Winship Cancer Institute
Emory University

Phase Ib/II trial of Siltuximab and Spartalizumab in Metastatic Pancreatic Cancer

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Research support: Novartis/ EUSA Pharmacovigilance EUSA Pharma

IND NUMBER: 146523

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1.0 TRIAL SUMMARY

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<tr><td>Abbreviated Title</td><td>Siltuximab/ Spartalizumab</td></tr>
<tr><td>Trial Phase</td><td>Phase Ib/II</td></tr>
<tr><td>Clinical Indication</td><td>Stage IV pancreas cancer</td></tr>
<tr><td>Trial Type</td><td>Single arm dose escalation</td></tr>
<tr><td>Type of control</td><td>None</td></tr>
<tr><td>Route of administration</td><td>IV</td></tr>
<tr><td>Purpose and Rationale</td><td>Purpose of the study is to evaluate the safety and biologic activity of the combination of spartalizumab and siltuximab in patients with advanced stage pancreatic cancer. The rationale is based on preclinical experiments (in vivo and in vitro) conducted by our group demonstrating that inhibition of IL-6 facilitates migration of lymphocytes into pancreatic tumor. Furthermore, combining IL-6 and PD-1 inhibitor was more effective in controlling tumor growth than either agent alone using syngeneic and genetically engineered mouse models.</td></tr>
<tr><td>Primary objectives</td><td>Primary objective of part 1 to determine RP2D of spartalizumab and siltuximab in advanced pancreatic CA.
Secondary objective to determine the safety profile of the RP2D of spartalizumab and siltuximab in advanced pancreatic CA</td></tr>
<tr><td>Secondary Objectives</td><td>Objective 1. To evaluate the activity of siltuximab and spartalizumab

Objective 2. Evaluate the effect of the combination on the immune profile in the serum and in tumor biopsies</td></tr>
<tr><td>Treatment Groups</td><td>Spartalizumab and siltuximab</td></tr>
<tr><td>Treatment cohorts</td><td>
<table>
<tr><th>No of pts</th><th>Cohort</th><th>Siltuximab</th><th>SPARTALIZUMAB</th></tr>
<tr><td>3 to 6</td><td>1</td><td>6 mg/KG IV every 3 weeks</td><td>300 mg every 3 weeks</td></tr>
<tr><td>3 to 6</td><td>2</td><td>11 mg/Kg every 3 weeks</td><td>300 mg every 3 weeks</td></tr>
<tr><td>3 to 6</td><td>2a</td><td>9 mg/Kg every 3 weeks</td><td>300 mg every 3 weeks</td></tr>
</table>
Dose level 2a will only be tested if we observe 2 DLT’s on dose level 2.</td></tr>
<tr><td>Selected Inclusion criteria</td><td>1. Patients with stage IV adenocarcinoma of the pancreas
2. Patients must have failed at least one prior line of therapy
3. ECOG PS 0 or 1
4. Adequate liver, hematologic and renal functions</td></tr>
<tr><td>Selected Exclusion criteria</td><td>1. Pancreatic neuroendocrine tumor
2. Prior PD-1, PDL-1 inhibitor
3. Active autoimmune disease that has required immunosuppressive systemic treatment in the past 2 years. Replacement therapy (e.g.,</td></tr>
</table>

	physiologic corticosteroid replacement therapy for adrenal or other hormone replacements) is allowed. 4. Diagnosis of immunodeficiency including systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. 5. Active infection
Number of trial subjects	*The total number of patients who will undergo treatment will range from 27 to 42 patients. In order to have 42 patients undergo treatment, we plan to enroll up to 70 patients to account for screen failures.*
Estimated enrollment period	*12 Months*
Estimated duration of trial	*2 years*
Duration of Participation	6 months
Estimated average length of treatment per patient	6 months

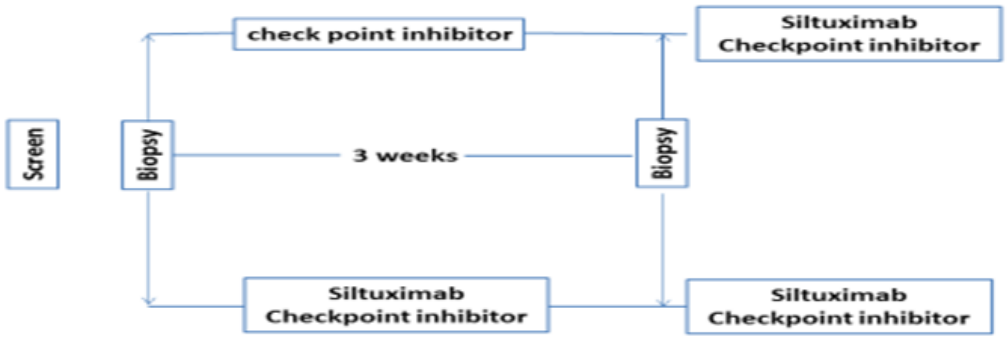
2.0 TRIAL DESIGN

Open label phase I trial. Primary objective is to determine the recommended phase 2 dose (RP2D) of the combination of spartalizumab and siltuximab. The design is 3+3 with 3 dose levels of siltuximab. Maximal Tolerated Dose (MTD)is defined as the dose at which less than one-third of the subjects experience a DLT in the first 6 weeks of treatment.

After determining the RP2D, an additional 24 patients with pancreatic cancer will be enrolled in an expansion phase to confirm toxicity profile and obtain paired biopsies. Paired biopsy performed on all patients in each group. Patient must have a primary or metastatic non-bone

site that is amenable to safe biopsy. Bone only lesions are not suitable for biopsy. Investigators will discuss with radiologist each case to ensure safety of biopsy procedure.

2.1 Trial Diagram: Figure 1. Study schema



3.0 OBJECTIVE(S) & HYPOTHESES

3.1 Primary Objective & Hypothesis

- **Objective: Determine the recommended phase II dose for the combination of spartalizumab and siltuximab**

  Hypothesis: The combination of a PD-1 inhibitor with IL-6 inhibitor is safe with no added toxicity.

3.2 Secondary Objectives & Hypotheses

(1) **Objective**:

A. Define the toxicity profile of the combination of the recommended phase II dose of spartalizumab and siltuximab. The additional patients enrolled on the expansion cohorts will help confirm the toxicity profile.

Hypothesis: The combination of a PD-1 inhibitor with IL-6 inhibitor is safe with no added toxicity.

B. Evaluate the activity of the combination of spartalizumab and siltuximab in previously treated patients with pancreatic cancer. Specifically, we will measure overall response rate (PR +CR), response duration and progression free survival. This will only be preliminary data since this is a secondary objective.

Hypothesis: The combination of a PD-1 inhibitor with IL-6 inhibitor will be active against pancreatic cancer resulting in tumor shrinkage.

3.3 Exploratory Objective

Objective: Evaluate the effect of the combination on the immune profile in the serum and in tumor biopsies.

Hypothesis: The IL-6 inhibitor will change the micro-environment to favor an immune response to the PD-1 inhibitor.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on spartalizumab and siltuximab. Neither siltuximab nor spartalizumab are approved in pancreatic cancer. The combination of both agents is also investigational.

4.1.1 Pharmaceutical and Therapeutic Background- spartalizumab

Spartalizumab is a high-affinity, ligand-blocking, humanized IgG4 antibody directed against Programmed Death-1 (PD-1) receptor that blocks the binding of PD-L1 and PD-L2. PD-1 is a critical immune-checkpoint receptor that is expressed on CD4 and CD8 T cells upon activation (Freeman, 2008). 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 (Riley, 2009). Monoclonal antibody (mAb) inhibitors of immunological checkpoints, including PD-1 and PD-L1, have demonstrated significant antitumor activity in patients with various solid tumors. For further details, please refer to the latest spartalizumab (PDR0001) Investigator's Brochure.

4.1.1.1 Non-clinical experience of spartalizumab

Spartalizumab binds specifically and with high affinity to human PD-1 and enhances interleukin-2 production in *ex-vivo* lymphocyte stimulation assays. It does not cross react with rodent PD-1; therefore, toxicology studies were performed only in cynomolgus monkeys where there was acceptable cross reactivity with monkey PD-1. Repeat administration of spartalizumab to monkeys was tolerated at all doses tested up to 100 mg/kg/week for 5 weeks

in the GLP toxicology single-agent study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no spartalizumab -related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given 100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, around the injection site blood vessel (saphenous vein) in a few animals given ≥25 mg/kg/week. These spartalizumab -related microscopic changes were fully reversible after an eight-week recovery. Additionally, mostly low grade mononuclear infiltrates in the vascular and perivascular space in several tissues of main and recovery treated animals and in recovery controls were observed but with a slightly higher incidence in treated animals. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any of the organs examined and the changes were not associated with any frank tissue injury. Dose-proportional exposure to spartalizumab in each dose group was confirmed. Anti-drug antibodies (ADA) to spartalizumab were observed in some spartalizumab treated cynomolgus monkeys. A trend of reduced drug exposure was observed in these ADA-positive animals. Based on the toxicology studies with spartalizumab as a single-agent, the Highest Non-Severely Toxic Dose (HNSTD) dose is 100 mg/kg. For further details, please refer to the latest spartalizumab [Investigator's Brochure].

4.1.1.2 Clinical experience of spartalizumab

As of 23-Jan-2017, 9 Novartis-sponsored clinical studies have treated patients with Spartalizumab. A total of 210 patients were exposed to spartalizumab single agent on an every 2 weeks (Q2W), every three weeks (Q3W) or every 4 weeks (Q4W) schedule, and 160 patients were exposed to spartalizumab in combination with other agents. Three studies have treated patients with spartalizumab as a single agent. These include the first-in-human phase I/II CPDR01X2101 study (160 patients of which 101 patients were treated at 400 mg Q4W), the CPDR001X1101 phase I study in Japanese patients (18 patients, Q2W), and the CPDR001X2201 phase II study in patients with nasopharyngeal carcinoma (32 patients, 400 mg Q4W). These studies have preliminarily identified safety risks associated with spartalizumab that are characteristic of agents that inhibit the PD-1 receptor (please refer also to approved drug labels of nivolumab and pembrolizumab).

