Point (hr)	PK	[redacted]
1	1	Pre-dose Cycle 1	canakinumab PK	
1	8	168 hr post-dose (±8 hr)	canakinumab PK	
1	15	336 hr post-dose (±24 hr)	canakinumab PK	
2	1	Pre-dose Cycle 2	canakinumab PK	
3	1	Pre-dose Cycle 3	canakinumab PK	
4	1	Pre-dose Cycle 4	canakinumab PK	
5	1	Pre-dose Cycle 5	canakinumab PK	
5	8	168 hr post-dose (±8 hr)	canakinumab PK	
6	1	Pre-dose Cycle 6	canakinumab PK	
EOT		Anytime	canakinumab PK	
Unscheduled		Anytime	canakinumab PK	

Table 5-4: Pharmacokinetic [redacted] Blood Collection Log for Spartalizumab (PDR001)

Cycle	Day	Scheduled Time Point (hr)	PK	[redacted]
1	1	Pre-dose Cycle 1	Spartalizumab PK	
1	1	End of infusion (within 5 min)	Spartalizumab PK	
1	8	168 hr post-dose (±8 hr)	Spartalizumab PK	
1	15	336 hr post-dose (±24 hr)	Spartalizumab PK	
2	1	Pre-dose Cycle 2	Spartalizumab PK	
3	1	Pre-dose Cycle 3	Spartalizumab PK	
4	1	Pre-dose Cycle 4	Spartalizumab PK	
5	1	Pre-dose Cycle 5	Spartalizumab PK	
5	1	End of infusion within 5 min)	Spartalizumab PK	
6	1	Pre-dose Cycle 6	Spartalizumab PK	
EOT		Anytime	Spartalizumab PK	
Unscheduled		Anytime	Spartalizumab PK	

Table 5-5: Pharmacokinetic draws for Gemcitabine

Cycle	Day	Scheduled Time Point (hr)
1	1	Pre-infusion
1	1	EOI (within 5 minutes)
1	1	0.5 hr (±10 minutes) post-EOI
1	1	1 hr (±10 minutes) post-EOI
1	1	2 hr (±10 minutes) post-EOI
1	1	4 hr (±10 minutes) post-EOI
2	1	Pre-infusion
2	1	EOI (within 5 minutes)
2	1	0.5 hr (±10 minutes) post-EOI
2	1	1 hr (±10 minutes) post-EOI
2	1	2 hr (±10 minutes) post-EOI
2	1	4 hr (±10 minutes) post-EOI
Unscheduled		Anytime
EOI- end of infusion		

Table 5-6: Pharmacokinetic draws of nab-paclitaxel

Cycle	Day	Scheduled Time Point (hr)
1	1	Pre-infusion
1	1	EOI (within 5 min)
1	1	4 hr (±10 minutes) post-EOI
1	1	6 hr (± 1 hour) post-EOI
1	2	24 hr (±1 hour minutes) post-EOI
2	1	Pre-infusion
2	1	EOI (within 5 min)
2	1	4 hr (±10 minutes) post-EOI
2	1	6 hr (± 1 hour) post-EOI
2	2	24 hr (±1 hour minutes) post-EOI
Unscheduled		Anytime
EOI- end of infusion		

5.7 As Needed Assessments

- [redacted]
- After every 8 weeks of study treatment, a Computerized tomography (CT) scans (with PO and IV contrast) of the chest, abdomen, and pelvis will be performed. In the case of CT contrast agent allergy, Magnetic Resonance Imaging (MRI) of the abdomen and pelvis (with IV contrast) along with CT scan of the chest is acceptable. Scans will be reviewed and interpreted at each site per standard a protocol detailed in the Study Manual/ Imaging Guidelines.

Note: the imaging modality chosen at baseline should remain the same throughout the duration of this study.

- Coagulation tests including *(to be performed prior to each biopsy at the Screening Visit and prior to the biopsy after 8 weeks of treatment (prior to Cycle 3 Day 1)*):
  - Prothrombin time (PT) and international normalized ratio (INR)
  - Partial thromboplastin time (PTT)
- Re-assessment of Tuberculosis Status at any time during Study treatment, if clinically indicated;

- Re-assessment of Hepatitis Status at any time during Study treatment, if clinically indicated;
- 12-lead ECG at any time during Study treatment, if clinically indicated;
- Re-assessment of HIV Status at any time during Study treatment, if clinically indicated;
- Brain CT or MRI at any time during Study treatment, if clinically indicated;
- Whole Body bone scan at any time during Study treatment, if clinically indicated;
- Localized bone CT, MRI or X-Ray at any time during Study treatment, if clinically indicated;

5.8 Safety Follow Up (30-day, 60-day, 90-day, 120-day and 150-day Assessments)

The following assessments below will occur at 30 days after the last study treatment, (and at 60-days, 90-days, 120-days and 150-days after treatment, when indicated). All patients will be followed for safety assessment 150 days following the last dose of spartalizumab and canakinumab or 30 days after the last dose of the combination chemotherapy, whichever is later.

- Vital signs (including blood pressure, temperature, and heart rate);
- Physical examination;
- Adverse Event and Serious Adverse Event assessment (at 30-day,60-day, 90-day, 120-day and 150- day after last study treatment (suspected AEs and SAEs), until resolution to Grade 1/baseline levels; unsuspected AEs or SAEs are followed up to the 150-day follow-up visit, or until the initiation of a new anti-cancer therapy (whichever is sooner));
- New concomitant medications since last visit (at 30-day,60-day, 90-day, 120-day and 150-day after last study treatment, or until the start of new anti-neoplastic medications;
- ECOG Performance Status (see **Table 5-2** above);
- Weight;
- Laboratory blood test (collected and assessed locally);
    - Complete blood count (CBC) with differential (absolute), including but not limited to:
        - Red blood cell (RBC) count
        - Hemoglobin
        - Hematocrit
        - Differential White blood cell (WBC) count

- Absolute neutrophil count (ANC)
- Platelet count

- Chemistry panel including, but not limited to:
  - Sodium
  - Potassium
  - Calcium
  - Chloride
  - Uric Acid
  - Blood urea nitrogen (BUN)
  - Creatinine
  - Glucose
  - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT)
  - Alanine aminotransferase (ALT/SGPT)
  - Alkaline phosphatase
  - LDH
  - Serum Lipase
  - Bilirubin (total and direct)
- Thyroid Panel (free T3, free T4, and TSH)
- Pregnancy test (Serum) is required for WOCBP at 30-day follow up only;
- Pregnancy test (Urine) is required for WOCBP at 60-day, 90-day, 120-day and 150-day follow-up visits;
- Urinalysis is required at 30-day and 150-day follow up visits;
- Recording of anti-neoplastic therapies since the discontinuation of the study treatment is required at 30-day, 60-day, 90-day, 120-day and 150-day follow-up visits;

5.9 Post Treatment Efficacy Follow Up

Post treatment efficacy follow-up is for those patients who discontinue treatment due to reasons other than disease progression, e.g. adverse event. Patients will be followed until disease progression, withdrawal of consent, or lost to follow-up, whichever comes first. The frequency of

tumor response assessments and Ca-19-9 measurements for patients in post-treatment efficacy follow-up is the same as during the treatment period.

5.10 Survival Follow Up

After the end of the Safety Follow-Up and Post Treatment Efficacy Follow Up periods above (where applicable), all patients will be followed for overall survival every three months (+/- 14 days) until death, withdrawal of consent, or lost to follow-up, whichever comes first. Survival follow-up will continue until the end of study, death, or withdrawal of consent by the patient.

If a patient starts a new anti-cancer therapy prior to disease progression during the follow-up period, those patients will continue to be followed for post treatment efficacy and overall survival. This data should be captured in the EDC.

The following procedures will be performed during the efficacy and survival follow-up period:

- Overall survival assessment (phone call every 3 months after the 150-day safety follow-up period);
- Documentation of new anti-cancer therapy if applicable;
- CT/MRI for response assessment, if applicable. For patients that discontinue study treatment in the absence of disease progression (unacceptable toxicity or patient/investigator discretion), CT/MRI scans should be performed accordingly to standard practice to assess efficacy status.

5.11 Patient Discontinuations

The reason for study discontinuation should be recorded in the eCRF and in the source documents. The decision to discontinue a patient remains the responsibility of the treating physician. However, prior to discontinuing a patient, the Investigator may contact the Medical Monitor with the decision to discontinue/withdraw a patient due to an AE (any unacceptable toxicity) and forward appropriate supporting documents for review and discussion. Every attempt should be made to collect all survival information, unless the patient has specifically withdrawn consent from further follow-up. The Investigator should make every effort to obtain minimal information regarding the patient's survival status before determining the patient is lost to follow-up.

6.0 [redacted]

[redacted]

6.1 Tumor Biomarker Collection

Unlike other solid tumors, where traditional imaging modalities provide an accurate and reliable means to assess tumor size and response, pancreatic cancer poses difficulties in lesion measurements. Due to the desmoplastic component of its lesions, unequivocal measurements are challenging (Brand et al. 1998). For this reason, there is increasing interest in identifying correlative endpoints by which to evaluate the effectiveness of therapy. Carbohydrate antigen 19-9 (CA 19-9), a tumor marker widely used in clinical practice in the assessment of patients with pancreatic cancer, has prognostic significance in overall survival and response to treatment in patients with metastatic PDAC (Maisey et al. 2005, Ko et al. 2005, Boeck et al. 2006). Although CA 19-9 is not detectable in 15% of metastatic pancreatic cancer patients, the opportunity for serial CA 19-9 measurements across a variety of novel therapeutic evaluations, including

immunotherapy, stromal disruption and DNA damage pathways, makes this an interesting target for further surrogate development (Poruk et al. 2013, Chiorean et al. 2016).

6.2 Specimen Collection Overview

[redacted]

6.2.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.0 SAFETY ASSESSMENTS

All patients will be uniformly monitored for safety and tolerability. Patient safety assessments will be performed based as outlined in the Schedule of Events in **Section 5.1.**

Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 criteria and assessed by a qualified clinician.

7.1 Definition of Adverse Event

An Adverse Event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during their study participation.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not, considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as if related to tumor progression.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.

- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

7.2 Definition of a Serious Adverse Event

A serious adverse event (SAE) is any adverse event that meets any of the following criteria:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or resulting in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

Events not considered to be SAEs are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment not related to the condition being studied
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite/hospice care

7.3 Monitoring

Patients will be monitored for S/AEs during the trial. All S/AEs will be recorded from the time the patient signs the Informed Consent Form (ICF) through study treatment. During the 150- day (5 months) period after the last dose of study treatment of canakinumab or spartalizumab (due to the half-life of this drug), only treatment-related S/AEs will be recorded.

Assessments may include monitoring of any or all the following parameters:

- Patients' clinical symptoms, laboratory, pathological, radiological or surgical findings
- Physical examination finding
- Findings from other tests and/or procedures

7.4 Reporting

All AEs and SAEs will be coded using MedDRA for reporting to the FDA, and Institutional Review Boards (IRBs), as required. All reportable adverse events should be recorded in the Electronic Data Capture (EDC) system.

7.4.1 Adverse Events

Pre-specified AEs that occur after signing the ICF through the completion of the Treatment Phase related or not to the study assessments, must be entered in the EDC. Refer to the detailed Data Plan with these definitions and specific data entry instructions. Adverse Event assessment will occur until there is a resolution to Grade 1/baseline levels, stabilization, or the initiation of new anti-cancer therapies.

For each reportable AE, the treating clinician will evaluate and report the following:

- Event onset date and event ended date
- AE verbatim term
- Severity grade
- Attribution to study agent (relatedness) with rationale for causality assessment
- Whether or not the event was reported as an SAE (if SAE, criterion/a for seriousness)
- Action taken with study drugs and any treatment given for the AE
- Outcome of the event
- Whether or not the patient discontinued study treatment due to AE
- If treatment was temporarily interrupted, date and dose of re-administration

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.1 criteria) should not be reported as an AE or SAE except if the investigator considers that progression of malignancy is related to study treatment.

AEs separate from the progression of malignancy (example, i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the study drug/s.
Conditions that were already present at the time of informed consent should be recorded as the medical history. Condition/s which developed or worsened after signing informed consent (including during the screening period) should be recorded as AE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as a S/AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.
Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

7.4.2 Severity of AEs

It is important to distinguish between serious and severe AEs. An AE of severe intensity may not necessarily be considered serious and vice versa. See definition of SAEs in **Section 7.2.**

Severity is a measure of intensity which will be graded by using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 criteria. These are based on the general guidelines described in **Table 7-1** below and should be used to assess severity for AE terms not listed in the CTCAE v 5.0.

Table 7-1. AE Severity and Intensity Assessment Scale

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

7.4.3 Causality of AEs

Treating clinicians must determine the relationship between the study treatment and the occurrence for all reportable S/AEs as Not Suspected .or Suspected as defined below in **Table 7-2:**

Table 7-2. AE Causality Assessment

Causality	Description
Not Suspected	Causal relationship of AE to study treatment is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected	Causal relationship of AE to study treatment is a reasonable possibility. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study treatment and the adverse event

(IB RSI is Only for 'Expectedness" for expedited reporting & INs and Not for assessment of causality)

7.4.4 Adverse Events of Special Interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data.

Based upon the available safety information from spartalizumab and canakinumab oncology clinical development programs and known mechanism of action of these drugs and potential overlapping toxicity of all combination drugs, following adverse events are considered ***of special interest*** in this trial population:

- Infections (severe infections and opportunistic infections), including sepsis
- Neutropenia CTCAE Grade ≥3
- Febrile neutropenia
- Peripheral/Sensory neuropathy CTCAE Grade ≥3
- Thrombocytopenia CTCAE Grade ≥3
- *In addition, the potential immune-related AEs considered to be AESIs include, endocrinopathies, colitis, skin reactions, hepatitis, nephritis, pneumonitis and infusion reaction.*

Details regarding these adverse events are provided in the spartalizumab and canakinumab Investigator's Brochures. Potential emergent new AEs will be monitored during the course of the study.

7.4.5 Serious Adverse Events

Any AE that meets any criterion for a SAE requires the completion of a SAE Report Form in addition to being recorded in the EDC. All SAEs must be reported to Sponsor or his/her authorized designee immediately, but no later than within 24 hours of the awareness of the event, via phone or e-mail, along with the SAE report form completed . The Investigator is required to ensure that the data on these forms is accurate and consistent. SAEs must be followed until resolved.

Complete information is important to assess the SAE, but at least the following information needs to be provided within initial 24-hour notification, and additional information may be collected in follow-up contacts:

- Date and time of SAE
- Name of reporter

- Institution Name
- Protocol number/title
- Description of SAE, including reason of seriousness and causality to study treatment

The Medical Monitor and safety/regulatory staff of the Pancreatic Cancer Action Network (PanCAN) or his/her designee will determine which SAEs require expedited FDA submission as safety reports.

All institutions will comply with applicable regulatory requirements related to reporting SAEs to the IRB. The Investigator must keep copies of all SAE information on file including correspondence with Sponsor or his/her authorized designee and the IRB.

7.4.6 Manufacturer Communications

SAEs and AEs will be communicated to the relevant agent manufacturer per their individual safety reporting requirements regarding timing, frequency, and format.

7.4.7 End of Treatment safety Follow-up

All S/AEs, including any laboratory abnormalities, that fit the reportable criteria described in **Section 7.4.1,** will be recorded from the time the patient signs the Informed Consent Form (ICF) until 150 days (5 months) after the last dose of study treatment of canakinumab or spartalizumab (due to the half-life of these drugs), or 30 days after the last dose of the combination chemotherapy, whichever is later.