In the dose escalation phase of study CPDR001X2101 in patients with advanced solid tumors, no Dose Limiting Toxicities (DLTs) were reported in any of the tested doses and regimens (1, 3, 10 mg/kg Q2W and 3 and 5 mg/kg Q4W). Based on the available PK and safety data, two recommended phase 2 doses (RP2Ds) for spartalizumab have been declared: 400 mg Q4W or 300 mg Q3W, with the choice between these two regimens determined by scheduling convenience, for example in combination settings.

Adverse events (AEs; all grades, regardless of relationship to study drug) were reported in 147 out of the 160 patients (91.9%) enrolled in study CPDR001X2101. The most frequent AEs (≥ 10% of patients) were nausea, fatigue, anemia, dyspnea, decreased appetite, cough, constipation, vomiting, abdominal pain, diarrhea, pyrexia, pleural effusion, dizziness, asthenia, increased aspartate aminotransferase and peripheral edema, which are consistent with the AEs reported in studies with other PD-1 inhibitors and with the AEs commonly reported for patients

with advanced solid malignancies. Eighty-four patients (52.5%) experienced Grade 3 or Grade 4 AEs regardless of relationship to study drug. Seventy-nine patients (49.4%) experienced AEs (all grades) suspected to be related to study treatment. Serious adverse events (SAEs; all grades, regardless of relationship to study drug) were reported in 61 (38.1%) patients. Five patients had SAEs suspected to be related to study treatment (colitis and pneumonitis, hepatitis, nausea and vomiting, dyspnea, vomiting). The safety was similar across the different dose and disease groups.

For further details on clinical experience with spartalizumab, please refer to the latest version of the spartalizumab [Investigator's Brochure].

4.1.2 Pharmaceutical and Therapeutic Background - Siltuximab

Siltuximab is a chimeric monoclonal antibody against interleukin-6 (IL-6) indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. [Package Insert]

4.1.2.1 Clinical experience with siltuximab

Study CNTO328MCD2001 (referred to as Study 1) (NCT01024036) was a Phase 2, multinational, randomized (2:1) double blind, placebo controlled study to evaluate the clinical efficacy and safety of SYLVANT for the treatment of patients with MCD. In this study 53 patients were randomized to Best Supportive Care (BSC) and SYLVANT at a dose of 11 mg/kg every 3 weeks and 26 patients were randomized to BSC and placebo. The median age was 48 years (range 20 to 78), 66% male, 48% Asian, 39% White, 4% Black or African American, 7% other. The histological subtype of MCD was similar in both treatment arms, with 33% hyaline vascular subtype, 23% plasmacytic subtype and 44% mixed subtype. Treatment was continued until treatment failure (defined as disease progression based on increase in symptoms, radiologic progression or deterioration in performance status) or unacceptable toxicity.

The major efficacy outcome of the study was durable tumor and symptomatic response, defined as tumor response (PR and CR based on modified International Working Group response criteria for malignant lymphoma) assessed by independent review and complete resolution or stabilization of MCD symptoms. Thirty-four MCD related signs and symptoms prospectively identified were collected and graded according to the NCI-CTCAE v 4, by investigators. A durable response was defined as tumor and symptomatic response that persisted for a minimum of 18 weeks without treatment failure. The durable tumor and symptomatic response in the SYLVANT arm was 34% compared to 0% in the placebo arm (95% CI: 11.1, 54.8; p=0.0012).

Other analyses included tumor response, time to treatment failure and an increase in hemoglobin of 1.5 g/dL or more, in patients who were anemic at time of study entry, at week 13. The results are summarized in Table 4.

Table 4: Efficacy Endpoints From Study 1

Efficacy Endpoint	**SYLVANT n=53**	**Placebo n=26**	**p-value[a]**
Durable tumor and symptomatic response (independent review)	34%	0	0.0012
Tumor response	38%	4%	<0.05
Median time to treatment failure (days)	NR[b]	134	<0.05
≥1.5 g/dL increase in hemoglobin	61% (19/31)	0% (0/11)	<0.05

[a] Adjusted for corticosteroid use at randomization

[b] NR="Not Reached"

A consistent treatment effect was confirmed on subgroup analysis for all parameters evaluated with the exception of the hyaline vascular histological subtype. There were no patients with hyaline vascular histology who demonstrated a durable tumor and symptomatic response. However, activity was suggested in this subtype based on change in hemoglobin and median time to treatment failure.

At the time of the analysis, overall survival data were not mature. One year survival rate was 100% in the SYLVANT arm and 92% in the placebo arm.

Subgroup analyses:

Analyses for both primary and secondary endpoints on various subgroups including age (<65 years and ≥65 years); race (White and non-White); region (North America, EMEA, and Asia Pacific); baseline corticosteroid use (yes and no); prior therapy (yes and no); and MCD histology (plasmatic and mixed histology) consistently showed that the treatment effect favored the siltuximab arm except for the hyaline vascular subgroup. A consistent treatment effect favoring siltuximab treated patients across all major secondary endpoints was shown in the hyaline vascular subgroup. Select efficacy results from Study 1 in the hyaline vascular subgroup are summarized in Table 2.

Table 2.0: Select Efficacy Endpoints for Hyaline Vascular Subgroup from Study 1

Efficacy endpoints	**SILTUXIMAB+BSC**	**Placebo+BSC**	**95% CI[a]**
Primary efficacy endpoint			
Durable tumor & symptomatic response (independent review)	0/18 (0%)	0/8 (0%)	(N/A; N/A)[b]
Secondary efficacy endpoints			
Durable tumor & symptomatic response (investigator review)	3/18 (16.7%)	0/8 (0%)	(-25.7; 55.9)
Best tumor response (independent review)	1/18 (5.6%)	1/8 (12.5%)	(-46.7; 35.3)
Best tumor response (investigator assessment)	4/18 (22.2%)	0/8 (0%)	(-20.3; 60.6)
Time to treatment failure	206 days	70 days	(0.17; 1.13)[c]
Hemoglobin increase > 15 g/L at Week 13/hemoglobin response-evaluable population	3/7 (42.9%)	0/4 (0%)	(-22.7; 83.7)
Durable complete symptomatic response[d]	3/18 (16.7%)	0/8 (0%)	(-25.7; 55.9)

[a] 95% confidence interval for the difference in proportions [b] N/A = "Not applicable", there were no responders therefore 95% CI is not applicable [c] 95% confidence interval for the hazard ratio

[d] Complete symptomatic response is defined as a 100% reduction in the baseline MCD overall symptom score sustained for at least 18 weeks prior to treatment failure

Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Study 1, in MCD, was an international, multicenter, randomized Phase 2 study of every 3 week infusions comparing SYLVANT and best supportive care (BSC) to placebo and BSC. There were 53 patients randomized to the SYLVANT arm at a dosage of 11 mg/kg and 26 patients randomized to the placebo arm. Of the 26 placebo-treated

patients, 13 patients subsequently crossed-over to receive SYLVANT. The median age was 48 years (range 20 to 78), 66% male, 48% Asian, 39% White, 4% Black or African American, 7% other. The patients randomized to SYLVANT received a median of 19 infusions (range 1 to 50) compared to patients randomized to placebo who received a median of 8 infusions (range 2 to 32). To control for disparate exposure between arms, Table 3 reports the per patient incidence of adverse reactions that occurred during the first 8 infusions. Adverse reactions that occurred >3% in the SYLVANT arm are presented.

The most common adverse reactions (> 10% compared to placebo) during treatment with SYLVANT in the MCD clinical trial were rash, pruritus, upper respiratory tract infection, increased weight, and hyperuricemia.

Table 3: Per Patient Incidence of Common Adverse Reactions in Study 1 During Initial 8 Infusions

Body System/Adverse Reactions	SYLVANT+BSC[a] n=53		Placebo+BSC n=26	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Skin disorders				
Rash (rash, rash generalized, rash maculo-papular, rash popular and rash pruritic)	15 (28%)	1 (2%)	3 (12%)	0
Pruritus	15 (28%)	0	2 (8%)	0
Skin hyperpigmentation	2 (4%)	0	0	0
Eczema	2 (4%)	0	0	0

Table 3: Per Patient Incidence of Common Adverse Reactions in Study 1 During Initial 8 Infusions

Body System/Adverse Reactions	SYLVANT+BSC[a] n=53		Placebo+BSC n=26	
Psoriasis	2 (4%)	0	0	0
Dry skin	2 (4%)	0	0	0
Infections				
Lower respiratory tract	4 (8%)	2 (4%)	1 (4%)	1 (4%)
Upper respiratory tract	14 (26 %)	1 (2%)	4 (15 %)	1 (4%)
Blood and lymphatic system disorders				
Thrombocytopenia	5 (9%)	2 (4%)	1 (4%)	1 (4%)
General disorders				
Edema (general and localized)	14 (26 %)	4 (8%)	7 (27 %)	0
Gastrointestinal disorders				
Constipation	4 (8%)	0	1 (4%)	0
Metabolism				

Table 3: Per Patient Incidence of Common Adverse Reactions in Study 1 During Initial 8 Infusions

Body System/Adverse Reactions	SYLVANT+BSC[a] n=53		Placebo+BSC n=26	
Hypertriglyceridemia	4 (8%)	0	0	0
Hypercholesterolemia	2 (4%)	0	0	0
Hyperuricemia	6 (11 %)	1 (2%)	0	0
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	4 (8%)	0	1 (4%)	0
Renal and urinary disorders				
Renal impairment	4 (8%)	0	0	0
Nervous system disorders				
Headache	4 (8%)	0	1 (4%)	0
Investigations				
Weight increased	10 (19 %)	1 (2%)	0	0
Vascular disorders				

Table 3: Per Patient Incidence of Common Adverse Reactions in Study 1 During Initial 8 Infusions

Body System/Adverse Reactions	SYLVANT+BSC [a] n=53		Placebo+BSC n=26	
Hypotension	2 (4%)	1 (2%) [b]	0	0

[a] Best Supportive Care

[b] Anaphylactic reaction

Study CNTO328MCD2002 (referred to as Study 2) (NCT01400503) was an open label, long term extension study of patients with MCD treated on prior trials. The median duration of siltuximab treatment was 5.52 years (range: 0.8 to 10.8 years); more than 50% of patients received siltuximab treatment for ≥5 years. The rate of serious or Grade ≥3 adverse events did not increase over time as a function of cumulative exposure.

Other important adverse reactions reported in MCD clinical studies, all of which were very common, were:

Infections and infestations: nasopharyngitis, urinary tract infection

Blood and lymphatic system disorders: neutropenia

Nervous system disorders: dizziness

Vascular disorders: hypertension

Gastrointestinal disorders: nausea, abdominal pain, vomiting, diarrhea, gastroesophageal reflux disease, mouth ulceration

Anaphylaxis and Infusion Related Reactions

During IV infusion of siltuximab, mild to moderate infusion reactions may improve following slowing of or stopping the infusion. Upon resolution of the reaction, reinitiating the infusion at a lower infusion rate and therapeutic administration of antihistamines, acetaminophen, and corticosteroids may be considered. For patients who do not tolerate the infusion following these interventions, siltuximab should be discontinued. During or following infusion, treatment with siltuximab should be discontinued in patients who have severe infusion related hypersensitivity reactions (e.g. anaphylaxis). The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

Immunogenicity

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to SYLVANT with the incidence of antibodies to other products may be misleading. The clinical significance of anti-siltuximab antibodies following treatment with SYLVANT is not known.

The immunogenicity of siltuximab has been evaluated using antigen-bridging enzyme immunoassay (EIA) and electrochemiluminescence-based immunoassay (ECLIA) methods. A total of 432 patients across the clinical studies were evaluated at multiple time points for anti-therapeutic antibody (ATA) responses to siltuximab after treatment with SYLVANT. Following SYLVANT dosing, 0/243 (0%) patients tested positive for anti-siltuximab antibodies by EIA and 4/189 (2%) patients tested positive by ECLIA. Further immunogenicity analyses were conducted for all positive samples from the 4 patients with detectable anti-siltuximab antibodies. None of these patients had neutralizing antibodies.

4.1.2.2 Non-Clinical experience with Siltuximab

No carcinogenicity or genotoxicity studies have been conducted with siltuximab.

Two fertility studies were conducted. In one study, drug-treated male mice were mated with untreated females and in the second study drug-treated female mice were mated with untreated males. A murine analog of siltuximab was administered subcutaneously at doses up to 100 mg/kg/week for a total of 7 doses in both studies. There was no effect on male or female fertility parameters. In addition, siltuximab did not produce any toxicity in the reproductive organs in cynomolgus monkeys in the 6-month repeat-dose toxicology study at doses up to 46 mg/kg (approximately 7 times) the systemic exposure in patients at the recommended dose.

5.0 RATIONALE

5.1 Study rationale and purpose

A. IL-6 orchestrates pancreatic carcinogenesis, immune suppression and is a poor prognostic indicator*.** Signaling downstream of IL-6 is important in PDAC genesis and progression. (Zhang et al., 2013, Lesina et al., 2011) This pleiotropic cytokine binds membrane receptor complexes containing the common signal transducing receptor chain gp130 (glycoprotein 130)(Rose-John, 2006) thereby initiating a complex series of signaling events that include the Jak/STAT, MAPK and PI3K pathways.(Fisher et al., 2014, Scheller et al., 2011) In particular, STAT3 is activated via phosphorylation at Tyr^{705} in most human PDAC specimens and cooperates with activated *Kras* to drive initiation and progression of PDAC in murine models. (Corcoran et al., 2011, Scholz et al., 2003)Recent studies using an inducible *Kras*-mediated PDAC mouse model further showed that IL-6 was instrumental for PDAC progression. (Zhang et al., 2013, Goumas et al., 2015) In fact, **lack of IL-6 completely ablated cancer progression even in the presence of oncogenic *Kras.(Zhang et al., 2013)

In addition to its impact on tumor cells, the IL-6/STAT3 axis is instrumental for regulating immune phenotype and function. This pathway facilitates the expansion of $CD4^+$ T cell subsets (i.e. Th17), which limit antitumor immune responses when present in the tumor microenvironment.(Amedei et al., 2013, He et al., 2011, Liyanage et al., 2002, McAllister et al., 2014, Viehl et al., 2006) This pathway can also simultaneously promote the expansion of immunosuppressive cells. Among the most notable of these subsets are MDSCs and T regulatory cells (T regs). Our group and others have shown that these cells are expanded, and are poor prognostic indicators in patients with advanced GI cancer.(Gabitass et al., 2011, Markowitz et al., 2015, Mundy-Bosse et al., 2011) In this manner, **IL-6 can cooperate with other cytokines either systemically or in the tumor microenvironment to further amplify immune changes in patients**. In agreement with these data, recent results from our group showed that systemic IL-6 had a strong inverse relationship (p=0.0007) with overall survival in metastatic PDAC patients(Farren et al., 2016). Further **studies by our group confirm abundant secretion of IL-6 by stromal cells derived from human PDAC tumors, and that this cytokine is a key factor that allows pancreatic stroma to promote expansion of myeloid-derived suppressor cells (MDSC)** .(Mace et al., 2013)

B. *IL-6 blockade improves the efficacy of immune checkpoint blockade in pre-clinical models of pancreatic cancer.* Blockade of T cell checkpoint receptors with Ab has emerged as a promising immunotherapeutic approach.(Jiang et al., 2013, Chen and Han, 2015) Programmed death-1-ligand 1 (PD-L1), also known as B7-H1, is a cell surface protein and one of 2 ligands for program death receptor 1 (PD-1), a costimulatory molecule that negatively regulates T cell responses.(Freeman, 2008, Goldberg et al., 2007) Ligation of PD-L1 on cancer cells to PD-1 expressed on T cells suppresses T cell activation, proliferation, and induces

apoptosis. PD-1/PD-L1 blockade has antitumor activity in preclinical models, while intratumoral expression of PD-L1 correlates with poor prognosis in patients with PDAC. (Jiang et al., 2013, Topalian et al., 2012)Indeed, increased PD-L1 expression by cancer cells or the stroma is a fundamental escape mechanism from host immunity. ***In theory, IL-6 blockade will downregulate immune suppressive features of PDAC in both the systemic circulation and the tumor stroma, thereby enhancing antitumor activity of antibodies directed against immune checkpoint blockades***. Fortunately, IL-6 blocking Ab like Siltuximab are FDA-approved for other indications. These data suggest blocking IL-6 and downstream pathways could enhance the efficacy of immunotherapy regimens.

Recently published work from our laboratory demonstrates that *in vivo* administration of antibodies (Ab) targeting interleukin-6 (IL-6) and PD-L1 limit tumor progression in subcutaneous, orthotopic and autochthonous, mutant *KRas*-driven models of PDAC (Fig. 1A-C and data not shown; (Mace et al., 2018)). We also demonstrate this treatment combination results in increased infiltration of effector T cells into pancreatic tumors, and reduced levels of activated pancreatic stellate cells within these same tumors. The efficacy of this treatment regimen was dependent upon $CD8^+$ T cells, and an increase in circulating cells with Th1 phenotypic characteristics was observed.

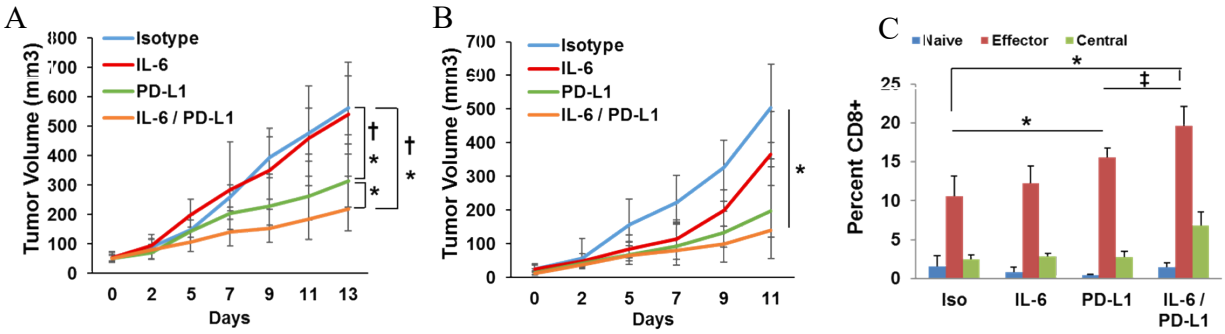


Figure 2. IL-6 and PD-L1 antibody blockade combination therapy decreases PDAC tumor progression and increases the percentage of intratumoral effector T cells. ***A)*** MT5 and ***B)*** Panc02 murine pancreatic tumor cells were subcutaneously injected into C57BL/6 mice with treatment beginning when tumors reached 50-100mm^3. Mice were treated with 200mg (intraperitoneal injection 3 times/week) with isotype control, anti-IL-6 and/or anti-PD-L1 antibodies (n=5-6 mice/group) until mice met pre-specified IACUC-approved early removal criteria. Geometric means ± SD; *p<0.01 compared to Isotype; †p<0.03 compared to PD-L1; ‡p<0.05 compared to IL-6. ***C)*** Panc02 tumors were dissociated using Collagenase II and the Miltenyi Biotec gentleMACS dissociator to obtain a single cell suspension. Cells were stained and analyzed by flow cytometry for activation markers for $CD8^+$ T cell subsets (n=3/group). Naïve ($CD62L^+CD44^-$), Effector Memory ($CD62L^-CD44^+$), and Central Memory ($CD62L^+CD44^+$). Means ± SD; *p<0.002 compared to Isotype; †p<0.01 compared to PD-L1; ‡p<0.02 compared to IL-6.