For SAEs, Investigator (or sub-investigator) and/or their research staff should submit follow-up reports when additional information is available or requested by Sponsor or his/her authorized designee.

8.0 RESPONSE ASSESSMENT

Response assessments (tumor evaluations) should be performed radiographically (CT/MRI) at screening (within a 28-day window prior to Day 1 of treatment), every 8 weeks (± 7 days) until disease progression, at suspected progression if off cycle for evaluation, or withdrawal of consent. CT is the imaging modality of choice for all patient evaluations, although MRI is permitted if CT

contrast allergies occur. Tumor/Response evaluations will be conducted according to RECIST 1.1 guidelines. RECIST evaluations at baseline must be performed at the treating institution.
The primary evaluation of response should be performed using RECIST 1.1 guidelines, by clinician assessment. The same modality (CT/ or MRI) chosen at screening should be used throughout the study. Please refer to Appendix C and Section 9.6 below for full details on the RECIST 1.1 Guidelines to follow for this study.

8.1 Methods for Evaluation of Measurable Disease

8.1.1 Imaging Requirements

Response assessments will be evaluated by imaging (either CT or MRI if CT contrast allergies occur). PET scans are not permissible. The regions to be imaged are the chest and abdomen/pelvis, as well as any other sites that in the opinion of the clinician and medical monitor required tumor imaging. The same mode of imaging for lesion evaluation at pretreatment must be used consistently throughout the study. Adherence to the planned imaging schedule is critical regardless of dose delays, unscheduled or missed assessments.
The CT imaging should include contrast unless medically contraindicated.

8.1.2 Tumor Marker Requirements

Tumor marker response assessments will be evaluated by measuring serum 19-9 (CA19-9) levels at the beginning of each cycle, including at the time of every CT/MRI scan assessment (+/- every 4 weeks). Measurements will be analyzed according to local practice. If feasible, the same assay should be used serially for each patient. Tumor marker levels will be recorded with response, although not included as official response criteria.
Please refer to **Appendix C** and **Section 9.6** below for full details on the RECIST 1.1 Guidelines to follow for this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Analysis Sets

9.1.1 Full Analysis Set

The Full Analysis Set (FAS) and Safety set are defined in the same way and comprise all patients who received at least one dose of study treatment.

9.1.2 Safety Set

See definition of Full Analysis Set (FAS) in **Section 9.1.1** above.

9.1.3 Dose-Determining Analysis Set (DDS)

The Dose-Determining Set (DDS) includes all patients from the safety set who meet the minimum exposure criterion and have sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) during the first two cycles (8 weeks) of dosing.

A patient meets the minimum exposure criterion if the patient received:

- 2 doses of canakinumab (for Q4W dosing regimen cohort) or 1 dose of canakinumab (for Q8W dosing regimen cohort in case the canakinumab dose is de-escalated) and 2 infusions of spartalizumab (full dose) within the first 56 days (8 weeks) of study treatment
- Takes at least 75% of planned doses of gemcitabine plus nab-paclitaxel chemotherapy within the first 56 days (8 weeks) of study treatment

If the patient did not receive the planned number of doses due to DLT, the patient will be considered as meeting the minimum exposure criterion. Patients who do not experience a DLT during the first 56 days (8 weeks) are considered to have sufficient safety evaluations if they have been observed for ≥ 56 days (8 weeks) following the first dose, and are considered by the dose level review team (DLRT) to have sufficient safety data to conclude that a DLT did not occur.

9.1.4 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PAS) consists of all subjects who received at least one dose of study drug and have at least one evaluable pharmacokinetic (PK) sample. The definition of an evaluable PK blood sample will be further specified in the statistical analysis plan (SAP). PAS will be defined for canakinumab, spartalizumab, nab-paclitaxel, and gemcitabine separately.

9.2 Subject Demographics and Other Baseline Characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term.

9.3 Study Treatment and Dose Exposure

The duration of exposure in months as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group; and all dosing data will be listed. The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last dose of study drug.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by dose level.

9.4 Study Primary Objective

The primary objective is to confirmation of the recommended dose for Phase II/III study. The primary endpoint is the incidence of dose limiting toxicities (DLT) in the first 56 days (8 weeks) of the study treatment.

9.4.1 Statistical Model, Hypothesis, and Method of Analysis

For the dose confirmation of canakinumab and spartalizumab in combination with nab-paclitaxel and gemcitabine, a Bayesian hierarchical logistic regression model (BLRM) will be applied to estimate the relationship between dose and the probability of a patient experiencing a dose limiting toxicity (DLT). Some dose-limiting toxicity data are available from previous studies on single agent and combination of canakinumab and spartalizumab (PDR001X2101, ACZ885I2202, PRD001X2103) and a phase I/II study of nab-paclitaxel + gemcitabine (Von Hoff D, et.al., 2011).

These data will be incorporated into BLRM model using a meta-analytic-predictive (MAC) approach (Neuenschwander et al 2016). The details of the historical study and the data are provided in **Appendix B**.

The decision on dose tolerability for will be based on the totality of all relevant data from the ongoing study and a review of safety data from during the DLT evaluation period (the first 8 weeks). A Bayesian logistic regression model (BLRM) for combinations using the escalation with overdose control (EWOC) criterion to evaluate the risk of DLT will guide the decision.

Additional information on the BLRM statistical model is located in **Appendix B.**

9.4.2 Assessment of Patient Risk

Dose recommendations will be based on summaries of the posterior distribution of DLT rates for each dose level of the respective combination therapy. After each cohort of patients, the posterior distribution for the risk of DLT for new patients at combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT for each dose regimen lies within the following intervals:

- Under-dosing: [0 , 0.16)
- Targeted toxicity: [0.16 , 0.33)
- Excessive toxicity: [0.33 , 1]

Dosing regimen decisions are guided by the escalation with overdose control (EWOC) principle **(Rogatko et al 2007).** The possibility of excessive toxicity is of interest in this study as the objective is to confirm the safety of the proposed dose regimen. A dosing regimen may only be used for newly enrolled patients if the risk of excessive toxicity (within the interval [0.33, 1]) at that dosing regimen is less than 25%.

Hypothetical on-study scenarios

To illustrate the performance of the BLRM model used to guide dose escalation, hypothetical dose escalations scenarios are presented in Table 9-1 . In each scenario, the table displays the next dose level with the mean expected probability of dose limited toxicity P(DLT) and the probability of having excessive toxicity P(excessive toxicity) at that dose level. Note that next dose level could be the same dose level. If P(excessive toxicity) is ≥ 25%, then the next dose level does not meet EWOC and no more patients should be enrolled at this dose level and a new cohort should be opened at a lower dose level. The hypothetical scenarios considered various cases with 10 evaluable patients or 6 evaluable patients. Scenario 1, 5, and 6 are cases such that the starting dose is considered safe to proceed (meet EWOC), while scenario 2, and 7 are cases such that starting dose is not considered safe (do not meet EWOC). In those cases, cohort 2 will be opened at a lower dose level (scenario 3, 4, 8, and 9). If cohort 2 is considered unsafe to proceed, no more cohort will be opened.

Table 9-1 Hypothetical Dose Escalation Scenarios

			Number of		Next dose level		
Scenario	**Cohort**	**Canakinumab dose Schedule***	**Evaluable patients**	**DLTs**	**Canakinumab dose schedule***	**Median P(DLT)**	**P(excessive toxicity)**
1	Cohort 1	Q4W	10	2	Q4W	0.152	0.081
2	Cohort 1	Q4W	10	3	Q4W	0.239	0.257
3	Cohort 1	Q4W	10	3			
	Cohort 2	Q8W	10	1	Q8W	0.126	0.019
4	Cohort 1	Q4W	10	3			
	Cohort 2	Q8W	10	2	Q8W	0.172	0.071
5	Cohort 1	Q4W	6	0	Q4W	0.038	0.008
6	Cohort 1	Q4W	6	1	Q4W	0.119	0.075
7	Cohort 1	Q4W	6	2	Q4W	0.240	0.301
8	Cohort 1	Q4W	6	2			
	Cohort 2	Q8W	6	1	Q8W	0.150	0.074
9	Cohort 1	Q4W	6	2			
	Cohort 2	Q8W	6	2	Q8W	0.226	0.234

* Canakinumab 250 mg Q4W or Q8W in combination with fixed dose of spartalizumab 400mg Q4W + nab-paclitaxel 125 mg/m2 + gemcitabine 1000 mg/m2 (Day 1, 8 ,15 of each cycle)

Listing/ summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 5.0, type of adverse event, and by treatment group in the dose escalation. The dose-determining set will be used for these summaries.

9.5 Secondary Safety Objective

Safety summaries will use the Safety Analysis Set.
The overall observation period will be divided into three mutually exclusive segments:

- **Pre-treatment period:** from day of subject's informed consent to the day before first dose of study treatment
- **On-treatment period:** from day of first dose of study medication to 30 days after last dose of study treatment
- **Post-treatment period:** starting at day 30+1 after last dose of study treatment

9.5.1 Adverse Events

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. Summary tables for adverse events (AEs) will include AEs with onset date during the on-treatment period, the treatment-emergent AEs. The incidence of treatment-emergent adverse events will be summarized by system organ class and or preferred term, severity (based on CTCAE 5.0 grades), type of adverse event, and relation to study treatment. All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those starting during the pre-treatment and post-treatment period will be flagged.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated. AESIs will be defined based on the current case

retrieval strategy (CRS). All reported deaths (on-treatment and post-treatment) will be summarized.

9.5.2 Clinical laboratory evaluations

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment/patient group summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.

Listing of all clinically relevant laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the SAP.

9.5.3 Other safety data

Other safety data, include vital signs and ECGs will be listed by dose level and subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

9.6 Secondary Efficacy and PK Objective(s)

9.6.1 Secondary Efficacy Objective(s)

- Analysis of efficacy endpoints will be performed on the Full Analysis Set.
- Tumor response will be determined per local investigators' assessment.
- Response related efficacy assessments will be defined and analyzed based on RECIST 1.1 (primary). ORR and DCR will be estimated, and the exact binomial 95% CI will be

reported. Time to event efficacy endpoints using Kaplan-Meier method and the median along with 95% confidence intervals.

Overall response rate (ORR)

ORR is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR), according to RECIST 1.1. ORR will be calculated based on the FAS. ORR and its 95% exact confidence interval will be presented

Duration of response (DOR)

DOR only applies to subjects in FAS whose BOR is CR or PR according to RECIST 1.1. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Subjects continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment. Kaplan-Meier method will be used to estimate median PFS and 95% confidence intervals will be presented by dose level in FAS (by investigator assessment).

Disease Control Rate (DCR)

DCR is defined as the proportion of subjects with a BOR of CR, PR, or SD, according to RECIST 1.1. DCR will be calculated based on the FAS. DCR and its exact 95% confidence interval will be presented.

Progression Free Survival (PFS)

PFS is defined as the time from the date of first dose to the date of the first documented disease progression based on local investigator assessment as per RECIST 1.1 (assessed by investigator) or death due to any cause. Kaplan-Meier method will be used to estimate median PFS and 95% confidence intervals will be presented by dose level in FAS (by investigator assessment).

Time to response (TTR)

Time to response (TTR) is defined as the time from the date of first doseto the date of first

documented response (CR or PR, which must be confirmed subsequently). Summary statistics will be presented.

Overall survival (OS)

OS is defined as the time from date of first dose of study treatment to date of death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

OS will be analyzed in the FAS population. The OS distribution will beestimated using the Kaplan-Meier method, and the Kaplan-Meier medians and 95% confidence intervals of the medians will be presented.

9.6.2 Secondary PK Objective(s)

PAS will be used in the pharmacokinetic data analysis.. Descriptive statistics (n, m (number of non-zero concentrations), mean, coefficient of variation CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for each analyte (canakinumab, spartalizumab, nab-paclitaxel and gemitabine) will be presented separately at each scheduled timepoint.
All concentration data for canakinumab, spartalizumab, nab-paclitaxel and gemitabine vs. time profiles will be displayed graphically.
The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented for PK parameters as well, except Tmax, where only n, median, minimum and maximum will be presented, when applicable. PK parameters (e.g. AUC, Cmin, Cmax, Tmax, T1/2) will be estimated and reported at appropriate timepoints, when derivation of selective PK parameters is feasible.

9.7 Exploratory Objectives

9.7.1 Biomarkers

This clinical trial is not designed to address specific biomarkers-related exploratory objectives, the analysis of the data should be viewed as hypotheses generating.

There may be circumstances when a decision is made to stop a collection, or not to perform or discontinue the analysis of samples due to either practical or strategic reasons. Under such

circumstances, the sample size number may be too small or the quality of the data not sufficient to perform any data analysis and the available data will be only listed.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the Statistical Analysis Plan or in a stand-alone analysis plan document, as appropriate.

Data transformations, such as base 2 logarithms, may be used to summarize and adequately analyze the data and will be described in detail in the statistical analysis plans.

9.7.2 Data Handling Principles

Analysis sets

Unless otherwise mentioned, the Full Analysis Set is used to describe biomarkers; Safety Set is used to assess the relationship between biomarkers and selected safety endpoints, while the PK Set is used to assess the relationship between PK parameters and biomarkers. Since no imputation is usually planned, the number of subjects included in a given analysis will reflect the number of subjects in the chosen analysis set which have valid biomarker assessments.

Basic tables, figures and listings

Unless otherwise specified, analysis will be performed by dose groups (if more than one dose) [redacted] will be summarized using means, medians, standard deviations, minimums, and maximums, by visit. Both level and change from baseline levels (absolute, percent and fold changes) will be summarized for biomarker that also have assessments at post-baseline visits.

[redacted] will be summarized using frequency counts and percentages.

If sample size is limited then the biomarker data will be listed. For large panels, selected sets of relevant markers will be selected for the listing.

9.7.3 [redacted]

[redacted]

9.8 Handling of Missing Values/ Censoring/ Discontinuations

Patients who are ineligible for the DDS will be excluded from the primary analysis (assessment of recommended dose using incidence of DLT during first 56 days of treatment with canakinumab in combination with spartalizumab, nab-paclitaxel and gemcitabine), although their data will be used for all remaining analyses.

Continuing events (e.g. AEs, concomitant medication, etc.) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing. For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above paragraph.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient. Other missing data will simply be noted as missing on appropriate tables/listings.

A subject whose disease has not progressed or died by the date of the analysis cut-off will have their PFS censored at the time of the last adequate tumor evaluation performed on or before the cut-off date. Clinical deterioration will not be considered as documented disease progression. Censoring rules for PFS follow the RECIST 1.1 guidelines and will be further detailed in the SAP.

A subject who has not died by the date of the analysis cut-off date will have their OS censored at the last known date the subject is alive.

9.9 Sample size

Approximately 10 patients will be enrolled to the starting dose level to have at least 6 evaluable patients. If the starting dose level is considered unsafe, the dose will be de-escalated to dose level -1 and approximatley 10 patients will be enrolled to achieve at least 6 evalulable patients. For further elaboration of safety and pharmacokinetic parameters, additional patients may be enrolled if considered neccessary by Novarits and PIs. Appendix B provided hypothetical scenarios to illustrate the dose recommedation by BLRM.

10.0 STUDY OVERSIGHT

10.1 Investigator Responsibilities

The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. PanCAN Chief Medical Officer or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study at his or her site are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality.