Finally, our data using an aggressive, genetically engineered model of PDAC indicates that combined inhibition of IL-6 and PD-L1 leads to significant prolongation of survival as compared to mice treated with isotype control antibodies (Figure 2A-C and data not shown; (Mace et al., 2018)).

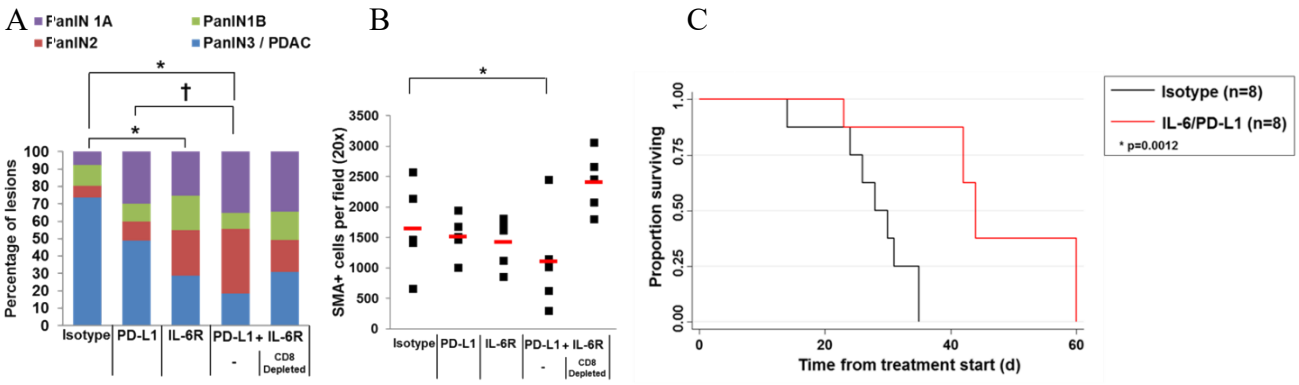


Figure 3. IL-6 and PD-L1 antibody blockade combination therapy decreases PDAC tumor progression and a-SMA$^+$ cells in the pancreata from KPC-Brca2 mice. A highly aggressive, autochthonous model of spontaneously arising PDAC driven by mutant *Kras, Trp53* and *Brca2 (*KPC-Brca2) was used to recapitulate a clinically relevant tumor model. KPC-Brca2 mice were treated at 5-6 weeks of age with 200mg (intraperitoneal injection 3 times/week) of isotype control, anti-IL-6R and/or anti-PD-L1 antibodies for 2 weeks (n=5 mice/group). A cohort of mice treated with anti-IL-6R and PD-L1 antibodies were also depleted for CD8$^+$ T cells. ***A)*** Quantification of the H&E stained slides was conducted by a board certified pathologist. Data revealed a statistically significant shift in the proportion of low grade PanIN lesions, with fewer PanIN3 or foci of adenocarcinoma in mice treated with antibodies targeting PD-L1 and IL-6R, as compared to animals treated with isotype control Ab; Means ± SD; *p<0.005 compared to Isotype; †p=0.01) compared to PD-L1; ***B)*** Pancreatic tissue was stained for alpha-SMA$^+$ stromal cells (red) by IHC and quantified at 20x magnification. Means ± SD; *p=0.0545 compared to Isotype. ***C)*** KPC-Brca2 beginning at 5 weeks of age (100% penetrance of adenocarcinoma) mice were treated with isotype control antibodies or antibodies targeting IL-6 and PD-L1 (200µg/each) until mice were moribund and met pre-specified IACUC-approved early removal criteria. Kaplan-Meier survival curves with log-rank test for significance between isotype control and IL-6/PD-L1 antibodies (p=0.0012).

Together, our data suggest that IL-6 blockade will modulate immunologic features of PDAC both systemically and in the tumor microenvironment, thereby enhancing the efficacy of immune checkpoint inhibitors.

5.2 Rationale for the study design

Because this is a new combination, the first part of the study is focused on safety of the combination and determining the recommended phase II dose. The expansion cohort will confirm the safety profile plus provide preliminary response data regarding activity.

In addition, the trial will include serial blood collections and tumor biopsies which will enable us to evaluate the biologic effect of the combination on tumor microenvironment and lymphocytes in the tumor and in circulation.

5.3 Rationale for dose and regimen selection for spartalizumab:

In study [CPDR001X2101], spartalizumab single-agent was administered as an intravenous infusion over 30 minutes at doses ranging from 1 to 10 mg/kg on every 2 weeks (Q2W) schedule or at 3 and 5 mg/kg every 4 weeks (Q4W) schedules. Approximately dose-proportional increase in exposure (C1D1 AUC0-336) was observed with doses from 1 to 10 mg/kg and no DLTs were observed. Accumulation of approximately 2.1-3.4-fold was observed with Q2W dosing and 1.6-2.2-fold with Q4W dosing. Population PK analysis indicated that weight-adjusted or flat dosing lead to similar exposure range Therefore, a flat dosing scheme was selected which has the added advantage of convenience and less risk for medication errors.

Two recommended dosing regimens have been established: 300 mg Q3W and 400 mg Q4W flat dosing schedules. A flat dose of 400 mg Q4W or 300 mg Q3W is expected to achieve a mean steady-state C_{trough} value higher than the ex vivo EC50 for antigen-stimulated IL-2 production, a translational biomarker for PD-1 blockade (Patnaik et al, 2015). Based on the safety profile observed in study [CPDR001X2101] and the expected C_{trough} values, 400 mg Q4W is expected to be a safe and efficacious dose.

The use of the Q3W regimen is intended to align the administration of Siltuximab and spartalizumab every 3 weeks.

5.4 Risks and benefits

Spartalizumab is a humanized IgG4 monoclonal antibody which belongs to a class of agents known as immune-checkpoint inhibitors, specifically anti-PD-1. This class of compounds has demonstrated significant improvement in efficacy combined with a tolerable and manageable safety profile, supporting regulatory approvals in various indications..

Immune-checkpoint inhibitors of this class may be associated with the occurrence of immune-mediated adverse events (irAE). In general, irAE can potentially involve every organ system but gastrointestinal (e.g. colitis), dermatologic (e.g. rash, pruritus), hepatic (e.g. hepatitis), pulmonary (e.g. pneumonitis), renal (e.g. nephritis) and endocrine toxicities (e.g. hypothyroidism, hyperthyroidism, type I diabetes, hypophysitis including hypopituitarism and adrenal insufficiency) being typically the most frequent. Other immune-mediated AEs may rarely include the nervous system (e.g. encephalitis, Guillain-Barre syndrome, myasthenia gravis), eye (e.g. uveitis), musculo-skeletal system (e.g. myositis, arthritis), cardio-vascular system (e.g. vasculitis, myocarditis) or blood system (e.g. anemia, cytopenias), and severe skin reactions such as toxic epidermonecrolysis or Steven Johnson syndrome. Furthermore, complications in patients with bone marrow or solid organ transplant have been reported (e.g. organ rejection, severe graft-versus-host disease). These side effects are generally manageable and reversible with dose interruption and administration of corticosteroids and/or other immunosuppressants. However, fatal events have been reported in some cases with checkpoint inhibitors; furthermore, some events like endocrinopathies may require life-long hormonal

replacement. While most irAEs are expected to occur during the treatment with spartalizumab, onset may be delayed and irAEs may also occur after discontinuation of study treatment (Eggermont, 2015 #13Champiat, 2016 #14; Hofmann, 2016 #).

In addition, monoclonal antibodies can be associated with infusion-related reactions some of which can be severe; these are often immediate and usually occur within minutes of the exposure to the study drug. Therefore, infusions must take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available, and patients monitored for respective signs and symptoms. Patients who experience severe or life-threatening irAEs or infusion reactions may need to permanently discontinue spartalizumab (see Section 6.3.1 for further guidance).

It is expected that spartalizumab would have a similar safety profile as other immune checkpoint inhibitors with the above mentioned side effects possibly occurring in patients treated in the present study (for most common adverse reactions observed in clinical studies with spartalizumab, please refer to the latest version of the Investigator's Brochure). It is therefore important to be vigilant and carefully identify events that may be suggestive of potential immune-mediated AEs, as their appearance may be sub-clinical (for example an asymptomatic laboratory abnormality), and early diagnosis is critical for appropriate management and possibly prevent complications. Serological, immunological and histological assessments (such as biopsy of the affected tissue) should be performed as deemed appropriate by the investigator to verify the potential immune-mediated nature of the AE and to exclude alternative diagnoses or disease progression. The protocol includes specific eligibility criteria (Section 5), DLT definitions, monitoring visits and assessments, dose modification and stopping rules as well as recommended guidelines for prophylactic or supportive treatment of expected toxicities, including identification and management of study-drug induced adverse events. The risks to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as, close clinical monitoring. There may be unforeseen risks with which could be serious.

Refer also to preclinical toxicity and or clinical data found in the latest [Investigator's Brochure]. Side effect of siltuximab reviewed in section 1.2.

The patient population selected for this trial advanced pancreatic cancer with at least one prior line of therapy, have very limited effective therapeutic options. The disease has uniform mortality. The treatment proposed in this trial has the potential to impact outcome based on the pre-clinical data. The study is designed to lower risks for participants through dose escalation to select the appropriate dose, strict eligibility criteria, and frequent monitoring on trial for side effects.

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints: This is a phase I trial. The primary endpoint is still toxicity. The plan is to evaluate the response rate, response duration, and progression free survival

of the patients on the trial. These endpoints will provide preliminary data in advanced pancreatic cancer.

5.4.1.2 **Biomarker Research:** We intend in all patients to evaluate the effects of the combination on T-cell population in peripheral blood. In addition, we plan to evaluate the effects of the combination versus spartalizumab alone in paired biopsy samples. These samples will be analyzed for tumor infiltrating lymphocytes, stromal/tumor markers and expression immune inhibitory molecules (PD-L1, PD-L2, PD1, etc). We anticipate to see a difference between the groups treated with the combination versus the group treated with spartalizumab alone.

Table 4.0 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Section 6.2
Evaluate the safety profile of the combination of siltuximab and spartalizumab	Determine the recommended phase II dose of siltuximab that can be combined with spartalizumab	
Key secondary		Section 14.3
To evaluate the activity of siltuximab and spartalizumab	Overall response rate (CR+ PR) in patients treated with siltuximab and spartalizumab	
Other secondary		Section 14.3
To evaluate the response duration, progression free survival and overall survival of patients with pancreatic cancer receiving siltuximab and spartalizumab	Response duration. progression free survival and overall survival time from treatment start until progression or death	
Exploratory		Section 7.1
Evaluate the effect of the combination on the immune profile in the serum and in tumor biopsies.	Characterization of immune cell phenotypes in serum and tissue pre and post treatment. Characterization of the effects of the combination on immune inhibitory pathways	

6.0 METHODOLOGY

6.1 Entry Criteria

6.1.1 Diagnosis/Condition for Entry into the Trial

Patients must have a cytological or histologic diagnosis and metastatic pancreatic adenocarcinoma disease that has failed at least one standard regimen. In the expansion phase, patients will participate in the paired biopsy studies. Patient selected for biopsy must have a primary or metastatic non-bone site that is amenable to safe biopsy. Bone only lesions are not suitable for biopsy. These patients will provide informed consent for the paired biopsy study.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

6.1.2 Subject Inclusion Criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Cytological or histologic diagnosis and metastatic pancreatic adenocarcinoma disease that has failed at least one standard regimen such as gemcitabine nab-paclitaxel or FOLFIRINOX.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Patient must meet the following laboratory values at the screening visit:
    - Absolute Neutrophil Count ≥1.5 x 10^9/L
    - Platelets ≥75 x 10^9/L
    - Hemoglobin (Hgb) ≥9 g/dL
    - Serum creatinine <1.5 mg/dL OR Creatinine Clearance ≥ 45 mL/min using Cockcroft-Gault formula
    - Total bilirubin ≤1.5 x ULN
    - Aspartate transaminase (AST) ≤ 2.5 x ULN, except for patients with liver metastasis, who may only be included if AST ≤5.0 x ULN
    - Alanine transaminase (ALT) ≤ 2.5 x ULN, except for patients with liver metastasis, who may only be included if ALT ≤5.0 x ULN
4. Presence of measurable disease by RECIST criteria
5. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0-2.(Appendix 1)
6. Written informed consent must be obtained prior to any screening procedures.
7. Normal ECG defined as the following:
    - Resting heart rate 50-90 bpm

- QTcF at screening <450 ms (male patients), <460 ms (female patients)

8. Before enrollment, a woman must be either:

    a. Not of childbearing potential: postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/mL); permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy

    b. Of childbearing potential and practicing (during the study and for 150 days after receiving the last dose of study agent) a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject)

    c. Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active) a woman must begin a highly effective method of birth control, as described above.

9. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening

10. During the study and for 150 days after receiving the last dose of study agent, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction

11. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 150 days after receiving the last dose of study drug

12. Sign an informed consent document indicating that they understand the purpose of and procedures required for the study, are willing to participate in the study, and are willing and able to adhere to the prohibitions and restrictions specified in this protocol. Informed consent must be obtained before performing any study specific procedures.

6.1.3 Subject Exclusion Criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Prior exposure to agents targeting PD-1, PD-L1, IL-6 or the IL-6 receptor. Prior chemotherapy is allowed as long as adequate washout period of ≥ 4 weeks.
2. Any untreated central nervous system (CNS) lesion. However, patients are eligible if: a) all known CNS lesions have been treated with radiotherapy or surgery and b) patient remained without evidence of CNS disease progression ≥ 4 weeks after treatment and c) patients must be off corticosteroid therapy for ≥ 2 weeks.
3. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment
4. Systemic chronic steroid therapy (≥ 10mg/day prednisone or equivalent) or any immunosuppressive therapy 7 days prior to planned date of first dose of study treatment. *Note: Topical, inhaled, nasal and ophthalmic steroids are allowed.*
5. Active, known or suspected autoimmune disease or a documented history of autoimmune disease *Note: Patients with vitiligo, controlled type I diabetes mellitus on stable insulin dose, residual autoimmune-related hypothyroidism only requiring hormone replacement or psoriasis not requiring systemic treatment are permitted).*
6. Allogenic bone marrow or solid organ transplant
7. History of severe hypersensitivity reactions to other monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction
8. Known history or current interstitial lung disease or non-infectious pneumonitis
9. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma *in situ*
10. Clinically significant infection, including known HIV or hepatitis C infection, or known hepatitis B surface antigen positivity
11. Clinically significant ongoing infection
12. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 14 days or 5 half-lives before enrollment (whichever is longer) or is currently enrolled in the treatment stage of an investigational study
13. A woman who is pregnant or breast-feeding, or a woman who is planning to become pregnant or a man who plans to father a child while enrolled in this study or within 150 days after the last dose of study agent

14. Had hospitalization for infection or major surgery (eg, requiring general anesthesia) within 2 weeks before enrollment or have not fully recovered from surgery. Note: subjects with surgical procedures conducted under local anesthesia may participate
15. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease, including any of the following:
    a. recent myocardial infarction (within last 6 months),
    b. uncontrolled congestive heart failure,
    c. unstable angina (within last 6 months),
    d. clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker).

6.1.4 Screen Failures

Minimal data for subjects who fail screening will be collected such as demographic information and the reason for screen failure. Such subjects may be re-screened at the discretion of the investigator after approval by the Data and Safety Monitoring Committee (DSMC). The reason for the need to re-screen a subject will be documented in the subject's source documents.

6.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table

Table 5. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Spartalizumab	300 mg	Q3W	IV infusion	Day 1 of each 3 week cycle
Siltuximab	As Below	Q 3W	IV Infusion	Day 1 of each 3 week cycle

Siltuximab will be infused first. Patients will be observed for at least 1 hour post infusion of siltuximab.

Spartalizumab will be administered via intravenous infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 3 weeks. The dose may be interrupted for up to 12 weeks. The safety assessments should be performed according to the actual day of 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 4 hours after the first two spartalizumab infusions. The same may apply for the subsequent spartalizumab infusions if medically indicated. Patients should be further provided instructions to notify study personnel if symptoms of infusion reaction occur after any spartalizumab infusion.

6.2.1 Siltuximab dose levels

Open label phase I trial. Primary objective is to determine the recommended phase 2 dose (RP2D) of the combination of siltuximab plus spartalizumab in a pancreatic cancer. The design is 3+3 with 3 dose levels of siltuximab.

Table 6. Dose escalation for siltuximab

No of pts	Cohort Level	Siltuximab	Spartalizumab
3 to 6	1	6 mg/Kg IV every 3 weeks	300 mg every 3 weeks
3 to 6	2	11 mg/Kg every 3 weeks	300 mg every 3 weeks
3 to 6	2a	9 mg/Kg every 3 weeks	300 mg every 3 weeks

Dose level 2a will only be tested if we observe 2 DLT's on dose level 2.

6.2.2 Dose Escalation

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level. The first cohort will be treated with the starting dose of 300 mg of spartalizumab and 6 mg/Kg of Siltuximab.

Patient will be considered evaluable for dose escalation decision if patients have received at least 2 infusions of both study drugs (spartalizumab and siltuximab) and had safety assessments for a minimum of 6 weeks or have had a DLT during the first 6 weeks. Dose escalation decisions will occur when the cohort of patients has met these criteria. All patients within a dosing cohort must have completed the DLT evaluation period and have been evaluated for DLT prior to dose escalation.

If 1 of the first 3 patients develops a DLT, then enroll up to 3 additional patients at the same dose level. If 2 or more patients in any dose cohort of 6 or fewer patients have a DLT, then the MTD of the combination is exceeded. If there are no DLTs in the first 3 patients at dose level 1 or 1 of 6 patients in dose level 1 has a DLT, enroll 3 patients into the 11 mg/Kg dose level. If 2 or more patients in this dose cohort have a DLT, reduce dose to 9 mg/Kg and enroll 3 more patients. If an acceptable dose is identified, then start the expansion phase. Prior to dose escalation, we will obtain approval from the Data Safety and Monitoring Committee (DSMC) for implementation of dose escalation decisions.

6.2.3 Dose limiting toxicity (DLT)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as at least possibly related to study treatment that occurs within the first 6 weeks and meets any of the criteria included in Table 7. National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

Table 7 Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERIA
Blood and lymphatic system disorders	Thrombocytopenia Grade 3 with clinically significant bleeding Thrombocytopenia Grade 4
	Neutropenia Grade 4 lasting more than 8 days
	Febrile neutropenia CTCAE Grade ≥ 3
Gastrointestinal disorders	Diarrhea CTCAE Grade ≥ 3 ≥ 72 hrs., despite the use of anti-diarrhea therapy
	Nausea/ vomiting CTCAE Grade ≥ 3 ≥ 72 hrs., despite the use of anti-emetic therapy
Pneumonitis (interstitial lung disease)	• CTCAE Grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids. • Second episode of grade 2 pneumonitis of any duration • Grade 3-4 pneumonitis of any duration
Immune-related toxicities (except pneumonitis)	• CTCAE Grade 3 immune-related toxicities that persist > 14 days with same severity despite treatment with corticosteroids. • Immune-related toxicities CTCAE Grade 4 of any duration
Other Adverse Events	• Grade 3-4 infusion reaction

	• Other non-hematologic treatment-related toxicity at Grade 3 or higher • Any AE that leads to permanent discontinuation of siltuximab or spartalizumab • Death

6.2.4 Dose expansion 24 patients will be treated on the dose expansion at the RP2D dose.

6.2.5 Duration of therapy: Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment.
- Administrative reasons

6.3 Dose Modification:

6.3.1 Dose modification and dose interruption

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

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

6.3.2 Dose modification and dose interruption for spartalizumab and siltuximab

General dose modification instructions:
Siltuximab and spartalizumab have class-specific safety profiles based on their mechanism of action but may also cause AEs that overlap. For management of AEs which can be clearly attributed to siltuximab or spartalizumab, independent dose modification for either agent is allowed. For AEs without clear attribution to either study treatment, management of toxicity should include dose modifications of both agents.