The Investigator should maintain a list of sub-Investigators and other appropriately qualified persons to whom he/she has delegated authority to perform significant study-related duties.
The Investigator is responsible for keeping a record of all patients who sign an ICF document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient's source documents.

The Investigator must ensure that a patient's records and documents pertaining to the conduct of the study and the distribution of the investigational agent are complete, accurate, filed and retained. The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to patient records. The Investigator must ensure timely and accurate completion of electronic Case Report Forms (eCRF) and queries.

10.2 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the sponsor, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

10.3 Data Management

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

Data will be entered into the RAVE-X electronic data capture (EDC) platform by study staff. This data will be electronically verified through the use of programmed edit checks specified by Covance. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

10.4 Data Monitoring

This study focuses data collection on critical and essential variables to ensure important efficacy and safety information are captured. The Data Plan specifies the variables collected and those that are not. The Data Plan also details the process (and systems) for data collection, cleaning, and verification in Precision Promise[SM]. The objective is to decrease data quality issues, improve site compliance and data completeness, control operational bias and ultimately improve patient management and safety.

10.5 Study Monitoring

PanCAN or its authorized designee will ensure that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study, including review the protocol, eCRFs, ICF documents and procedures for obtaining and withdrawing informed consent, record keeping, and reporting of AEs/SAEs, are reviewed with the Principal Investigator, sub-investigators and the study research staff at a study initiation visit and/or at an Investigator meeting. Monitoring will include remote and on-site visits with the Investigator, sub-investigators, and study research staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational agent storage area, eCRFs, patients' source documents, and all other study documentation will be inspected/reviewed by PanCAN or its authorized designee(s) in accordance with the Study Monitoring Plan.

10.6 Audits and Inspections

PanCAN or its authorized designee(s), local IRB or the FDA may conduct audits of clinical research activities to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study takes place, source documents, eCRFs and applicable supporting records of study participation for audits and inspections by IRBs, FDA and PanCAN or his/her authorized designees. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact PanCAN or his/her authorized designee immediately.

10.7 Pharmaceutical Agreements

Investigational agents are provided under a contract between Agent Manufacturer and PanCAN. They may not be used outside of the study protocol.

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Good Clinical Practice

This protocol describes procedures pertaining to conduct, evaluation, and documentation to ensure that PanCAN, its authorized designee(s), and the study Investigators, sub-investigators and site staff abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

11.2 Record Keeping

Study sites selected for participation in this study will be responsible for submitting essential regulatory documents to PanCAN or its authorized designee.

The collection of regulatory documents will take place in accordance with applicable ICH GCP guidelines, state and federal regulations. Regulatory documents must be maintained per all applicable institutional and federal regulations. All questions related to regulatory document submission should be directed to the attention of PanCAN or his/her authorized designee. The following documents comprise the essential regulatory document packet required.

11.2.1 Form FDA 1572

The Investigator will provide an **original signed** Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing all the sub-investigators at that institution that will participate in the protocol prior to study initiation.

11.2.2 Other Required Documents

- **CV/Biosketch** for the Investigator and all sub-investigators listed on Form FDA 1572
- **Current professional licenses** (where applicable) for the Investigator and all sub-

investigators listed on Form FDA 1572

- **Financial Disclosure Form** for the Investigator and all sub-investigators listed on Form FDA 1572
- **Certification of Human Subjects Protection Training** (NIH or institution-based training program certificate) for the Investigator and all sub-investigators listed on Form FDA 1572
- **Delegation of Responsibilities Log** signed by the Investigator. This document lists the names and responsibilities of all study staff, including all sub-investigators listed on Form FDA 1572
- **Lab certifications** *(*CLIA and CAP) and lab normal ranges for all labs listed on each site's Form FDA 1572.
- **Documentation of Federal wide Assurance (FWA).** A print-out of the institutional FWA number may be accessed *via* the OHRP website as follows: http://ohrp.cit.nih.gov/search/fwasearch.aspx?styp=bsc. (Click the button for FWAs [FWA number])
- **Investigator's Brochure (IB) Acknowledgment Form** signed by the Investigator for **each** IB received
- **IRB approval** for all PanCAN-approved Protocol versions, ICFs, IB versions (if applicable) and patient educational and recruitment materials

11.2.3 Submission of Required Documents

All required documents may be transmitted *via* email with the exception of the following documents for which signed originals must be sent via traceable courier: 1) Form FDA 1572 2) Financial Disclosure Form.

11.3 Patient Information and Informed Consent

The investigator or his/her authorized designee must obtain informed consent of a patient and/or a patient's legal representative prior to any study-related procedures.

Documentation that informed consent occurred prior to the patient's entry into the study and of the informed consent process should be recorded in the study patient's source documents including the date. The original ICF documents signed and dated by the patient and by the person consenting

the patient prior to the patient's entry into the study, must be maintained in the Investigator's study files and a copy given to the study patient.

In addition, when the protocol is amended and the information changes patient risk, the ICF document will be revised. Study patients who are active in the study when the updated relevant informed consent is implemented must be re-consented with the revised version of the appropriate ICF. Those patients that are on active treatment must be re-consented only to the treatment phase ICF and investigational arm ICF, if appropriate. If the Screening ICF is updated once a patient proceeds to the Treatment Phase, re-consenting to the Screening ICF is not required. The revised ICF document signed and dated by the study patient and by the person re-consenting the study patient must be maintained in the Investigator's study files and a copy given to the study patient.

11.3.1 Informed Consent Form(s) Review and Approval Process

Prior to study initiation, the ICF documents must be reviewed and approved by PanCAN or his/her authorized designee, and the IRB at each institution at which the protocol will be implemented. Any subsequent changes to the ICF document(s) must be approved by PanCAN or his/her authorized designee, and then submitted to each institution's IRB for approval prior to initiation.

11.4 Institutional Review Board (IRB) Approval

Prior to initiating the study and receiving the investigational agent(s), written approval to conduct the study from the appropriate IRB must be obtained. As changes to the study become necessary, protocol amendments will be submitted to PanCAN according to Amendment Guidelines. PanCAN-approved amended protocol must be approved by the IRB prior to implementation.

As investigational arms move in and out of the trial, protocol amendments will be issued.

11.4.1 IRB Approval Timeline Guidelines

Participating institutions will be notified of the allowable timeframe permitted to get each amendment approved by their institutional IRB.

- **Major Modification**: Participating institutions have 60 calendar days to submit and obtain IRB approval. If an institution's IRB approval letter is not received by PanCAN or his/her authorized designee ≤ 60 calendar days, accrual at that institution may be placed on hold until IRB approval is obtained and approval letters have been received and processed by

PanCAN or his/her authorized designee.

- **Minor Modification (not including administrative amendments)**: Participating institutions have 30 calendar days to submit and obtain IRB approval. If an institution's IRB approval letters are not received by PanCAN or his/her authorized designee ≤30 calendar days, accrual at that institution may be placed on hold until institutional IRB approval is obtained, and approval letters have been received and processed by PanCAN or his/her authorized designee.
- **Administrative Amendments**: Amendments that are administrative in nature do not require IRB approval will be submitted to the IRB for information purposes.

11.5 Joint Safety Committee and Dose Confirmation Meeting

Decisions for confirmation of dose or to assess a different dose level will be made jointly by Investigators and study personnel that will include at least Medical Monitor and a biostatistician. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during the first two cycles, and PK data from evaluable patients. The recommended dose for the next cohort of patients will be guided by the BLRM.

11.6 Study Termination

The Sponsor (PanCAN) or FDA can terminate the trial at any time. Appropriate measures would be made to try to ensure support and continuance of patient care.

12.0 RECORD KEEPING/QUALITY CONTROL

12.1 Inspection

PanCAN or its authorized designee must be allowed to conduct site visits for monitoring any aspects of the study. Source data/documents must be available for inspection for PanCAN, its authorized designee or any Regulatory Authority. Monitoring can include inspection of drug storage area, study drug stocks, drug accountability records, patient medical records and study source documents, and other records related to study conduct.

12.2 Record Retention

In accordance with applicable regulatory requirements, following closure of the trial, the Investigator will maintain a copy of all essential documents in a safe and secure location. Essential documents must be retained by the Investigator according to the period of time outlined in the Clinical Trial Agreement.

Documents included in this retention policy include but is not limited to:

- Signed ICF's for all patients
- Pre-screening and screening logs and enrollment logs
- Record of all communication with Investigator and IRB
- Composition of IRB or confirmation statement that the IRB is composition is in accordance with GCP, if composition may not be disclosed.
- Communication between Investigator and Sponsor and authorized designees
- Delegation of Responsibility Log
- Access to eCRFs
- Study treatment accountability records
- Record of and body fluid or samples retained
- All other source documents listed in Section 8 of ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

PanCAN or his/her authorized designee must be notified, in writing, if the Investigator wishes to assign the study records to another party or move them to another location or destroy any documents. Institutions/Investigators should take measured to prevent accidental or premature destruction of these documents.

13.0 CONFIDENTIALITY

The information contained in this Study Protocol (except for the information provided by PanCAN in public scientific presentations and publications, public websites or through press releases) is considered PanCAN confidential information. Only information that is previously disclosed by PanCAN in public scientific presentations and publications, public websites or through press releases may be freely disclosed by the Investigator, his/her sub-investigators, study staff or institution, or as outlined in the Clinical Trial Agreement. This Study Protocol is not to be made publicly available (for example on the Investigator's or his/her institution's website) without written approval from PanCAN.

14.0 REFERENCES

American Cancer Society. *Cancer Facts & Figures 2017.*

Apte RN, Dotan S, Elkabets M, et al. The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions. Cancer Metastasis Rev. 2006; p. 387-408.

Arranz L, Arriero MDM, Villatoro A. Interleukin-1β as emerging therapeutic target in hematological malignancies and potentially in their complications. Blood Rev. 2017; p. 306-317.

Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med. 1998; 17(10):1103-20.

Becker Y. Molecular immunological approaches to biotherapy of human cancers-a review, hypothesis and implications. Anticancer Res. 2006; p. 1113-34.

Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature 2012; 491:399-405.

Biotechnology Innovation Organization, BIomedtracker, Amplion. Clinical development success rates, 2006-2015. Published. 2016

Boeck S, Haas M, Laubender RP, Kullmann F, Klose C, Bruns CJ, Wilkowski R, Stieber P, Holdenrieder S, Buchner H, Mansmann U, Heinemann V. Application of a Time-Varying Covariate Model to the Analysis of CA 19-9 as Serum Biomarker in Patients with Advanced Pancreatic Cancer. Clin Cancer Res. 2006; 16(3):986–94.

Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012; 366: 2455-65

Brahmer, J. R., Lacchetti, C., Schneider, B. J., 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.

Brand RE and Tempero MA. Pancreatic cancer. Curr Opin Oncol. 1998; 10:362–366.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424)

Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul J-L, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet J-B, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E. Chauffert B, Michel P, Montoto-Grillot C, Ducreaux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer N Engl J Med. 2011; 364(19):1817-1825.

Daley D, Mani VR, Mohan N, Akkad N, Pandian G, Savadkar S, et al. NLRP3 signaling drives macrophage-induced adaptive immune suppression in pancreatic carcinoma. J Exp Med 2017; 214:1711–24.

Das S, Shapiro B, Vicic E et al. Tumor Cell–Derived IL1b Promotes Desmoplasia and Immune Suppression in Pancreatic Cancer January 8, 2020; DOI: 10.1158/0008-5472.CAN-19-2080

Dinarello CA. Biologic basis for interleukin-1 in disease. Blood 1996; p. 2095-147

Ebrahimi B, Tucker SL, Li D, et al. Cytokines in pancreatic carcinoma: correlation with phenotypic characteristics and prognosis. 2004; 101:2727-36.

EMA, Guideline on Clinical Trials in Small Populations, February 1 2007

FDA, Challenges and Opportunities Report. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. March 2004.

Fox BA, Schendel DJ, Butterfield LH et al. Defining the critical hurdles in cancer immunotherapy. J Transl Med. 2011; 9:214. doi: 10.1186/1479-5876-9-214

Freeman GJ. Structures of PD-1 with its ligands: sideways and dancing cheek to cheek. Proc Natl Acad Sci USA 2008; 105:10275-6.

Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. Immunity 2013; p. 1003-18.

Gowen M, Wood DD, Ihrie EJ, et al. An interleukin 1 like factor stimulates bone resorption in vitro. Nature 1983; p. 378-80.

Guo Q, Jin Z, Yuan Y, et al. New Mechanisms of Tumor-Associated Macrophages on Promoting Tumor Progression: Recent Research Advances and Potential Targets for Tumor Immunotherapy. J Immunol Res 2016; p. 9720912.

Haanen JBAG, Carbonnel F, Robert C et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 1;28(suppl_4):iv119-iv142.

Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

Hu ZI, Shia J, Stadler ZK et al. Evaluating Mismatch Repair Deficiency in Pancreatic Adenocarcinoma: Challenges and Recommendations. Clin Cancer Res 2018; 24:1326-1336.

Incio J, Liu H, Suboj P, Chin SM, Chen IX, Pinter M, et al. Obesity-induced inflammation and desmoplasia promote pancreatic cancer progression and resistance to chemotherapy. Cancer Discov 2016; 6:852–69.

Johnson BE, Kim TA, Hilterman JN et al. Safety Run-in Results From Phase 3 Study of Canakinumab (CAN) or Placebo in Combination with Pembrolizumab (PEM) Plus Platinum-based Doublet Chemotherapy (Ctx) as 1st Line Therapy in Patients (pts) with Advanced or Metastatic NSCLC (CANOPY-1). Poster Presented at AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 26-30, 2019

Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin MT, Calhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Maitra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses. Science. 2008; 321(5897): 1801–1806.

Kaplanov I, Carmi Y, Kornetsky et al. Blocking IL-1β reverses the immunosuppression in mouse breast cancer and synergizes with anti–PD-1 for tumor abrogation. PNAS 2019; 116:1361-1369

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008; 26:677-704.

Ko AH, Hwang J, Venook AP, Abbruzzese JL, Bergsland EK, Tempero MA. Serum CA19-9 response as a surrogate for clinical outcome in patients receiving fixed-dose rate gemcitabine for advanced pancreatic cancer. Br J Cancer 2005; 93(2):195–199.

Koch AE, Kunkel SL, Chensue SW, et al. Expression of interleukin-1 and interleukin-1 receptor antagonist by human rheumatoid synovial tissue macrophages. Clin. Immunol. Immunopathol. 1992; p. 23-9

Krelin Y, Voronov E, Dotan S, et al. Interleukin-1beta-driven inflammation promotes the development and invasiveness of chemical carcinogen-induced tumors. Cancer Res. 2007; p. 1062-71.

Le DT, Wang-Gillam A, Picozzi V, et al. Safety and survival with GVAX pancreas prime and Listeria Monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. J Clin Oncol 2015; 33:1325-33.

Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017; 357:409-413

Lesina M, Kurkowski MU, Ludes K, et al. Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. Cancer Cell 2011; 19:456-69.

Lewis AM, Varghese S, Xu H, et al. Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment. J Transl Med 2006; p. 48.

Maisey NR, Norman AR, Hill A, Massey A, Oates J, Cunningham D. CA19-9 as a prognostic factor in inoperable pancreatic cancer: the implication for clinical trials. Br J Cancer. 2005; 93(7):740-743.