Overall AEs are to be graded according to NCI-CTCAE v4.03 (http://ctep.cancer.gov). All dose interruptions and the reason for the dose interruption must be documented in the eCRF.

Overall, patients with AEs suspected to be related to ***spartalizumab*** including those of potential immune-mediated etiology (irAE) may need to interrupt or permanently discontinue spartalizumab as outlined in Section 6.3.2. In general, study treatment with spartalizumab must be permanently discontinued in case of:

- Any 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 after last dose of study treatment
- Inability to reduce the dose of steroids (for the management of irAE) to 10 mg/day or less of prednisone or equivalent (or as indicated in the tables below) within 12 weeks
- Any severe or Grade 3 recurring treatment-related adverse reaction

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

Overall, patients with AEs suspected to be related to ***siltuximab*** include pruritus, increased weight (edema), rash, hyperuricemia, neutropenia, and upper respiratory tract infection. Rare side effects include gastrointestinal perforation. Toxicities may require interruption of therapy,

dose reduction or permanent discontinuation from trial as detailed in section 6.3 and Tables 8-8 and 8-9. In general study treatment with siltuximab must be discontinued for:

- Gastrointestinal perforation
- Grade 4 weight gain
- Grade 4 upper respiratory tract infection
- Recurrent or severe grade 3 treatment-related adverse events.
- Life threatening adverse events
- Interruption of therapy for longer than 12 weeks

If either study drug (siltuximab or spartalizumab) is on **temporary hold**, therapy with the other agent will continue. Cross sectional imaging will be performed every 3rd cycle as per protocol. If there is disease progression, the subject should be removed from the study. The only exception is siltuximab may be continued as a single agent to control immune-related adverse events (irAEs) attributed to spartalizumab, but siltuximab therapy must be stopped after the irAEs can be adequately controlled with corticosteroids therapy.

If either study drug (siltuximab or spartalizumab) is being **permanently** discontinued, the remaining study drug should also be permanently discontinued given that either drug alone is unlikely to have adequate anti-tumor activity to justify its continuation for a prolonged period of time with the following exceptions:

1. In subjects who are demonstrating objective benefit from treatment (radiologic CR, PR or SD), a discussion regarding continuing single agent therapy will be conducted with PI and patient. Subject will be informed single agent activity of either agent is unlikely in pancreatic cancer. If the subject is agreeable, single agent therapy may continue until progression. No single agent therapy beyond progression will be offered.

2. Siltuximab may be continued as a single agent to control immune-related adverse events (irAEs) attributed to spartalizumab, but siltuximab therapy must be stopped after the irAEs can be adequately controlled with corticosteroids therapy.

6.3.2.1 Dose Modification requirements for potential immune- mediated adverse events

6.3.2.1.1 Identification of and management requirements for AEs of potential immune-mediated etiology (irAE)

Adverse events of special interest (AESI) include AEs of a potential immune-mediated etiology (irAE) that are associated with spartalizumab treatment. An irAE may be experienced by patients treated with spartalizumab due to its mechanism of action and predicted based on the reported experience with other immunotherapies that have a similar mechanism of action.

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.

An irAE may be of low grade and self-limited, most frequently involving the GI tract (i.e. diarrhea/colitis), skin (i.e. rashes), liver (i.e. hepatitis), lung (i.e. pneumonitis), kidneys (i.e. nephritis) and endocrine systems (a variety of endocrinopathies) and rarely CNS (i.e. encephalitis), 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 (TNFa) 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 immune suppressants. Some events like endocrinopathies may require life-long hormonal replacement. Tapering of steroids should not be too rapid 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 experience from compounds with similar mechanism of action of spartalizumab and published guidelines (Haanen, 2017), instructions have been developed regarding how to identify, assess severity and manage irAEs that may occur in patients receiving spartalizumab. Dose modification requirements and AE management guidelines for the potential irAEs are provided in the following tables: diarrhea/colitis (Table 8-0), hepatitis (liver laboratory alterations) (Table 8-1), skin (rash) (Table 8-2), nephritis (Table 8-3), pneumonitis (Table 8-4), endocrinopathies (Table 8-5), and other potential immune-related AEs (Table 8-6). Any Grade 4 irAE must result in permanent discontinuation of spartalizumab. In addition, guidance for management of spartalizumab -infusion reaction & cytokine release syndrome is provided in (Table 8-7).

Under the category of OTHERS (Table 8-9) are included several irAE of interest that must be managed specifically and for which no specific guidance are provided in the table below. OTHERS include (but is not restricted to) the following events : Autoimmune neuropathy, demyelinating polyneuropathy, Guillain-Barre, myasthenia Gravis-like syndrome, non-infectious myocarditis, non-infectious pericarditis, pancreatitis, encephalitis, and, rapid onset of Grade 3 fatigue in the absence of disease progression.

Patients receiving spartalizumab, may experience other irAEs than those listed in this document, therefore, all AEs of unknown etiology associated with drug exposure should be evaluated to determine if it is possibly immune-related. In cases where the specific irAE is not listed in the tables below, the investigator should follow the dose modification requirements in section 6.3.2 which details the measures to be taken for suspected (could be potentially immune-related or non-immune-related) AEs. Investigators are encouraged to contact the Sponsor as needed to discuss cases that warrant separate discussion outside of the scope of the current instructions.

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

Table 8.0 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related diarrhea/colitis

Diarrhea/Colitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 (< 4 bowel actions per day over baseline) mild Grade 2 (4-6 bowel actions per day over baseline) and / or abdominal pain/ blood in stool.	• Diet • Hydration • Loperamide: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours; • Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea > 48hrs: loperamide 2 mg every two hours; maximum 16 mg/day. Consider other second-line therapies for diarrhea (e.g: (octreotide, oral diphenoxylate) and oral antibiotics • If Grade 2 and no improvement in 5 days may require oral steroids • If Grade 2 diarrhea persists >1 week consider GI consultation and endoscopy to evaluate for colitis.	• Continue spartalizumab treatment • If diarrhea is Grade 2, despite loperamide at 2 mg every two hours for > 48hrs: o Interrupt spartalizumab until diarrhea recovers to Grade ≤1 and then restart spartalizumab treatment at the same dose and schedule.

Diarrhea/Colitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	• If Grade 2 persists for 5 days and worsening of symptoms or diffuse ulcerations and bleeding seen on endoscopy , commence steroids at a dose of 0.5-1mg/kg per day of prednisone (or IV equivalent) and continue until symptoms improve to Grade 1. If no improvement occurs, manage as per Grade 3. Steroids can be tapered as per section 6.3.1.2.2. • Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the evidence of macroscopic and microscopic inflammation.	
Grade 3 Diarrhea: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care ADL; Grade 3 Colitis: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	• Clinical evaluation and hospitalization indicated; rule out bowel perforation and intravenous hydration. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • In addition to symptomatic treatment (diet, hydration, loperamide, antibiotics if indicated); initiate immediate treatment with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) is recommended. • When symptoms improve to ≤Grade 1, steroid taper should be done as per section 6.3.1.1.2. • Taper over 6 to 8 weeks in patients with diffuse and	1st occurrence: • Interrupt spartalizumab until diarrhea/colitis recovers to Grade ≤1 or baseline o Once recovered restart spartalizumab treatment at the same dose and schedule and after appropriate steroid tapering (if initiated). AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since a Grade 3 event has been identified, otherwise spartalizumab must be permanently discontinued 2nd occurrence: Permanently discontinue spartalizumab

Diarrhea/Colitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	severe ulceration and/or bleeding. • If no improvement in 2-3 days: consider initiating infliximab 5mg/kg and continue steroids. (Infliximab is contraindicated in patients with sepsis or a perforation). Upon symptomatic relief initiate a prolonged steroid taper over 45 to 60 days. • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. • If symptoms persist despite the above treatment a surgical consult should be obtained.	
Grade 4: Life-threatening consequences; urgent intervention indicated	Same as Grade 3	Permanently discontinue spartalizumab

Table 8-1 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related liver laboratory alterations

Abnormal liver function tests		
Severity	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 2: AST or ALT > 3x ULN to ≤ 5.0x ULN and/or bilirubin > 1.5x ULN to ≤ 3x ULN (if patient meets criteria for Hy's law refer to section 6.5)	Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values	• Interrupt spartalizumab treatment until recovery to Grade ≤1 or baseline ○ Once recovered restart spartalizumab treatment at the same dose and schedule • Patients with baseline grade 2 AST/ALT value (>3.0-5.0 ULN) may continue spartalizumab treatment

Abnormal liver function tests		
Severity	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 3 or 4: AST or ALT >5.0xULN and/or bilirubin > 3.0x ULN	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values. • Consider viral serology (i.e. hepatitis A/B/C, CMV, and rule out other potential cause of liver injury such as conmeds or alcohol), consultation with hepatologist and liver biopsy to establish etiology of hepatic injury • If after 2-3 days new liver assessment shows worsening of laboratory test consider to initiate treatment with steroids prednisone 1-2 mg/kg/day or IV equivalents. • Add prophylactic antibiotics for opportunistic infections as appropriate • When symptoms/liver function tests improve to Grade ≤1, taper steroids over at least 4 weeks. • If serum transaminase levels or bilirubin do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given as per local treatment guidance. • Infliximab is not recommended due to its potential for hepatotoxicity	• Permanently discontinue spartalizumab • Patients with baseline grade 2 AST/ALT value (>3.0-5.0 ULN) will discontinue spartalizumab treatment if value increased to grade 3 with increase >=2x baseline

Table 8-2 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related skin events

Rash Events (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Rash covering < 10% Body Surface Area (BSA)	• Initiate prophylactic and symptomatic treatment measures. • Consider use of topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks.	Continue spartalizumab treatment
Grade 2: 10-30% of BSA	• If tolerable, treat as per Grade 1; • If intolerable, initiate systemic steroids (e.g. oral prednisolone 0.5-1mg/kg daily) and consider dose interruption until tolerable or recovery to grade <=1 or baseline; once recovered resume spartalizumab treatment at the same dose and schedule. • If symptoms persist or recur consider skin biopsy.	Continue spartalizumab treatment o AE resolution to ≤1 or baseline must occur within a period of 12 weeks since Grade 2 event has been identified, otherwise spartalizumab must be permanently discontinued.
Grade 3: More than 30% of BSA	• Obtain a skin biopsy and dermatology consult. • Initiate systemic steroids with 1mg/kg of prednisolone or IV equivalent.	1st occurrence: • Interrupt spartalizumab until rash recovers to Grade ≤1 or baseline o Once recovered restart spartalizumab treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since Grade 3 event has been identified.

Rash Events (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
		Otherwise, spartalizumab must be permanently discontinued 2nd occurrence: Permanently discontinue spartalizumab
Grade 4: Life-threatening	Same as Grade 3; additional measures as per local institutional guidelines	Permanently discontinue spartalizumab
Other skin events		
Stevens-Johnson syndrome, toxic epidermal necrolysis and other serious or life-threatening skin reactions	Institute supportive care immediately as per institutional guidelines	Permanently discontinue spartalizumab

Table 8-3 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related nephritis

Nephritis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Creatinine >ULN to ≤1.5x ULN)	• Monitor creatinine weekly • If creatinine return to baseline resume routine creatinine monitoring per protocol • Promote hydration and cessation of nephrotoxic drugs	Continue spartalizumab
Grade 2: Creatinine >1.5 to ≤3 x ULN	• Monitor creatinine every 2 to 3 days • Initiate 0.5 to 1 mg/kg/day prednisone or equivalents • If worsening or no improvement: 1 to 2 mg/kg/day prednisone or equivalents • Promote hydration and cessation of nephrotoxic drugs • Consult with specialist and consider renal biopsy	• Interrupt spartalizumab until serum creatinine recovers to ≤ Grade 1 or baseline. ○ Once recovered restart spartalizumab at the same dose and schedule AE resolution to ≤ Grade 1 must occur within a period of 12 weeks since Grade 2 event has been identified, otherwise spartalizumab must be permanently discontinued.

Nephritis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 3: Creatinine >3.0 to <u>≤6</u> <u>x</u> ULN	• Monitor creatinine every 1 to 2 days • Start 1 to 2 mg/kg/day prednisone or equivalents • Consult with nephrologist and consider renal biopsy	1st occurrence: • Interrupt spartalizumab until serum creatinine recovers to ≤Grade 1 or baseline. ○ Once recovered restart spartalizumab treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since the Grade 3 event has been identified, otherwise spartalizumab must be permanently discontinued 2nd occurrence: Permanently discontinue spartalizumab.
Grade 4: Creatinine >6x ULN	• Monitor creatinine daily • Initiate steroids with 1 to 2 mg/kg/day prednisone or equivalent • Consult with nephrologist and consider renal biopsy	Permanently discontinue spartalizumab

Table 8-4 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related pneumonitis

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Radiographic changes only- Asymptomatic	• CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks • Monitor for symptoms every 2-3 days - Clinical	

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse oximetry recommended • Consultation of pulmonologist recommended	
Grade 2: Symptomatic-medical intervention indicated; limits instrumental ADLs	• CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated).	1st occurrence: • Interrupt spartalizumab until recovery to Grade ≤1 or baseline ○ Once recovered restart spartalizumab treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since Grade 2 event has been identified, otherwise spartalizumab must be permanently discontinued. If worsens treat as Grade 3 or 4 2nd occurrence: Permanently discontinue spartalizumab
Grade 3: Severe symptoms; limits self-care ADLs; oxygen indicated Grade 4: Life- threatening respiratory compromise; urgent intervention required	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL if possible • Treat with IV steroids (methylprednisolone 125 mg) as indicated. When	Permanently discontinue spartalizumab

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). • If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication	

Table 8-5 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related endocrine events

Endocrine events (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Asymptomatic, intervention not indicated (e.g. hyperthyroidism or hypothyroidism)	• 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 • Consider endocrinologist consult • If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis) • Repeat labs in 1 to 3 weeks/MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan	Continue spartalizumab

Endocrine events (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Symptomatic endocrinopathy (e.g., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)	• Consider Endocrinology consultation • Rule out infection/sepsis and other alternative causes with appropriate cultures and imaging • Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. (only for life-threatening endocrinopathies) • Replacement of appropriate hormones may be required as the steroid dose is tapered • Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis • Consider hospitalization and intravenous methylprednisolone should be initiated.	• Interrupt spartalizumab until recovery to mild or no symptoms, and controlled with hormone replacement therapy ○ Once recovered or controlled with hormone replacement, restart spartalizumab at the same dose and schedule ○ Hypothyroidism may be managed with replacement therapy without treatment interruption (unless life-threatening) 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.
Autoimmune diabetes (Grade 3 or symptomatic hyperglycemia)	• Initiate anti-glycemic therapy (i.e. insulin) as medically indicated and monitor glucose levels regularly until metabolic control is achieved	• Interrupt spartalizumab until recovery to grade 1 or baseline ○ Once recovered, restart spartalizumab treatment at the same dose and schedule • Second occurrence: permanently discontinue
Autoimmune diabetes (Grade 4 hyperglycemia or life-threatening complications)	• Same as Grade 3	Permanently discontinue spartalizumab

***M*anagement for immune-related**:

a. For non-life-threatening immune-related endocrinopathy, the administration of corticosteroids can be omitted, and the patient can be treated with physiologic replacement of the deficient hormone (e.g. provide levothyroxine for immune-related hypothyroidism, and omit administration of corticosteroids).

b. Use corticosteroids only used if endocrinopathy is life-threatening or as physiologic replacement for primary or secondary adrenal insufficiency.

Table 8-6 Mandatory dose modification requirements and recommended clinical management guidelines for "other" potential immune-related AEs of special interest

Other(e.g. Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, Non-infectious myocarditis, pericarditis, pancreatitis, encephalitis, and Grade 3 Fatigue with rapid onset in absence of disease progression)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Mild (Grade 1)	Provide symptomatic treatment	Continue spartalizumab
Moderate (Grade 2)	• Consider interruption of spartalizumab until recovery to ≤ Grade 1 or baseline. • Ensure adequate evaluation to confirm etiology or exclude other causes • Provide symptomatic treatment • Systemic corticosteroids may be indicated • Consider biopsy for confirmation of diagnosis • A specialist should be consulted	
Severe (Grade 3)	• Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg QD and other therapies as appropriate • Monitor closely and consult with a specialist	1st occurrence: • Interrupt spartalizumab until recovery to ≤ Grade 1 or baseline o May restart spartalizumab treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a maximum period of 12 weeks since

Other(e.g. Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, Non-infectious myocarditis, pericarditis, pancreatitis, encephalitis, and Grade 3 Fatigue with rapid onset in absence of disease progression)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
		a Grade 3 event has been identified, otherwise spartalizumab must be permanently discontinued. 2nd occurrence: Permanently discontinue spartalizumab
Grade 4	Refer to management of severe AEs	Permanently discontinue spartalizumab
Encephalitis (any grade)	• 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 spartalizumab
Myocarditis or cardiac event grade>=3	Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg QD, and consult with specialist.	Permanently discontinue spartalizumab

Table 8-7 Mandatory dose modification requirements and recommended clinical management guidelines for infusion reaction events and cytokine release syndrome

Infusion reaction (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	Continue spartalizumab
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS,	• Stop Infusion • Additional appropriate medical therapy may include but is not limited to: o IV fluids	spartalizumab may continue with close monitoring and premedication as per local institutional guidelines for prophylaxis of infusion reaction

Infusion reaction (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	○ Antihistamines ○ NSAIDS ○ Acetaminophen ○ Narcotics • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be re-premedicated for the next scheduled dose. • Patient may be premedicated 1.5hr (± 30 minutes) prior to infusion of spartalizumab with: ○ Diphenhydramine 50 mg po (or equivalent dose of antihistamine). ○ Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). • Consider discontinuation of spartalizumab in case of recurring infusion reaction despite premedication and prolonged infusion	
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	• Stop Infusion • Additional appropriate medical therapy may include but is not limited to: ○ IV fluids ○ Antihistamines ○ NSAIDS	Permanently discontinue spartalizumab

Infusion reaction (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	○ Acetaminophen ○ Narcotics ○ Oxygen ○ Pressors ○ Corticosteroids ○ Epinephrine • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	

2nd occurrence of grade 2 irAE (including colitis/diarrhea, LFT abnormalities, rash, nephritis and other AEs as listed in table 8-6) or for grade 2 irAE lasting more than 12 weeks. Permanently discontinue spartalizumab.

6.3.2.1.2 Guidance for corticosteroids tapering for management of immune-related AEs:

Steroids should be tapered slowly and based on response/recovery of clinical symptoms. Consider to complete tapering over a period of at least 4 weeks. Slower tapering of corticosteroids therapy may be recommended if the adverse event is not showing improvement.

Once corticosteroid tapering is achieved at a level of 10 mg of prednisone/day (or equivalent), spartalizumab can be restarted as indicated in the dose modification tables.