Mahadevan D, Von Hoff DD. Tumor-stroma interactions in pancreatic ductal adenocarcinoma. Mol Cancer Ther. 2007; 6(4):1186-97

Maker AV, Katabi N, Qin LX, Klimstra DS, Schattner M, BrennanMF, et al. Cyst fluid interleukin-1beta (IL1beta) levels predict the risk of carcinoma in intraductal papillary mucinous neoplasms of the pancreas. Clin Cancer Res 2011; 17: 1502–8.

Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2013. Ann Oncol. 2013; 24(3):792-800.

Mangsbo SM, Sandin LC, Anger K, et al. Enhanced tumor eradication by combining CTLA-4 or PD-1 blockade with CpG therapy. J Immunother. 2010; 33:225-35.

Mantovani A, Barajon I, Garlanda C. IL-1 and IL-1 regulatory pathways in cancer progression and therapy. Immunol. Rev. 2018; p. 57-61.

McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev. 2013; 39:534-40

Minchinton AI, Tannock IF. Drug penetration in solid tumours. Nat Rev Cancer. 2006; 6(8):583-92.

Mkrtichyan M, Najjar YG, Raulfs EC, et al. Anti-PD-1 synergizes with cyclophosphamide to induce potent anti-tumor vaccine effects through novel mechanisms. Eur J Immunol 2011; 41:2977-86.

Moore MJ, Goldstein D, Hamm J et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group J Clin Oncol. 2007; 25: 1960-1966.

Mora J, Weigert A. IL-1 family cytokines in cancer immunity - a matter of life and death. Biol. Chem. 2016; p. 1125-1134.

Natanegara F, Neuenschwander B, Seaman JW Jr, et al. The current state of Bayesian methods in medical product development: survey results and recommendations from the DIA Bayesian Scientific Working Group. Pharm Stat. 2014 Jan-Feb;13(1):3-12.

Neuenschwander, B, Branson M,. and Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in medicine, 2008. 27(13), pp.2420-2439

Neuenschwander B, Capkun-Niggli G., Branson M., and Spiegelhalter D.J. Summarizing historical information on controls in clinical trials. Clinical Trials, 2010; 7(1), pp.5-18.

Neuenschwander B, Roychoudhury S, Schmidli H. On the Use of Co-Data in Clinical Trials. Statistics in Biopharmaceutical Research. 2016; 8:345-354.

Neuenschwander, B. et al. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceutical statistics, 2016; 15(2), pp.123–134.

Nomi T, Sho M, Akahori T, et al.: Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007; 13: 2151–2157.

Parseghian CM, Patnana M, Bhosale et al Evaluating for Pseudoprogression in Colorectal and Pancreatic Tumors Treated with Immunotherapy. J Immunotherapy 2018; 41:284-291.

Poruk KE, Gay DZ, Brown K, Mulvihill JD, Boucher KM, Scaife CL, Firpo MA, Mulvihill SJ. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. *Curr Mol Med.* 2013; 13(3): 340–351.

Pu N, Wnhui L and Jun Y. PD-1 immunotherapy in pancreatic cancer current status. J Pancreatol. 2019; 2:6-10

Ridker PM. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. Circ. Res. 2016; p. 145-56.

Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N. Engl. J. Med. 2017; a. p. 1119-1131.

Riley JL. PD-1 signaling in primary T cells. Immunol Rev. 2009; 229:114-25.

Rogatko A, Schoeneck D, Jonas W, et al. Translation of innovative designs into phase I trials. J Clin Oncol 2007; 25:4982-6.

Rosenblatt J, Glotzbecker B, Mills H, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. J Immunother. 2011; 34:409-18.

Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010; 33:828-33.

Salmiheimo A, Mustonen H, Stenman UH et al. Systemic inflammatory response and elevated tumour markers predict worse survival in resectable pancreatic ductal adenocarcinoma. PLoS One 2016; 11:e0163064

Siegel R, Miller K, Jemal A: Cancer statistics, 2020. CA Cancer J Clin. 2020; 70(1):7-30

Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci. Lett. 2004; p. 184-7.

Spiegelhalter, DJ. Incorporating Bayesian Ideas into Health-Care Evaluation. Statistical Science, 2004. 19(1), 156-174.

Tan CR, Yaffee PM, Jamil LH, et al. Pancreatic cancer cachexia: a review of mechanisms and therapeutics. Front Physiol 2014; 5:88. doi: 10.3389/fphys.2014.00088

Thompson JA, Schneider BJ, Brahmer J. et al. Management of Immunotherapy-Related Toxicities, Version 1.2019. J Natl Compr Canc Netw. 2019; 17:255-289

Wang W, Lau R, Yu D, et al. PD1 blockade reverses the suppression of melanoma antigen-specific CTL by CD4+ CD25(Hi) regulatory T cells. Int Immunol. 2009; 21:1065-77.

Whatcott CJ, Han H, Von Hoff DD. Orchestrating the tumor microenvironment to improve survival for patients with pancreatic cancer: normalization, not destruction. Cancer J. 2015; 21(4): 299–306.

Weiss GJ, Blaydorn L, Beck J, et al. Phase Ib/II study of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic adenocarcinoma. Invest New Drugs 2018; **36:** 96–102.

Werner J, Combs SE, Springfeld C, Hartwig W, Hackert T, Büchler MW. Advanced-stage pancreatic cancer: therapy options. Nat Rev Clin Oncol. 2013; 10(6):323-33.

Wu T, Hong Y, Jia L, et al. Modulation of IL-1β reprogrammes the tumor microenvironment to interrupt oral carcinogenesis. Sci Rep 2016; p. 20208.

Von Hoff DD, Ramanathan R, Borad M, Laheru D, Smith L, Wood TE, Korn R, Desai N, Trieu V, Iglesias J, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A, Hidalgo M. Gemcitabine plus Nab-Paclitaxel is an Active regimen in patients with advanced pancreatic cancer: A Phase I/II trial. J Clin Oncol. 2011; 29(34): 4548-4554.

Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013; 369(18):1691-1703.

Zhang J, Xiang D, Zhu S, et al. Interleukin 1 receptor antagonist inhibits normal hematopoiesis and reduces lethality and bone marrow toxicity of 5-fluouracil in mouse. Biomed. Pharmacother. 2009; p. 501-8.

Zhang D, Li L, JiangH, LiQ,Wang-Gillam A, Yu J, et al. Tumor-Stroma IL1beta- IRAK4 feedforward circuitry drives tumor fibrosis, chemoresistance, and poor prognosis in pancreatic cancer. Cancer Res 2018; 78:1700–12

Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity 2013 39: 74–88;

Zitvogel L, Kepp O, Kroemer G Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat Rev Clin Oncol 2011; 8: 151–160.

15.0 APPENDICES

APPENDIX A

Gemcitabine and Nab-paclitaxel Package Inserts

Gemzar USPI 2019 http://uspl.lilly.com/gemzar/gemzar.html

Abraxane USPI 2019 https://media2.celgene.com/content/uploads/abraxane-pi.pdf

APPENDIX B

BLRM Statistical Model

This appendix provides details of the statistical model used for each treatment arm, the derivation of prior distributions, and the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios.

1 Statistical model for triple combination

For each treatment arm, the statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity information, and interaction parts to describe two-way drug safety interactions. The proposed statistical model uses a meta-analytic framework (Neuenschwander 2016) to combine all historical and concurrent data.

1.1 Single agent parts

Let $\pi_i(d_i)$ be the risk of DLT for compound i given as a single agent at dose d_i (i=1, 2, 3). The single agent dose-DLT models are logistic:

$$\text{logit}\big(\pi_{\text{i}}(d_i)\big) = \log(\alpha_i) + \beta_{\text{i}} \log(d_{\text{i}}/d_{\text{i}}^*) \quad \text{i=1, 2, 3} \qquad (1)$$

where d_i^* , the reference dose, is used to scale the doses of each compound. The reference doses are defined in the appropriate model specification sections.

Hence, α_i (>0) is the single-agent odds of a DLT at d_i^* and β_i (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

1.2 Interaction

Under no interaction, the risk of a DLT for combination dose (d_1, d_2, d_3) is:

$$\pi_{123}^0(d_1, d_2, d_3) = 1 - \big(1 - \pi_1(d_1)\big)\big(1 - \pi_2(d_2)\big)\big(1 - \pi_3(d_3)\big)$$

To allow for interaction between each pair of compounds, odds multipliers, $\eta_{12}, \eta_{13}, \eta_{23}$ are introduced.

The risk of DLT for combination dose (d_1, d_2, d_3) is then given by:

$$\text{odds}\big(\pi_{123}(d_1, d_2, d_3)\big) = \exp\left(\eta_{12}\frac{d_1 d_2}{d_1^* d_2^*} + \eta_{13}\frac{d_1 d_3}{d_1^* d_3^*} + \eta_{23}\frac{d_2 d_3}{d_2^* d_3^*}\right) \times \text{odds}\big(\pi_{123}^0(d_1, d_2, d_3)\big)$$

Where,

$\text{odds}(\pi) = \pi/(1-\pi)$;

η_{ij} is the log of the odds ratio between the interaction and no interaction model at dose d_{i}^* and d_{j}^* for treatments i and j and a zero dose of the third treatment;

$\eta_{\cdot} = \eta_{12} + \eta_{23} + \eta_{32}$ is the log of the odds ratio between the interaction and no interaction model at dose d_1^*, d_2^* and d_3^* for all three treatments. Here $\eta_{\cdot} = 0$ corresponds to no overall interaction, with $\eta_{\cdot} > 0$ and $\eta_{\cdot} < 0$ representing overall synergistic and antagonistic toxicity respectively.

1.3 Meta-analytic framework

Assume we have data from J historical or concurrent trials, which we want to use in combination with data in the new treatment arm.

1.3.1 Single agent part

Let $\pi_{ij}(d_{ij})$ (i=1, 2, 3) be the risk of single agent DLT in trial (stratum) j (j=*, 1, …, J) as defined in (1), where * corresponds to the risk in the current treatment arm. The current treatment will be split in different strata representing the different dosing regimens explored.

The model assumes exchangeable parameters ("random effects"), and introduces a variance component accounting for between-trial heterogeneity.

$$\theta_{ij} = \left(\log(\alpha_{ij}), \log(\beta_{ij})\right) \sim BVN(\mu_i, \Gamma_i),$$

Where,

$$\mu_i = (\mu_{i\alpha}, \mu_{i\beta}) \text{ and } \Gamma_i = \begin{bmatrix} \tau_{i\alpha}^2 & \rho_i \tau_{i\alpha} \tau_{i\beta} \\ \rho_i \tau_{i\alpha} \tau_{i\beta} & \tau_{i\beta}^2 \end{bmatrix}$$

i = 1, 2, 3

j = *, 1, …, J

However, as these studies may involve different regimens or patient populations, they can have different safety profiles. Therefore, a non-exchangeable component in the parameter model may be included to handle deviation from the exchangeability assumption.

The final single agent model parameter, for each component, is as follows:

$$\theta_{ij} \sim p_{ij} BVN(\mu_i, \Gamma_i) + (1 - p_{ij}) BVN(m_i, S_i^2)$$

i = 1, 2, 3; j = *, 1, …, J

1.3.2 Interaction

Let $\eta_{12j}, \eta_{13j}, \eta_{23j}$ be the two-way interaction parameters in trial j (j=*, 1, …, J). As above, a robust exchangeability model is assumed for the two-way interaction parameters.

$$\eta_{12j} \sim p_{\eta_{12j}} N(\mu_{\eta_{12}}, \tau_{\eta_{12}}^2) + (1 - p_{\eta_{12j}}) N(m_{\eta_{12}}, S_{\eta_{12}}^2)$$

$$\eta_{13j} \sim p_{\eta_{13j}} N(\mu_{\eta_{13}}, \tau_{\eta_{13}}^2) + (1 - p_{\eta_{13j}}) N(m_{\eta_{13}}, S_{\eta_{13}}^2)$$

$$\eta_{23j} \sim p_{\eta_{23j}} N(\mu_{\eta_{23}}, \tau_{\eta_{23}}^2) + (1 - p_{\eta_{23j}}) N(m_{\eta_{23}}, S_{\eta_{23}}^2)$$

1.4 Reference doses for spartalizumab, canakinumab and chemotherapy

The dose level for each drug used in the BLRM model is total dose admininstered during the DLT period (2 cycles). The reference dose for spartalizumab is set at [redacted] The reference dose for the canakinumab is [redacted].

[redacted]

1.5.1 Single agent

[redacted]

[redacted]

[redacted]

1.6 [redacted]

[redacted]

[redacted]

[redacted]	[redacted]
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1.7 Historical data

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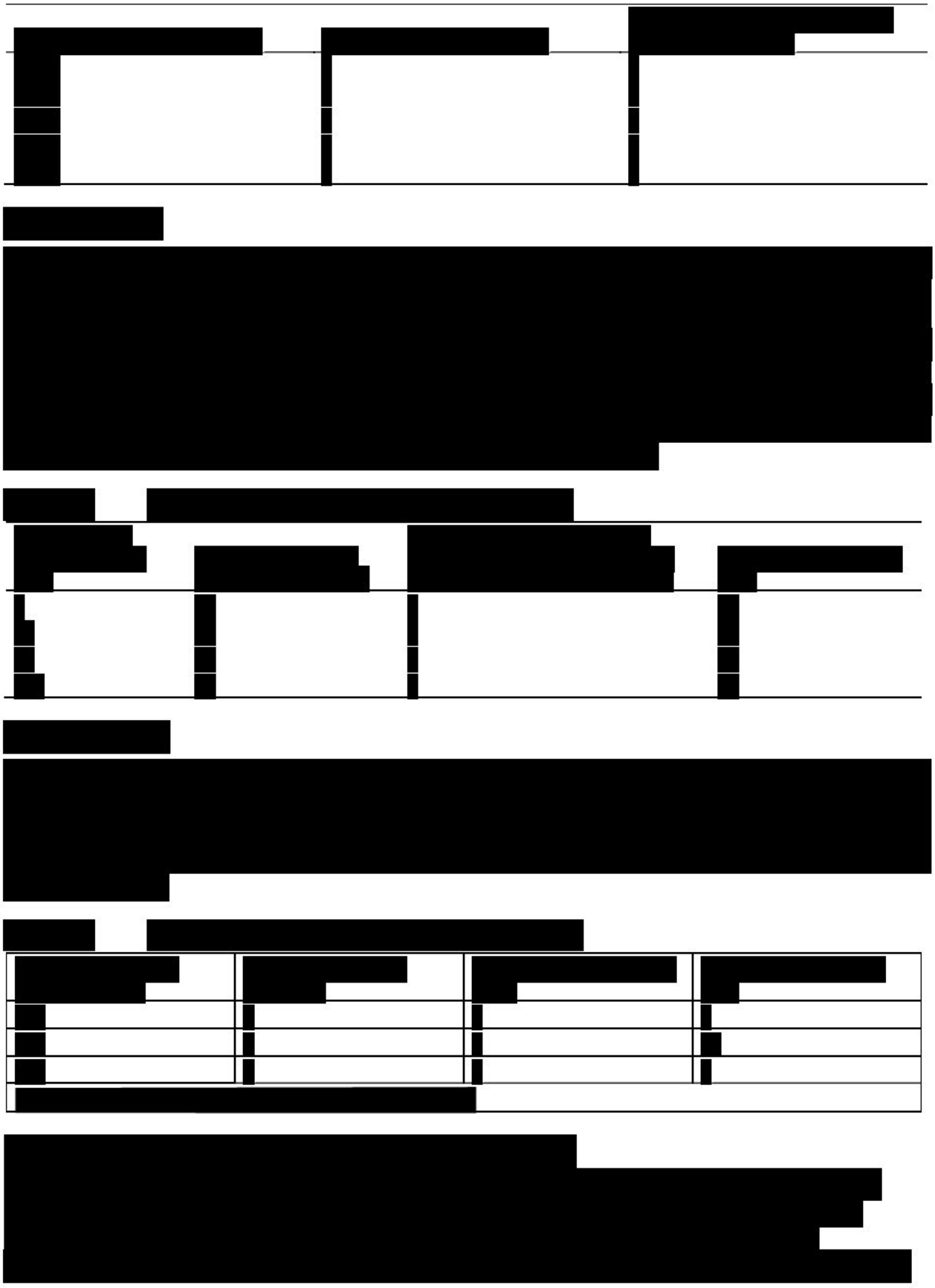

APPENDIX C

RECIST Guidelines 1.1

THIS DOCUMENT WILL BE PROVIDED SEPARATELY

Statistical Analysis Plan

Pancreatic Cancer Action Network

PanCAN-SR1

Labcorp Drug Development Study ID: 000000203412
Document Version: 1.0
Document Date: 16Sep2022

Labcorp Drug Development

Table of Contents

Reviewers

The following reviews of the Statistical Analysis Plan (SAP) were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted]	[redacted]	[redacted]	[redacted]
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Glossary of Abbreviations

Abbreviation	Term
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{last}	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
BSA	Body Surface Area
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
BOR	Best Overall Response
BP	Blood Pressure
BUN	Blood urea nitrogen
C_{last}	Last plasma concentration
C_{max}	Maximum plasma concentration
CI	Confidence Interval
CR	Complete response
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical Study Report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDS	Dose determining analysis set
DCR	Disease control rate
DLT	Dose Limiting Toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDISH	Evaluation of Drug Induced Serious Hepatotoxicity
FAS	Full Analysis Set
GCV(%)	Geometric Coefficient of Variation
Gmean	Geometric mean
HR	Heart Rate
IG	Immunogenicity
IL-1β	Interleukin-1β cytokine
IL-6	Interleukin-6 cytokine
IND	Investigational Drug
INR	International Normalised Ratio
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria
NE	Not evaluable
NQ	Not Quantifiable
ORR	Overall Response Rate

OS	Overall Survival
PAS	Pharmacokinetic analysis set
PD	Progressive disease
PDAC	Pancreatic adenocarcinoma
PK	Pharmacokinetic
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SoC	Standard of Care
t_{last}	Time of the last quantifiable concentration
t_{max}	Time to reach maximum plasma concentration
TTR	Time to response
TFLs	Tables, figures, and listings
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper Limit of Normal
WBC	White Blood Cell

STATISTICAL ANALYSIS PLAN AMENDMENT 1

This section is not required at this time, but may be populated in a future approved version of this document.

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	22 Jul 2020	1.2
Electronic Case report form (eCRF)	08 Apr 2021	3.01

2. Protocol Details

2.1 Study Objectives

2.1.1 Study Primary Objective

The primary objective is to confirm the recommended phase II/III dose regimen of canakinumab in combination with spartalizumab, gemcitabine and nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) as first line treatment.

2.1.2 Study Secondary Objectives

The secondary safety, efficacy and pharmacokinetic (PK) objectives respectively are:

- To determine the safety and tolerability of canakinumab in combination with spartalizumab, nab-paclitaxel and gemcitabine;
- To assess the preliminary clinical anti-tumor activity of canakinumab in combination with spartalizumab, nab-paclitaxel and gemcitabine;
- To characterize the pharmacokinetics of canakinumab, spartalizumab and chemotherapy agent in combination regimen.

[redacted]

[redacted]

- [redacted]
- [redacted]

2.2 Overall Study Design

This is an open-label multi-center phase Ib study to confirm the recommended phase II/III dose of canakinumab and spartalizumab in combination with nab-paclitaxel and gemcitabine as first-line therapy for patients with metastatic pancreatic cancer.

Patients will be treated until disease progression per RECIST 1.1, unacceptable toxicity, or until the patient or treating physician decides to stop treatment. Pharmacokinetic (PK) [redacted] samples will be collected at specific time points throughout treatment. Each treatment cycle is 4 weeks.

The study population is treatment naïve patients with metastatic PDAC.

All patients must be followed for safety up to 150 days after the last dose of spartalizumab or canakinumab, or 30 days after the last dose of the combination chemotherapy, whichever the later.

After the end of safety follow-up, patients will be followed for disease progression if discontinuation of treatment is due to any reason other than progression, and for survival until the end of study. The study completion is defined as when the last patient has completed the study treatment, safety follow-up, and completed survival follow up period up to 1 year from first treatment, whichever is later or in the event of an early study termination decision, the date of that decision.

For this study, the investigational drugs (INDs) are spartalizumab (PDR001) and canakinumab (ACZ885) while the non-investigational drugs are gemcitabine and nab-paclitaxel. The study treatment is defined as canakinumab in combination with spartalizumab, gemcitabine and nab-paclitaxel.

Table 1 defines the starting dose level. In case of unacceptable toxicity of the starting dose level, the enrollment to the current dose level will be stopped and a lower dose (-1 dose level) will be used.

Table 1 Initial Dose and Treatment Schedule

Study treatments	Pharmaceutical form and route of administration	Strength	Starting Frequency and/or Regimen	Dose Administered
Spartalizumab (PDR001)	Concentrate for solution for IV infusion	4 x 100 mg vials	Day 1 of each 28-day cycle	400 mg
Canakinumab (ACZ885)	Solution for SC. injection in prefilled syringe	200 mg/1.33 mL AND 1 x 50 mg/0.5 mL	Day 1 of each 28-day cycle	250 mg

Study treatments	Pharmaceutical form and route of administration	Strength	Starting Frequency and/or Regimen	Dose Administered
Gemcitabine	IV		Days 1, 8, 15 of each 28-day cycle	1000 mg/m^2
Nab-paclitaxel	IV		Days 1, 8, 15 of each 28-day cycle	125 mg/m^2

IV = intravenous; SC = subcutaneous

Table 2 below describes the starting dose and the -1 dose level in case the starting dose has unacceptable toxicity.

Table 2 Provisional dose levels for the canakinumab with fixed dosage of spartalizumab, Gemcitabine and nab-paclitaxel

Dose level	Proposed dose of canakinumab
1 (starting dose)	250 mg SC Q4W Canakinumab
*-1**	250 mg SC Q8W Canakinumab

SC = subcutaneous Q4W= every 4 weeks Q8W= every 8 weeks

Spartalizumab: 400 mg SC. Q4W; Gemcitabine: 1000 mg/m^2+ nab-paclitaxel 125 mg/m^2 (on day 1, 8, and 15 of every cycle).

**Dose level -1 represents the treatment dose for patients requiring a dose reduction from the starting dose level.*

Approximately 10 patients will be enrolled initially to have at least 6 evaluable patients per dose level (additional patients may be enrolled as needed in order to have 6 evaluable patients). Patients must complete a minimum of 56 days (8 weeks) of dosing of study treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first 56 days of study treatment to be considered evaluable for recommended dose decisions. Additionally, approximately ten patients (to have at least 6 additional evaluable patients) may be enrolled at lower dose level in case a dose de-escalation is necessary. This could occur if a minimum of 6 evaluable patients has been treated and deemed evaluable at this dose and unacceptable toxicity is observed at that dose.

The decision on dose tolerability will be based on all relevant data from the ongoing study and a review of safety data from the first 8 weeks (see section 4.1.5 of CSP).

2.3 Sample Size and Power

Approximately 10 patients will be enrolled to the starting dose level to have at least 6 evaluable patients. If the starting dose level is considered unsafe, the dose will be de-escalated to dose level -1 and approximately 10 patients will be enrolled to achieve at least 6 evaluable patients. For further elaboration of safety and PK parameters, additional patients may be enrolled if considered necessary by Novartis and Principal Investigators. Appendix B of the clinical study protocol (CSP) provided hypothetical scenarios to illustrate the dose recommendation by Bayesian hierarchical logistic regression model (BLRM).

3. Efficacy and Safety Variables

3.1 Primary Safety Endpoint

The primary endpoint is the incidence of dose limiting toxicities (DLT) in the first 56 days (8 weeks) of the study treatment.

See Section 4.1.5.1 of the CSP for the definition of DLTs.

A dose-limiting toxicity (DLT) is defined as an adverse event (AE) or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 8 weeks of study treatment and at least possibly related to the study drug. The investigator must notify the sponsor immediately (within 24 hours of the treating physician's knowledge) of any unexpected CTCAE grade ≥ 3 AEs or laboratory abnormalities. National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) v5.0 will be used for all grading as per Table 4-3 of CSP.

Events which will NOT be considered as DLT are:

- Clinically insignificant laboratory values ≤ grade 2.
- For electrolyte abnormalities ≥ grade 3, the maximum allowable time limit for correction to ≤ grade 1 is 72 hours.

3.2 Secondary Efficacy Endpoints

3.2.1 Derivation of RECIST Visit Responses

For all patients, the Response Evaluation Criteria in Solid Tumors (RECIST) tumor response data will be used to determine each patient's visit response according to RECIST Version 1.1 It will also be used to determine if and when a patient has progressed in accordance with RECIST and their best overall response (BOR) to study treatment.

Baseline tumor evaluations are to be performed radiographically (computed tomography [CT] or magnetic resonance imaging [MRI]) no more than 28 days before the administration of first dose of study medication and ideally as close as possible to the start of study treatment (prior to Day 1 of treatment). Tumor assessments are then performed every 8 weeks (±7 days) from the date of study treatment until either disease progression, at suspected progression if off cycle for evaluation, or withdrawal of consent.

From the investigator's review of the imaging scans, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST Version 1.1. At each visit, patients will be assigned a RECIST 1.1 visit response of complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions, and dependent upon the status of their disease compared with baseline and previous assessments. If a patient has had a tumor assessment that cannot be evaluated then the patient will be assigned a visit response of not evaluable (NE), (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to section 3.2.1.2 for the full definitions of CR, PR, SD and PD.

RECIST outcomes (progression free survival (PFS), overall response rate (ORR), disease control rate (DCR), and duration of response (DOR), time to response (TTR)) and overall survival (OS) will be calculated programmatically for the site investigator data (see sections 3.2.2 and onwards) from the overall visit responses.

3.2.1.1 Target lesions (TLs) – site investigator data

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements. A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ

(representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than 1 baseline scan is recorded, then measurements from the one that is closest and prior to first dose/administration of study treatment will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

All other lesions (or sites of disease) pathological lymph nodes not recorded as TL should be identified as non-target lesions (NTLs) at baseline. Measurements are not required for these lesions, but their status (present or absent or unequivocal progression) should be followed at subsequent visits.

Table 3 TL Visit Responses (RECIST 1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all TLs. Any pathological lymph nodes (whether target or non-target) selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥20% increase in the sum of diameters of TLs and an absolute increase of ≥5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters. Note: the appearance of one or more new lesions is also considered progression
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not evaluable (NE)	Only relevant in certain situations (i.e. if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions – see 'Scaling' later in this section). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

Missing TL data

If all TL measurements are missing, then the TL visit response is NE. Overall visit response will also be NE, unless there is a progression of non-TLs or new lesions, in which case the response will be PD.

Lymph nodes

For lymph nodes, if the size reduces to <10mm then these are considered non-pathological. However, a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are <10mm and all other TLs are 0mm then although the sum may be >0mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

Only CR, PD or NE can follow a CR. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (ie 0mm or <10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains <10mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or <10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are also met.
- Step 3: If not all lesions meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis >10mm or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR

3.2.1.2 Non-target lesions (NTLs) and new lesions – site investigator data

3.2.1.2.1 Non-target lesions (NTLs)

At each visit, the investigator should record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

NTL response will be derived based on the investigator's overall assessment of NTLs as follows:

Table 4 NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis and normalization of tumour marker level).
Progressive disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression and/or maintenance of tumour marker level above the normal limits.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if there are no NTLs at baseline.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

3.2.1.2.2 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

3.2.1.3 Overall visit response – site investigator data

Table 5 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 5 Overall visit responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE	No (or NE)	**PR**
SD	Non-PD or NE	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Not PD	No (or NE)	**NE**

3.2.2 Overall response rate (ORR)

ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), according to RECIST 1.1. and will be based on a subset of all treated patients with measurable disease at baseline per the site investigator.

BOR is calculated based on the overall visit responses from each RECIST assessment, described in section 3.1. It is the best response a patient has had following the first day of study treatment, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorization of BOR will be based on RECIST using the following response categories: CR, PR, SD, PD and NE.

Overall visit responses of CR or PR must be confirmed for the purpose of BOR assignment. A confirmed response of CR/PR means that a response of CR/PR recorded at 1 visit requires confirmation by repeat imaging not less than 4 weeks after the visit when the response was first observed, with no evidence of progression between the initial and CR/PR confirmation visit.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 8 weeks minus 1 week, i.e. at least 49 days (to allow for an early assessment within the assessment window), after first dose of study treatment. For CR/PR, the initial overall visit assessment that showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

BOR will be determined programmatically based on RECIST from the overall visit response using all site investigator data up until the first progression event.

For patients whose progression event is death, BOR will be calculated based upon all evaluable RECIST assessments prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurs ≤17 weeks (i.e. 2x8 weeks + 1 week to allow for a late assessment within the assessment window) after first dose of study treatment, then BOR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks after first dose of study treatment then BOR will be assigned to the NE category.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time following first dose of study treatment, prior to RECIST progression and prior to starting any subsequent cancer therapy.

3.2.3 Duration of response (DOR)

DOR is defined for patients whose BOR is either CR or PR and is calculated as the time from the date of first documented response of CR or PR (which is subsequently confirmed, i.e., the start date of response, not the date when response was confirmed) until the date of the first documented progression or death due to underlying cancer in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1).

Patients continuing without progression or death due to underlying cancer, will be censored at the date of their last adequate tumor assessment. However, patients who progress or die immediately after two or more consecutive missed visits will be censored at the time of the latest evaluable assessment prior to the two missed visits (note that an overall visit response of NE is not considered as a missed visit).

3.2.4 Disease control rate (DCR)

DCR is defined as the proportion of patients with a BOR of CR, PR, or SD (without subsequent cancer therapy) for at least 7 weeks after start of treatment (to allow for an early assessment within the assessment window) according to RECIST 1.1.

3.2.5 Progression free survival (PFS)

PFS is defined as the time from the date of first dose to the date of the first documented disease progression based on local investigator assessment as per RECIST 1.1 (assessed by investigator) or death (due to any cause in the absence of progression) (i.e. date of PFS event or censoring – date of first dose of study treatment + 1). Patients who have not progressed or died by the date of the analysis cut-off will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment (on or before the cut-off date). Clinical deterioration will not be considered as documented disease progression. However, if the patient progresses or dies immediately after two or more consecutive missed visits, they will

be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits (Note: NE visit is not considered as missed visit).

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- The date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression.
- When censoring a patient for PFS the patient will be censored at the **latest** of the dates contributing to a particular overall visit assessment.

Note: for TLs only the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

3.2.6 Time to response (TTR)

TTR is defined as the time from the date of first dose to the date of first documented response (CR or PR, which must be confirmed subsequently). The date of first documented response should coincide with that used for the DOR endpoint.

Time to response will not be defined for those patients who do not have a documented response which is subsequently confirmed.

3.2.7 Overall survival (OS)

OS is defined as the time from the date of first dose of study treatment to the date of death due to any cause (i.e., date of death or censoring – date of first dose of study treatment + 1). If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive (on or before the cut-off date). If a patient is confirmed to be alive or if the death date is post the data cut-off date, then this patient will be censored at the date of data cut-off.

If a patient is known to have died where only a partial death date is available then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

a) For Missing day only – using the 1st of the month

b) For Missing day and Month – using the 1st of January

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e. censored at the last known alive date.

3.3 Safety Variables

3.3.1 Secondary Safety Endpoints

3.3.1.1 Adverse events

All AEs and SAEs, including any laboratory abnormalities, that fit the reportable criteria described in Section 7.4.1 of CSP, will be recorded from the time the patient signs the Informed Consent Form until 150 days (5 months) after the last dose of study treatment of canakinumab or spartalizumab (due to the half-life of these drugs), or 30 days after the last dose of the combination chemotherapy, whichever is later.

Events will be defined as treatment emergent if they onset or worsen (by investigator report of a change in severity) during the treatment period as defined in the CSP.

More specifically,

when the start times of adverse events are not available:

treatment-emergent AEs (TEAEs) are events with a start date on or after the first dose date of canakinumab or spartalizumab up until the last dose date of canakinumab or spartalizumab plus 30 days. TEAEs are also events with a start date prior to the first dose date of any of the canakinumab or spartalizumab whose severity worsens on or after the earliest first dose date of any of the canakinumab or spartalizumab Events with an onset date during the on-treatment period will be considered as TEAEs. Ongoing events with a start date as described above will be considered as ongoing TEAEs.

when the start times of adverse events are available:

TEAEs are events with a start date-time on or after the first dose date-time of canakinumab or spartalizumab up until the last dose date of canakinumab or spartalizumab plus 30 days. TEAEs are also events with a start date-time prior to the first dose date-time of any of the canakinumab or spartalizumab whose severity worsens on or after the earliest first dose date-time of any of the canakinumab or spartalizumab Events with an onset date-time during the on-treatment period will be considered as TEAEs. Ongoing events with a start date-time as described above will be considered as ongoing TEAEs.

The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest effective MedDRA version) will be used to code the AEs. AEs will be graded according to the NCI-CTCAE for AEs (using the CTCAE version 5.0).

AEs of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor's program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data.

An adverse event of special interest (AESI) is a grouping of AEs that are of scientific and medical concern specific to compound canakinumab.

These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), high level group terms, high level terms, and PTs. Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of participants with at least one event of the AESI occurring during on-treatment period will be summarized. As more safety data and AE/SAE data are collected, we may identify different risks and change the list of AESI.

A non-exhaustive list of AESI is provided below for investigational drug. This may change as further data becomes available.

- Renal toxicity/serum creatinine ≥ Grade 2
- Neutropenia ≥ Grade3
- Febrile neutropenia
- Immunogenicity/Hypersensitivity reactions ≥ Grade3
- Infusion reactions ≥ Grade3
- Diarrhea ≥ Grade3
- Hypertension ≥ Grade3
- Haemorrhage ≥ Grade3
- Cardiac valvulopathy (symptomatic) ≥ Grade3

- Skin reactions ≥ Grade3
- Eyelid abnormality (≥ Grade 2)

In addition, following health authority requests the following will also be assessed as AESIs:

- Covid-19 / SARs-CoV2 positive cases, irrespective of causality
- Covid-19 vaccination status in study subjects & subsequent infection incidence

Summaries of these AESI will be provided by treatment arms (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose interruption, hospitalization, death etc.). A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

The CRS will be used to determine the MedDRA search criteria to be used to identify events of special interest.

Based upon the available safety information from spartalizumab and canakinumab oncology clinical development programs and known mechanism of action of these drugs and potential overlapping toxicity of all combination drugs, following adverse events are considered ***of special interest*** in this trial population:

- Infections (severe infections and opportunistic infections), including sepsis
- Neutropenia CTCAE Grade $\geq$3
- Febrile neutropenia
- Peripheral/Sensory neuropathy CTCAE Grade $\geq$3
- Thrombocytopenia CTCAE Grade $\geq$3
- *In addition, the potential immune-related AEs considered to be AESIs include, endocrinopathies, colitis, skin reactions, hepatitis, nephritis, pneumonitis and infusion reaction.*

Details regarding these adverse events are provided in the spartalizumab and canakinumab Investigator's Brochures..

3.3.1.2 12-lead electrocardiogram (ECG)

Twelve-lead electrocardiograms (ECGs) will be performed and assessed at the scheduled time points according to the Schedule of Events Table 5-1 of the CSP.

An overall Investigator assessment of ECG will be provided (categories <"normal", "abnormal, not clinically significant" and "abnormal, clinically significant">).

The following quantitative 12-lead ECG measurements will be taken during the study:

- heart rate (beats/min);
- RR interval (ms);
- PR interval (ms);
- QRS interval (ms);
- QT interval (ms);
- Bazett corrected QT (QTcB) interval (ms)
- Fridericia corrected QT (QTcF) interval (ms)

3.3.1.3 Clinical laboratory evaluations

Laboratory blood tests will be collected at the scheduled time points according to the Schedule of Events Table 5-1 of the CSP and assessed locally. The protocol required laboratory parameters are:

- Complete blood count (CBC) including but not limited to:
  - Red blood cell (RBC) count
  - Hemoglobin
  - Hematocrit
  - Platelet count
  - White blood cells (WBC) total Count
  - Neutrophils absolute count
  - Lymphocytes absolute count
  - Monocytes absolute count
  - Eosinophils absolute count
  - Basophils absolute count
  - Neutrophils %
  - Lymphocytes %
  - Monocytes %

- Eosinophils %
- Basophils %

- Chemistry panel including, but not limited to:
  - Total Bilirubin
  - Direct Bilirubin
  - Alkaline Phosphatase
  - ALT (SGPT)
  - AST (SGOT)
  - Albumin
  - Total Protein
  - Serum Creatinine
  - Blood Urea Nitrogen (BUN)
  - Sodium
  - Potassium
  - Calcium
  - Chloride
  - Glucose
  - C-reactive protein
  - Pre-Albumin

- Thyroid Panel
  - TSH
  - T3FREE
  - T4FREE

- Coagulation
  - INR
  - Prothrombin Time (PT)
  - Activated Partial Thromboplastin Time (APTT)

- Urinalysis

- Gravity
- pH
- Color
- Viscosity
- Appearance (Clear, Cloudy, Not Done, Other)
- Turbidity (Negative, Trace 1+, 2+, 3+_, 4+)
- Ketones (Negative, Trace 1+, 2+, 3+_, 4+, Not Done, Other)
- Bilirubin ((Negative, Trace 1+, 2+, 3+_, 4+ Not Done, Other)
- Blood (Negative, Trace 1+, 2+, 3+_, 4+ Not Done, Other)
- Glucose (Negative, Trace 1+, 2+, 3+_, 4+ Not Done, Other)
- Protein (Negative, Trace 1+, 2+, 3+_, 4+ Not Done, Other)
- Nitrites (Negative, Trace 1+, 2+, 3+_, 4+ Not Done, Other)
- Urobilinogen (Negative, Trace 1+, 2+, 3+_, 4+ Not Done, Other)
- Leukocyte Esterases (Negative, Trace 1+, 2+, 3+_, 4+ Not Done, Other)
- Urine Microscopy
    - Red blood Cells
    - White blood cells
    - Epithelial cells
    - Bacteria
    - Crystals
    - Casts

For laboratory tests covered by the CTCAE version 5.0, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on local laboratory normal ranges.

Laboratory test with any clinically significant results will also be collected.

3.3.2 Other safety variables

3.3.2.1 Duration of exposure

The duration of (total or intendedexposure (in months) will be calculated separately for each study drug.

The duration of (total or intended) exposure (in months), to any drug will also be calculated.

Exposure will be defined as follows:

For canakinumab:

- (Total or intended) duration of exposure (months) = ((date of last dose where dose >0 [units]– date of first dose where dose >0 [units]) + length of dose frequency)/ (365.25 / 12).

  Where length of dose frequency = 28 if last dose is given on Q4W and 56 if last dose is given on Q8W

For spartalizumab:

- (Total or intended) duration of exposure (months) = ((date of last dose where dose >0 [units]– date of first dose where dose >0 [units]) + 28)/ (365.25 / 12).

For nab-paclitaxel or gemcitabine:

- (Total or intended) duration of exposure (days) = ((date of last dose where dose >0 [units]– date of first dose where dose >0 [units]) + i)) / (365.25 / 12).

  Where i =7 if last dose is given on cycle day 1 or 8, i =14 if last dose is given on cycle day 15

For Any Drug:

- (Total or intended) duration of exposure (days) = ((date of last dose where dose >0 [units]– date of first dose where dose >0 [units]+x) / (365.25 / 12).

Where x is:

- the length of dose frequency when the date of last dose is the last dose date of canakinumab

- 28 for date of last dose of spartalizumab
- x = i =7 if last dose of nab-paclitaxel or gemcitabin is given on cycle day 1 or 8
- x= i =14 if last dose nab-paclitaxel or gemcitabin is given on cycle day 15

3.3.2.2 Dose intensity

The actual dose intensity and the relative dose intensity (RDI) will be summarized for each study drug component nested within the groups as defined for the cumulative dose (i.e. total dose given during the study drug exposure) by descriptive statistics. In addition, categorical summary of RDI for each study drug will be presented. The number of administrations (or treatment cycles) of each study drug component of the study treatment nested within the treatment groups as defined for the cumulative dose will be summarized by frequencies and descriptive statistics.

The actual dose intensity (DI) is defined as:

DI=actual cumulative dose / number of cycles on treatment, for subjects with non-zero duration of exposure. For subjects who did not take the drug, the DI is by definition equal to zero.

Number of cycles on treatment are defined as:

For canakinumab

Number of cycles on treatment = (last date of administration of study drug - first date of administration of study drug + length of dose frequency)/28

For spartalizumab

Number of cycles on treatment = (last date of administration of study drug - first date of administration of study drug + 28)/28

For nab-paclitaxel or gemcitabine

scheduled for Day 1, 8 and 15 of every 28-day cycle, with the last non-zero administration of nab-paclitaxel or gemcitabine at Cycle u Day v:

If v=1, number of cycles on treatment = (u-1)+1/3

If v=8, number of cycles on treatment = (u-1)+2/3

If v=15, number of cycles on treatment = u

PDI (dosing unit/unit of time) = planned dose intensity

PDI is the assigned dose by unit of time planned to be given to subjects as per protocol in the same dose unit and unit of time as that of the dose intensity.

PDI and relative dose intensity (RDI) is defined as:

For canakinumab:

- PDI is the planned dose as per protocol in mg (i.e. 250 mg Q4W)
- RDI (%) = DI (mg/cycle) / PDI (mg/cycle) * 100

For spartilizumab:

- PDI is the planned dose as per protocol in mg (i.e. 400 mg Q4W)
- RDI (%) = DI (mg/cycle) / PDI (mg/cycle) * 100

For chemotherapy:

- nab-paclitaxel
  - PDI is the planned dose as per protocol in mg/m^2 (i.e. 375 mg/m^2/cycle)
  - RDI (%) = DI (mg/m^2/cycle) / PDI (mg/m^2/cycle) * 100
- gemcitabine
  - PDI is the planned dose as per protocol in mg/m^2 (i.e. 1000 mg/m^2/cycle)
  - RDI (%) = DI (mg/m^2/cycle) / PDI (mg/m^2/cycle) * 100

3.3.2.3 Vital signs

Vital signs will be performed and assessed at the scheduled time points according to the Schedule of Events Table 5-1 of the CSP. Vital signs include temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg). Results will be graded by the low/normal/high classifications based on normal ranges CTCAE will be used to define low/high classification.

3.3.2.4 Physical examination

A complete physical examination will be performed at the scheduled time points indicated in Schedule of Events Table 5-1 of the CSP and will include an assessment of the following: general appearance, cardiovascular, abdomen, skin, neck, lymph nodes, HEENT, thorax/lungs, musculoskeletal, neurological and other.
An overall Investigator assessment of physical examination will be provided (categories <"normal", "abnormal, not clinically significant" and "abnormal, clinically significant">)

3.3.2.5 Previous and Concomitant medications

Medications and significant non-drug therapies received prior to, concomitantly (after the start of the study treatment) or post-treatment will be coded by Covance using the WHODrug Dictionary Version B3 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those taken prior to study treatment with a stop date prior to the first dose date of study treatment (i.e. the earliest first dose of any of the canakinumab or spartalizumab).

Concomitant medications are those with a start date on or after the first dose date of study treatment, or those with a start date before the first dose date of study treatment and a stop date on or after the first dose date of study treatment or ongoing end of study.

Post-treatment medications are those with a start date after the last dose date of study treatment.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Missing coding terms should be listed and summarized as "Not coded".

[redacted]

[redacted]

- [redacted]

4. Secondary Pharmacokinetic (PK) endpoint

The secondary PK endpoint comprises PK concentrations and parameters of canakinumab, spartalizumab, gemcitabine and nab-paclitaxel.

The specific Pharmacokinetic blood collection for canakinumab, spartalizumab, gemcitabine and nab-paclitaxel is outlined in **Section 5.6 of CSP**.

Blood draws for canakinumab and spartalizumab will be performed on Days 1,8, and 15 of Cycle 1, and Day 1 of Cycles 2-6 (pre-dose), (8 days post dose of Cycle 5 for canakinumab and spartalizumab) and at End of Treatment. PK draws for both gemcitabine and nab-paclitaxel will be performed on Day 1 of Cycles 1 and 2.

All PK samples collected will be sent to Novartis.

The merging of PK concentration data for canakinumab, spartalizumab, gemcitabine and nab-paclitaxel with eCRF data, i.e actual PK sampling times and actual doses or infusion duration will be performed by Covance Clinical and Periapproval Services Limited, UK, who will also be responsible for the summaries, figures, and data listings.

The non-compartmental analysis will be carried out by the Covance Clinical Pharmacokinetic Alliance (CPKA). Pharmacokinetic parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 8.1, or higher. The PK parameters to be reported are: AUC_{last} C_{min}, C_{max}, t_{max}, and t_{last}. Half-life ($t_{1/2}$) may be estimated for nab-paclitaxel and gemitabine if data allow.

The actual sampling times will be used in the final plasma PK parameter calculations. If actual times are missing, nominal times may be used.

Plasam concentration below assay lower limited of quantitation (BLQ) will be treated as zero if it occurs prior to the first quantifiable concentration; thereafter, any BLQs will be treated as missing for PK parameters calculation.

C_{max}, C_{min}, t_{max}, and t_{last} are observed values based on concentration-time profile. AUC_{last} will be calculated using linear up-log down trapezoidal method.

5. Analysis populations

5.1 All Screened

All patients who consent to participate in the study and who undergo screening will be included in the All Screened population.

5.2 Safety Analysis Set (SAF)

All patients treated with at least one dose of any of the constituent study treatments will be included in the safety population.

5.3 Full Analysis Set (FAS)

The full analysis set FAS is defined in the same way as the SAF in section 5.2 and will comprise all patients who received at least one dose of any of the constituent study treatments.

5.4 Dose-Determining Analysis Set (DDS)

The dose determining set (DDS) includes all patients from the SAF who meet the minimum exposure criterion and have sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) during the first two cycles (8 weeks) of dosing.

A patient meets the minimum exposure criterion if the patient received:

- 2 doses of canakinumab (for Q4W dosing regimen cohort) or 1 dose of canakinumab (for Q8W dosing regimen cohort in case the canakinumab dose is de-escalated) and 2 infusions of spartalizumab (full dose) within the first 56 days (8 weeks) of study treatment
- Takes at least 75% of planned doses of gemcitabine plus nab-paclitaxel chemotherapy within the first 56 days (8 weeks) of study treatment.

If the patient did not receive the planned number of doses due to DLT, the patient will be considered as meeting the minimum exposure criterion. Patients who do not experience a DLT during the first 56 days (8 weeks) are considered to have sufficient safety evaluations if they have been observed for ≥56 days (8 weeks) following the first dose, and are considered by the dose level review team (DLRT) to have sufficient safety data to conclude that a DLT did not occur.

5.5 Pharmacokinetic Analysis Set (PAS)

The Pharmacokinetic Analysis Set (PAS) is defined for canakinumab, spartalizumab, nab-paclitaxel, and gemcitabine separately.

More specifically **PAS** $_{\text{canakinumab}}$ will consist of:

All patients who received at least 1 dose of canakinumab and have at least one reportable concentration of canakinumab.

PAS $_{\text{spartalizumab}}$ will consist of:

All patients who received at least 1 dose of spartalizumab and have at least one reportable concentration of spartalizumab

PAS nab-$_{\text{paclitaxel}}$ will consist of:

All patients who received at least 1 dose of paclitaxel and have at least one reportable concentration of paclitaxel

and **PAS** $_{\text{gemcitabine}}$ will consist of:

All patients who received at least 1 dose of gemcitabine and have at least one reportable concentration of gemcitabine

5.6 Important Protocol Deviations

For the purposes of this study, the following criteria have been identified as important protocol deviations. Patients will be assessed purely by comparison of their eCRF data with the criteria below.

Type	Important Protocol Deviation	Method of Identification
Inclusion/Exclusion Criteria Violation	Any violation of inclusion/exclusion criteria as specified in section 3.2 and 3.3 of the CSP	**Non-programmable** Violations will be identified through site monitoring and entered into the deviation log.
Prohibited Medication	Prohibited medications identified in section 4.4.3 of the CSP	**Programmable** Identified using the concomitant medications eCRF

As defined in the above table, the majority of the important protocol deviations will be determined programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock.

All important protocol deviations occurring during the study will be reviewed and approved by Novartis prior to database lock. Should additional important protocol deviations not anticipated at the time of preparing this SAP, be identified during the

study they will be documented in a SAP amendment and included in all relevant protocol deviation reviews and approvals.

6. DATA Handling

6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of study treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date).

The day prior to Day 1 is Day -1.

The following visit windows will be used for the by-visit analyses of laboratory, ECG and vital sign data. All other analysis will use the nominal study visit as defined in the Study Schedule and eCRF.

Table 1 Definition of visit windows

Visit	Acceptable visit window
Screening	Cycle 1 Day -28 to -3
Cycle 1 Day 1	Cycle 1 Day -2 to 4 (Day 1±3 days)
Cycle 1 Day 8	Cycle 1 Day 5 to 11 (Day 8±3 days)
Cycle 1 Day 15	Cycle 1 Day 12 to 18 (Day 15±3 days)
Cycle 2 Day 1	Cycle 2 Day -1 to 3 (Day 1±2 days)
Cycle 2 Day 8	Cycle 2 Day 6 to 10 (Day 8±2 days)
Cycle 2 Day 15	Cycle 2 Day 13 to 16 (Day 15±2 days)
For Cycles > 2	
Cycle X Day 1	Cycle X Day -1 to 3 (Cycle X Day 1±2 days)
EOT	-7 days to +14 days of date of last dose or decision to discontinue study treatment (whichever date comes later)
30 Day Safety Follow-up	EoT + 23 to EoT + 37 (EoT +30 ±7 days)
60 Day Safety Follow-up	EoT + 53 to EoT + 67 (EoT +60 ±7 days)
90 Day Safety Follow-up	EoT + 83 to EoT + 97 (EoT +90 ±7 days)
120 Day Safety Follow-up	EoT + 113 to EoT + 127 (EoT +120 ±7 days)
150 Day Safety Follow-up	EoT + 143 to EoT + 157 (EoT +150 ±7 days)

NA = not applicable; EoT = Date of last dose;

Multiple visits within the same window will be dealt with as follows:

- If both scheduled and unscheduled visits fall within the same visit window, the scheduled visit will be used for analysis.
- If multiple scheduled visits occur within a single visit window, then the visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis.>

- If multiple unscheduled visits occur within a single visit window (with no scheduled visit within the window) then the unscheduled visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later unscheduled visit will be used in the analysis.

6.2 Handling of Dropouts, Missing Data, and Outliers

No rules for outlier detection are planned.

Missing safety data will generally not be imputed. However, safety assessment values of the form of "<x" (i.e. below the lower limit of quantification) or ">x" (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings. Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

For missing start AE dates, the following will be applied:

- Missing day – impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date.
- Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date.
- Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

Note: When imputing a start date ensure that the new imputed date is logical, i.e. is prior to the end date of the AE or treatment.

For missing end AE dates, the following will be applied:

- Missing day – impute the last day of the month unless month is the same as month of the last dose of study drug then impute last dose date.
- Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date.

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using Covance's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

Descriptive statistics will be used for all variables, as appropriate. Summary statistics will be presented for continuous variables, by way of number (n), mean, standard deviation (SD), median, minimum and maximum and by way of group

frequencies and percentages for categories of categorical variables. Unless otherwise stated, percentages will be calculated out of the analysis set total.

A separate supportive document will be produced containing the templates and/or descriptions of each table, listing and figure to be produced for reporting this study.

The following principles will be applied to all tables, figures and listings (TFLs) unless otherwise stated:

Principle	Value
Treatment group labels and order presented	125 mg/m^2 nab-paclitaxel 1000 mg/m^2 gemcitabine 250 mg canakinumab 400 mg spartalizumab Overall
Dose level labels and order presented	250 mg s.c. Q4W Canakinumab ...
Baseline definition	The baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study treatment. For post-baseline, only data from scheduled visits will be included in the summary tables.
Treatment period definition	The overall observation period will be divided into three mutually exclusive segments: • Pre-treatment period: from day of patient's informed consent to the day before first dose of any of the study treatments, whichever is the earliest • On-treatment period: from day of first dose of study medication to 30 days after last dose of any of the study treatment. • Post-treatment period: starting at day 30+1 after last dose of any of the study treatment, whichever is the latest
Tables	Data in summary tables will be presented by assessment, dose level and time point (where applicable), unless otherwise specified.
Listings	All data collected presented by patient, assessment and time point (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of patients/observations (n), mean, standard deviation, median and range.
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]

Principle	Value
Denominator for percentages	Number of patients in the analysis population, unless stated otherwise in table shell(s).
Include "Missing" as category	Yes, when the number missing is greater than zero for at least one dose level.
Display for 0 percentages	Blank
Display to one more decimal place than collected value	Mean Standard Error Median
Display to two more decimal places than collected value	Standard Deviation Confidence Interval
Limit of precision for displays	3 decimal places
Date Format	YYYY-MM-DD
Source footnotes	Each table will have a footnote that lists the source data listing(s). Each figure will have a footnote that lists the source table(s).
Dictionary names and versions	The dictionary names and versions will be included in a footnote in all AE and prior or concomitant medication TFLs that present coded terms from the dictionaries.

7.2 Patient Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized by dose level and overall and will include the number and percentage of patients:

- screened;
- received treatment;
- not received treatment
- included in each study population (SAF, FAS, DDS, PAS $_{\text{canakinumab}}$, PAS $_{\text{spartalizumab}}$, PAS $_{\text{nab-paclitaxel}}$, PAS $_{\text{gemcitabine}}$).

In addition, the number and percentage of patients who complete the study, who discontinue treatment early with associated primary reasons for treatment discontinuation and who discontinue from the study early including a breakdown of the primary reasons for discontinuation, will be presented for the FAS.

A summary of patient enrollment by site, will also be provided by dose level and overall for the SAF population.

The number of patients that were screen failuresas well as the number of patients screened but not assigned to treatment will be produced. No other information for screen failures will be presented.

7.3 Protocol Deviations

All protocol deviations will be listed and summarized by dose level for the FAS.

All important protocol deviations see section 5.6 will be listed and summarized by dose level for the FAS population.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by dose level and overall for the FAS. Standard descriptive statistics will be presented for the continuous variables of:

- age (years);
- baseline weight (kg);
- baseline height (cm);
- baseline body mass index (kg/m^2) (BMI) [calculated as ($weight/height^2$) where weight is in kg and height is in m];
- baseline body surface area (m^2) (BSA) (calculated as ([body $weight^{0.425}$ (kg) × $height^{0.725}$ (cm) × 0.007184] or as ([sqrt(height (cm) × body weight (kg)/3600]), depending on the formula each site has used)

The total counts and percentages of patients will be presented for the categorical variables of:

- age group (years) (grouped as <65 and ≥65);
- sex (Male, Female);
- race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple, Other);
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown);
- childbearing potential for females (Yes, No);
- tumor treatment history (medications, surgery, radiation);
- baseline Eastern Cooperative Oncology Group (ECOG) performance status (Grade 0,1, 2, 3, 4, 5);
- baseline Ca 19-9 tumor marker

- number of target lesions (1, 2, ≥3) and locations of lesions (liver, lung, pancreas, lymph nodes, other)
- baseline tuberculosis/ hepatitis status (Present, Absent);
- disease history or diagnosis;
    - Pancreatic tumor location (Head, Body, Tail, Neck);
    - Disease type (Locally advanced, Metastatic);
    - Cancer type from biopsy pathology report (Ductal adenocarcinoma, Adenosquamous carcinoma, Mucinous adenocarcinoma, Hepatoid carcinoma, Medullary carcinoma, Signet ring cell carcinoma, Undefferentiated carcinoma, Undefferentiated carcinoma with osteoclast-like cells, Primary histology, Secondary histology, Other);
    - TNM Classification at Initial Diagnosis (TX, T0, Tis. T1a, etc.);
    - Prior anti-cancer therapies (Yes, No);

- prior systemic therapy;
    - Prior systemic therapy (Yes, No);
    - Treatment setting (Adjuvant, Neoadjuvant, Not Applicable);
    - Best Response (CR, PR, SD, PD, NE, NA, NR NA);
    - Treatment regimen ending reason (Progressive Disease, Toxicity, Completion of planned regimen, Other);

- prior anti-pancreatic cancer surgeries
    - Prior pancreatic cancer related surgery (Yes, No);
    - Surgery (Pancreaticoduodenectomy, Distal pancreatectomy, Total pancreatectomy, Other);
    - Location;
    - Outcome (No residual tumor after resection, Tumor/metastases not resected completely with microscopic residual lesions, not resected completely with macroscopic residual lesions; Metastases, Other)

- prior anti-cancer radiotherapy;
    - Prior cancer related radiotherapy (Yes, No);
    - Radiotherapy site;

No formal tests of statistical significance will be performed on the demographic and baseline data.

Other baseline measurements, such as vital signs, ECG, will be summarized by dose level with the post-baseline measurements.

ECOG will be also summarized by dose level.

7.4.1 Medical History

Medical history will be coded using the MedDRA Version 23.1 (or a later version if updated during the study)]. Relevant medical history and current medical conditions at baseline will be listed, and the number and percentage of patients with any medical history will be summarized separately for the FAS by system organ class (SOC) and preferred term (PT) for each dose level and overall.

7.4.2 Previous and Concomitant Medications

Prior medications and concomitant medications will be listed together for the SAF.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term by dose level separately for prior and concomitant medications.

7.5 Efficacy

7.5.1 Primary Efficacy Analysis

7.5.1.1 Statistical Model, Hypothesis and Method of Analysis

For the dose confirmation of canakinumab and spartalizumab in combination with nab-paclitaxel and gemcitabine, a BLRM will be applied to estimate the relationship between dose and the probability of a patient experiencing a DLT. Some DLT data are available from previous studies on single agent and combination of canakinumab and spartalizumab (PDR001X2101, ACZ885I2202, PRD001X2103) and a phase I/II study of nab-paclitaxel + gemcitabine (Von Hoff D, et.al., 2011). These data will be incorporated into BLRM using a meta-analytic-predictive (MAC) approach (Neuenschwander et al 2016). The details are provided in Appendix B of the CSP.

The decision on dose tolerability will be based on the totality of all relevant data from the ongoing study and a review of safety data from the first 8 weeks. A BLRM for combinations using the escalation with overdose control (EWOC) criterion to evaluate the risk of DLT will guide the decision. Additional information on the BLRM statistical model is provided in Appendix B of the CSP.

7.5.1.2 Assessment of Patient Risk

Dose recommendations will be based on summaries of the posterior distribution of DLT rates for each dose level of the respective combination therapy. After each cohort of patients, the posterior distribution for the risk of DLT for new patients at combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT for each dose regimen lies within intervals (33%, 100%).

Dosing regimen decisions are guided by the EWOC principle (Rogatko et al 2007). The possibility of excessive toxicity is of interest in this study as the objective is to confirm the safety of the proposed dose regimen. A dosing regimen may only be used for newly enrolled patients if the risk of excessive toxicity at that dosing regimen is less than 25%.

Listing/Summary of DLTs

All DLTs will be listed and their incidences summarized by primary SOC, worst grade based on the CTCAE Version 5.0, type of adverse event, and by treatment group in the dose escalation. The DDS will be used for these summaries.

Patients who are ineligible for the DDS will be excluded from the primary analysis (assessment of recommended dose using incidence of DLT during first 56 days of treatment with canakinumab in combination with spartalizumab, nab-paclitaxel and gemcitabine), although their data will be used for all remaining analyses.

Reports on DLT Analysis

Following reports will be produced for DLTs based on the DDS:

- The table of summary posterior interval probabilities will be presented in the body of the clinical study report (CSR)
- For each DEM, summary of recommendations will be included in Appendix 16.1.9 of the (CSR)

7.5.2 Secondary Efficacy Analysis

Analyses of secondary efficacy endpoints as defined in section 3.2 will be performed in the FAS.

ORR and DCR will be summarized by dose level. Summaries will present the number and percentage of patients achieving disease control (BOR of CR, PR and SD).

The point estimate of the ORR along with the exact Clopper-Pearson (exact CI for a binomial proportion) 95% CI will be reported by dose level in the FAS

Accompanying KM estimates of the median PFS and OS alongside associated 95% CIs will be presented by dose level in the FAS (by investigator assessment). The CIs will be derived based on Brookmeyer-Crowley method.

KM estimates of PFS and OS at 3-monthly intervals will also be presented along with associated 95% confidence bands (derived based on Hall-Wallner method).

The TTR and DOR . based on the investigator assessment of RECIST 1.1. will be listed

7.5.3 Secondary Pharmacokinetic Analysis

A listing of PK blood sample collection times as well as derived sampling time deviations and all reportable concentrations will be presented for each analyte (canakinumab, spartalizumab, nab-paclitaxel and gemcitabine) separately for all patients for the PAS. Plasma concentrations will be summarised for the PK analysis set for each time point by dose level using protocol scheduled times and appropriate descriptive statistics (i.e., n, n below LLOQ, geometric mean [gmean], gmean+geometric standard deviation [gSD], gmean-gSD, geometric coefficient of variance expressed as a percentage [gCV%], arithmetic mean [mean], arithmetic SD [SD], coefficient of variance expressed as a percentage [CV%], median, minimum and maximum.

The gmean is calculated as exponential (μ), where μ is the arithmetic mean calculated using log transformed data.

The gCV% is calculated as 100 x sqrt[exp(s^2)-1], where s is the SD of the log-transformed data.

The gmean±gSD (gmean-gSD and gmean+gSD) are calculated as exp[μ±s].

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as Not Quantifiable (NQ) in the listings with the LLOQ defined in the footnotes of the relevant tables, figures and listings.

Individual plasma concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings.

Plasma concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

Any values reported as NR or NS or flaggged for exclusion by pharmacokineticist (eg. due to concomitant medication, dose modification, etc) will be excluded from the summary tables and corresponding figures.

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged.

LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing

If all values are NQ at a time point, no descriptive statistics will be calculated for that time point. The gmean, mean, minimum, median and maximum will be reported as NQ and gmean±gSD, gCV%, SD and CV% as NC.

The number of values below LLOQ (n <LLOQ) will be reported for each timepoint together with the total number of collected values (n).

Three observations >LLOQ are required as a minimum for a plasma concentration to be summarised. Two values >LLOQ are presented as a minimum and maximum with the other summary statistics as NC.

Plasma concentrations that are NQ will be handled as follows for display in figures:

- For gmean concentration-time plots: NQ concentrations will be handled as described for the descriptive statistics. If this handling results in a geometric mean of "NQ", then the value plotted at that time-point will be zero for linear plots and set to missing for semi-logarithmic plots. Any gmean±gSD error bar values that are negative will be truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.
- For individual plots and combined individual plots: NQ values prior to the first quantifiable concentration in that profile will be set to zero (linear plots only); after the first quantifiable concentration of the profile any NQ values will be set to missing.

Plasma PK parameters such as mentioned below (if reportable) for each analyte separately will be summarised for the PAS by dose level using the following descriptive statistics:

- C_{max}, C_{last} and AUC_{last}, will present n, gmean, gmean+gSD, gmean-gSD, gCV(%), mean, SD, CV%, median, min and max.
- t_{max} and t_{last} will present only n, median, min and max.
- $t_{1/2}$ (if reported) will present n, mean, SD, CV%, median, min and max.

It should be noted that not all PK parameters are applicable to all study drugs. For the calculation of summary statistics of PK parameters, all not reportable (NR) and not calculated (NC) values or parameters flagged for exclusion by the pharmacokineticist (eg. due to concomitant medication, dose modification, etc) will be set to missing. Three reportable values are required as a minimum for a PK parameter to be summarised. Two values are presented as a minimum and maximum with the other summary statistics as NC. If one or more values for a given parameter is zero (or imputed with zero), then no geometric statistics will be

calculated for that parameter and the results for geometric statistics will be set to "NA", not applicable.PK concentration and parameter data from patients excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in mean figures or combined individual figures. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in patient listings.

Individual plasma concentrations versus actual elapsed time after dose will be plotted on both the linear and semi-logarithmic scales for each analyte (each analyte will have a different timeframe).

Combined individual plasma concentration versus actual elapsed times after dose will be plotted on both the linear and semi-logarithmic scale for each analyte separately. Plots will be grouped by dose level.

[redacted]

7.7 Safety

The overall observation period will be divided into three mutually exclusive segments:

- **Pre-treatment period:** from day of subject's informed consent to the day before first dose of study treatment
- **On-treatment period:** from day of first dose of study medication to 30 days after last dose of study treatment
- **Post-treatment period:** starting at day 30+1 after last dose of study treatment

Safety summaries (tables, figures) will include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries) and deaths, which will be presented for the on-treatment and post-treatment period. AE data will be summarised separately for the on-treatment and post-treatment period.

7.7.1 Secondary Safety Analysis

7.7.1.1 Adverse Events

All adverse events (AEs) recorded on the eCRF will be coded using the MedDRA dictionary Version 23.1 (or a later version if updated during the study).

Assessment of AE severity will be based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0).

The number of patients experiencing TEAEs (as defined in section 3.3.1.1) by MedDRA system SOC (sorted alphabetically) and or MedDRA PT (sorted by descending overall total) will be presented for each dose level and overall, with further splits by CTCAE 5.0 severity grade, causal relationship to study medication and type of adverse event. TEAE data will be summarised separately for the on-treatment and post-treatment period

The relationship between an AE and each of study drugs is assessed as suspected or not suspected. A study drug-related AE is an AE considered by the investigator as related to study drug or with unknown/missing relationship to study drug.(AEs with unknown/missing relationship to study drug will be summarized along with study drug related AEs and separately).An overview table will summarize the number and percentage of patients with at least one of the following TEAEs by dose level, where patients with more than one TEAE in a particular category are counted only once in that category:

- Any TEAEs;
- Any TEAEs causally related to treatment;
- Any TEAEs by maximum CTCAE severity (Grade 1, Grade 2 , Grade 3 , Grade 4 [life-threatening], Grade 5 [death]);
- Any TEAEs of CTCAE grade 3 or higher causally related to any study treatment;
- Any TEAEs with outcome of death;
- Any TEAEs with outcome of death causally related to treatment;
- Any TESAEs;
- Any TESAEs causing discontinuation of each of the study medications;
- Any TESAEs causing discontinuation of each of the study medications; causally related to treatment;
- Any TEAEs leading to dose interruption (or to dose interval modified for canakinumab)of each of the study medications;
- Any TEAEs causing discontinuation of each of the study medications;
- Any TEAEs causing discontinuation of each of the study medications; causally related to treatment;
- Any AESIs

The number and percentage of patients reporting each AE will be summarized by System Organ Class (SOC), Preferred Term (PT) and dose level for the SAF. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- TEAEs, by SOC and PT;
- TEAEs by PT;
- TEAEs causally related to treatment, by SOC and PT;
- TEAEs causally related to treatment, by PT;

- TEAEs by maximum severity (mild, moderate, severe, life-threatening, death);
- TEAEs of CTCAE grade 3 or higher, by SOC and PT;
- TEAEs of CTCAE grade 3 or higher causally related to treatment, by SOC and PT;
- TEAEs with outcome of death, by SOC and PT;
- TEAEs with outcome of death causally related to treatment, by SOC and PT;
- TESAEs leading discontinuation of each of the study medications, by SOC and PT;
- TESAEs leading to discontinuation of each of the study medications causally related to treatment, by SOC and PT;
- TEAEs leading to discontinuation of each of the study medications, by SOC and PT;
- TEAEs leading to discontinuation of each of the study medications causally related to treatment, by SOC and PT;
- TEAEs leading to dose modification/reduction of nab-paclitaxek and gemcitabine, by SOC and PT;
- TEAEs leading to dose interruption (or to dose interval modified for canakinumab) of each of the study medications, by SOC and PT;
- AESIs by SOC and PT

A summary of deaths with associated primary reason for death by dose level will be provided during the on-treatment and post-treatment period separately.

A separate summary will be produced that presents any adverse events that occur prior to dosing (Pre-treatment period) or starting more than 30 days after discontinuing therapy (Post-treatment period);

The number and percentage of patients who reported treatment-emergent adverse events of special interest will be summarized by SOC, preferred term and dose level.
SOC names will be sorted alphabetically and, within each risk name, the preferred terms will be sorted in descending order of frequency in the overall dose level. If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same system organ class, the patient will be counted only once at that SOC.

All AE data will be listed by dose level. In addition, corresponding listings of serious AEs , deaths, SAEs, AESIs, AEs leading to discontinuation of study drug, AEs resulting

in death, AEs that led to dose reduction, discontinuation of treatment or death, and treatment-related AEs will be produced and those starting during the pre-treatment and post-treatment period will be flagged. Dose Limiting Toxicity AEs will be flagged as well.Deaths will also be listed and post-treatment deaths will be flagged.

No statistical comparisons of AEs between dose levels will be performed.

7.7.1.2 Clinical Laboratory Evaluations

Laboratory data (biochemistry, hematology, and urinalysis) will be summarized by dose level and listed as described below:

Shift tables will be provided for select tests, where shift from baseline to the worst on-treatment value will be summarized using CTCAE grades(for tests where grades are not defined by CTCAE , laboratory normal ranges will be used).Laboratory data outside the reference ranges will be indicated in the listings.

Laboratory data absolute and change from baseline values for biochemistry, hematology and urinalysis will be summarized at each scheduled assessment time by dose level.

Continuous laboratory parameters will be summarized with descriptive statistics. If a patient has multiple results for a particular test at a particular time window, the first non-missing scheduled value will be used for the summary

Listings of all laboratory values for each patient will be presented with abnormal values flagged. Abnormal lab values which qualify as DLT will be flagged as well.

Shift tables for laboratory values by worst common toxicity criteria (CTC) grade will be produced. For parameters with no CTCAE grading, shift tables from baseline to worst value on-treatment will be provided.
For all laboratory variables included in the current version of CTCAE, the CTCAE grade will be summarized.

Raw values and changes from baseline for laboratory data at each timepoint will presented using box and whiskers plots and any data not included between the whiskers should be plotted as outliers.

Liver function parameters of interest are total bilirubin (TBL), ALT, AST, and alkaline phosphatase (ALP). The number (%) of participants with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN

- TBL > 2xULN
- TBL > 3xULN
- AST and ALT =< ULN at baseline
  - ALT or AST >3x ULN & BILI >2x ULN
  - ALT or AST >3x ULN & BILI >2x ULN & ALP >=2x ULN
  - ALT or AST >3x ULN & BILI >2x ULN & ALP <2x ULN
- AST and ALT > ULN at baseline
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN)
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP >=2x ULN
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP <2x ULN

* Elevated AST or ALT defined as: >3x ULN if =< ULN at baseline, or (>3x Bsl or 8x ULN) if > ULN at baseline

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI > 2xULN, ALT> 3xULN or AST > 3xULN will be provided.

A plot of maximum (worst) post-baseline total bilirubin vs maximum (worst) post-baseline ALT, both relative to the ULN will be provided with different symbols for different dose level groups. This eDISH plot (evaluation of drug-induced hepatoxicity) will have reference lines at 3xULN for ALT and at 2xULN for total bilirubin.An additional eDISH plot might be considered of peak total bilirubin versus peak AST" if there are potential cases based on AST rather than ALT.

Data for the following hematology, biochemistry, and urinalysis analytes as presented in the below table will be provided:

Hematology	Biochemistry	Thyroid Panel	Coagulation	Urinalysis
RBC count Hemoglobin Hematocrit Platelet count WBC total count Neutrophils absolute count Lymphocytes absolute count Monocytes absolute count Eosinophils absolute count Basophils absolute count Neutrophils (%) Lymphocytes (%) Monocytes (%) Eosinophils (%) Basophils (%)	Total Bilirubin Direct Bilirubin Alkaline Phosphatase ALT (SGPT) AST (SGOT) Albumin Total Protein Potassium Sodium Urea Creatinine Calcium Chloride Glucose C-reactive protein Prealbumin	TSH T3FREE T4FREE	INR Prothrombin Time (PT) Activated Partial Thromboplastin Time (APTT)	pH Color Viscosity Appearance Turbidity Ketones Bilirubin Blood Glucose Protein Nitrites Urobilinogen Leukocyte Esterases Red blood cells White blood cells Epithelial cells Bacteria Crystals Casts

All laboratory data will be reported in International System of Units (SI)/Conventional units.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

7.7.1.3 Electrocardiograms

The ECG measurements and changes from baseline in ECG will be listed by dose level, patient and time point and summarized by dose level and visit using standard descriptive statistics for the SAF.

The Investigator assessment will be listed and the number and percentage of patients within each assessment category will be tabulated by dose level group and visit for the SAF. Shifts from baseline (normal, abnormal not clinically significant and abnormal clinically significant) to each post-baseline visit will be presented.

7.7.2 Other Safety Variables

7.7.2.1 Extent of Exposure and Dose intensity

The duration of (total or intended) exposure (in days) as well as dose intensity (percentage dose intensity and relative dose intensity) , as defined in sections 3.3.2.1 and 3.3.2.2 will be listed and summarized separate for each study drug using descriptive statistics for each dose level group and by cycle for the SAF.

The number and percentage of patients with duration of exposure in the following categories will also be summarized for the SAF:

- ≤2 months
- >2 and ≤6 months
- >6 and ≤10 months
- >10 months

Total exposure will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations.

Dose intensity data will be summarised using means, standard deviation, medians, and quartiles as well as the minimum and maximum values and number of observations.

In addition, the number and percentage of patients with neither dose interruption nor dose reduction , at one dose interruption or dose reduction, at least one dose interruption, at least one dose reduction along with their associated reasons where applicable will be presented by dose level and study drug.

All dosing data will be listed.

7.7.2.2 Vital Signs

Vital signs as described in 3.3.2.3 will be listed by dose level, patient and visit/time and summarized by dose level and visit and normal range groups Vital sign values measured outside of on-treatment period will flagged.

Vital signs data and changes from baseline in vital signs will be summarized by visit and dose level using standard descriptive statistics for the SAF.

7.7.2.3 Physical Examination

Physical examination will be summarised by dose level and listed by dose level, patient and visit/time.

7.8 Interim Analysis

No interim analysis will be performed for this study.

8. Changes in Planned Analysis

[redacted]

9. .Data Issues

This section is not required at this time, but will be populated in a future approved version of this document.

10. References

1 ICH. Statistical Principles for Clinical Trials, Guideline E9, 1998. Available at http://www.emea.eu.int/pdfs/human/ich/036396en.pdf

2 CPMP. *Points to Consider on Missing Data*. EMEA: London, 2001. Available at http://www.emea.eu.int/pdfs/human/ewp/177699EN.pdf

3 Phillips A and Haudiquet V. *ICH E9 guideline "Statistical principles for clinical trials": a case study*. Statistics in Medicine 2003; 22:1-11

4 Brown D J. *ICH E9 guideline "Statistical principles for clinical trials": a case study. Response to A. Phillips and V. Haudiquet.* Statistics in Medicine 2003; 22:13-17

5 Phillips A, Ebbutt A, France L, Morgan D, Ireson M, Struthers L and Heimann G. *Issues in applying recent CPMP "Points to Consider" and FDA guidance documents with biostatistical implications.* Pharmaceutical Statistics 2003; 2:241-251

6 Neuenschwander B, Wandel S, Roychoudhury S, Bailey S (2015). Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceutical Statistics. 15:2, 123-134

7 Neuenschwander B, Roychoudhury S, Schmidli H (2016). On the Use of Co-Data in Clinical Trials. Statistics in Biopharmaceutical Research. 8:3, 345-354.

8 Spiegelhalter D (2004). Incorporating Bayesian Ideas into Health-Care Evaluation. Statistical Science. 19:1, 156–174

9 Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, et al. (2011) Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. Journal of Clinical Oncology. 29:34, 4548–4554.

11. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1.0, Final, ”16Sep 2022	Include revisions of Version 1.0 of 02Oct 2020 and 18 Feb2022 (inclusive of updated definition for exposure) , 21Jul2022 & 29Aug
Version 1.0, Final, 02Oct 2020	Include revisions of Version 0.2
Version 0.2, Draft, 04 Sep 2020	Include revisions of Version 0.1
Version 0.1, Draft, 31 Jul 2020	Not applicable; the first version