6.3.2.2 Dose modification requirements for adverse events suspected to be related to study treatment

The required dose modification and management of adverse events that are considered to be related to study medication and do not have specific management requirements noted elsewhere in the protocol are provided in Table 8-8 & Table 8-9.

Table 8-8 Mandatory dose modification requirements and recommended clinical management guidelines for hematologic adverse events suspected to study treatment

Hematologic suspected AEs (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Neutropenia		
Grades 1, 2	NA	Continue spartalizumab and siltuximab
Grade 3, 4	Monitoring blood test more frequently (every 7 days for grade 3, and 3-5 days for grade 4) Consider consulting with a specialist, initiation of corticosteroids or other therapies as medically appropriate and as per institutional guidelines.	1st occurrence: • Interrupt spartalizumab and siltuximab until toxicity recovers to Grade ≤2 or baseline. o Once recovered restart spartalizumab and siltuximab treatment at the same dose and schedule o Grade 4 febrile neutropenia or thrombocytopenia should lead to permanent discontinuation of spartalizumab and siltuximab 2nd occurrence: • Interrupt spartalizumab and siltuximab until toxicity recovers to Grade ≤2 or baseline o Once recovered restart spartalizumab and siltuximab treatment at the same dose and schedule AE resolution to ≤ Grade 2 or baseline must occur within a maximum period of 12 weeks since Grade 3 or 4 event has been identified, otherwise spartalizumab

Hematologic suspected AEs (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
		and siltuximab must be permanently discontinued 3rd occurrence: Permanently discontinue spartalizumab and siltuximab
Febrile Neutropenia	Apply Institutional guidelines	Follow- neutropenia Grade 4 requirements (above)
Thrombocytopenia (NCI-CTCAE v4.03)		
Grade 1, 2, 3 without clinical significant bleeding	Grade 3: monitoring blood test more frequently (every 7 days)	Continue spartalizumab and siltuximab
Grade 3 with clinical significant bleeding OR Grade 4	Monitoring blood test more frequently (every 3-5 days) Consider consulting with a specialist, initiation of corticosteroids or other therapies as medically appropriate and as per institutional guidelines.	1st occurrence: • Interrupt spartalizumab and siltuximab until toxicity resolves to Grade ≤2 or baseline. o Once recovered restart spartalizumab and siltuximab at the same dose and schedule 2nd occurrence: • Interrupt spartalizumab and siltuximab until toxicity resolves to Grade ≤2 or baseline o Once recovered restart spartalizumab and siltuximab at the same dose and schedule AE resolution to ≤ Grade 2 or baseline must occur within a maximum period of 12 weeks since Grade 3 with clinically significant bleeding or Grade 4 event has been identified, otherwise spartalizumab and siltuximab must be permanently discontinued. 3rd occurrence: permanently discontinue spartalizumab and siltuximab

Table 8-9 Mandatory dose modification requirements and recommended clinical management guidelines for non-hematologic adverse events suspected related to study treatment (excluding alopecia, grade 2 fatigue and irAE)

Non-Hematologic suspected AEs (except Grade 2 alopecia, Grade 2 fatigue, irAE) (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1-2 tolerable	• Monitor closely • Provide supportive care according to institutional standards	Continue spartalizumab and siltuximab treatment at the same dose and schedule
Grade 2 intolerable or Grade 3	• Monitor closely • Provide supportive care according to institutional standards • Consider consulting with a specialist, initiation of corticosteroids or other therapies as medically appropriate and as per institutional guidelines.	1st or 2nd occurrence: • Interrupt spartalizumab and siltuximab until toxicity recovers to Grade ≤1 or baseline. ○ Once recovered restart spartalizumab and siltuximab at the same dose and schedule AE resolution to Grade ≤1 or baseline must occur within a maximum period of 12 weeks since intolerable Grade 2 or Grade 3 event has been identified, otherwise spartalizumab and siltuximab must be permanently discontinued. 3rd occurrence: Permanently discontinue spartalizumab and siltuximab
Grade 4	• Monitor closely • Provide supportive care according to institutional standards • Consider consulting with a specialist, initiation of corticosteroids or other therapies as medically appropriate and as per institutional guidelines.	1st occurrence: • Interrupt spartalizumab and siltuximab ○ Consider permanently discontinuing spartalizumab. If benefit risk assessment support treatment continuation, restart spartalizumab and siltuximab at the same dose and schedule.

Non-Hematologic suspected AEs (except Grade 2 alopecia, Grade 2 fatigue, irAE) (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
		2nd occurrence: Permanently discontinue spartalizumab and siltuximab

6.3.3 Dose modifications Siltuximab

Table 9. Dose reduction steps for siltuximab

Overall, patients with AEs suspected to be related to siltuximab include pruritus, increased weight (edema), rash, hyperuricemia, and upper respiratory tract infection. Rare side effects include gastrointestinal perforation.

Each patient can receive a maximum of 2 dose reductions of siltuximab prior to permanent discontinuation of siltuximab.

Siltuximab can be held for a maximum of 12 weeks, if no resolution of toxicity to grade 1 or less, then siltuximab will be permanently discontinued.

Dose reduction*			
	Starting dose level – 0	Dose level - 1	Dose level – 2
Siltuximab	11 mg/kg	9 mg/kg	6 mg/kg **
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
**Dose reduction below 6 mg/Kg is not allowed.			

1. Weight gain due to edema **grade 1 or 2** manage symptomatically with diuretics. Patients with **grade 3** hold siltuximab treat symptomatically resume at one dose level lower once grade 1. Patients with **grade 4** hold siltuximab and treat symptomatically. Permanently discontinue siltuximab for first occurrence of grade 4 weight gain.
2. Hyperuricemia **grade 1 or 2** continue treatment with siltuximab and monitor. **Grade 3** start therapy for hyperuricemia (allopurinol) and hold siltuximab until it resolves to grade 1. Resume at a lower dose level. **Grade 4** hold siltuximab permanently, treat hyperuricemia (rasburicase).

3. Upper respiratory tract infection **grade 1 and 2** treat infection and continue siltuximab. **Grade 3 or 4** hold siltuximab treat infection. First occurrence of grade 4 upper respiratory tract infection will lead to permanent discontinuation of siltuximab. For Grade 3, resume after infection treated no dose reduction for first occurrence. Dose reduce by one dose level for second occurrence. Hold permanently for third occurrence.
4. Pruritus **grade 1 and 2** treat symptomatically and continue siltuximab. **Grade 3** hold siltuximab, treat symptomatically, resume siltuximab after symptoms resolve.
5. Gastrointestinal perforation **any grade** permanently hold siltuximab.
6. Dose modifications of siltuximab for hematologic and non-hematologic toxicities also review 6.3.2.2.

6.3.4 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Spartalizumab 300 mg will be administered as a 30 minute IV infusion every 3 weeks. Given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Siltuximab will be administered IV infusion over a period of 1 hour on day 1 of every 3-week cycle. Given the variability of infusion pumps, a window of -10 minutes and +10 minutes is permitted (i.e., infusion time is 60 minutes: -10 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the spartalizumab and siltuximab infusion fluid and administration of infusion solution.

6.3.5 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

6.4 Concomitant Medications/Vaccinations (allowed & prohibited)

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

vaccination may be required. The investigator should discuss any questions regarding this with the PI. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

6.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded.

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed.

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

blood transfusions) administered during the study must be listed on the Concomitant Medications.

6.4.2 Prohibited Concomitant Medications

During the course of the study, patients must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) or any other therapies that may be active against cancer or modulate the immune responses. However, limited-field palliative radiotherapy may be allowed as concomitant therapy (see above).

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, and for prophylaxis against imaging contrast dye allergy, standard pre-medication for chemotherapy 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. 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 before the administration of next dose of study treatment then spartalizumab or siltuximab must be discontinued (note: next dose can be delayed up to 12 weeks).

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

There are no prohibited therapies during the post-treatment follow-up period except for live vaccines within 4 weeks of last administration of siltuximab.

6.5 Rescue Medications & Supportive Care

6.5.1 Supportive Care Guidelines

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events until start of new antineoplastic medication or 150 days after discontinuation of siltuximab and spartalizumab, whichever is sooner. If the patient begins post treatment antineoplastic medications before the 150-Day safety follow-up, only suspected AEs and suspected SAEs will be collected thereafter up to the 150 days following the last dose of siltuximab or spartalizumab. Suspected SAEs will continue to be collected beyond the 150-Day safety visit. This will be done by return clinic visits, laboratory checks, and phone calls .

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. If cytokine release syndrome is suspected, the assessments outlined below must be performed. All patients must be followed-up for AEs and SAEs for 150 days following the last dose of spartalizumab or siltuximab. However, if the patient begins post treatment antineoplastic medication before the 150-Day safety visit the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected SAEs and suspected AEs will continue to be collected to Day 150. If SAEs suspected to be related to study medication occur beyond Day 150, information should also be collected. This will be done by return clinic visits, laboratory checks, and phone calls until SAE resolves.

6.5.1.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up 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 > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not 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).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2 . 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.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.5.1.2 Infusion Reactions

Spartalizumab: If a patient experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status.

If a patient experiences a Grade 3 infusion or anaphylactic/anaphylactoid reaction, the patient will discontinue spartalizumab treatment. Further guidelines on management of spartalizumab infusion reactions are provided in Section 6.3.2.

The CTCAE category of "Infusion related reaction" should be used to describe study treatment related infusion reactions, unless the investigator considers another category, such as "Allergic reaction", "Anaphylaxis," or "Cytokine release syndrome" more appropriate in a specific situation.

Siltuximab (infusion reactions)

During IV infusion of siltuximab, mild to moderate infusion reactions may improve following slowing of or stopping the infusion. Upon resolution of the reaction, reinitiating the infusion at a lower infusion rate and therapeutic administration of antihistamines, acetaminophen, and corticosteroids may be considered. For patients who do not tolerate the infusion following these interventions, siltuximab should be discontinued. During or following infusion, treatment with siltuximab should be discontinued in patients who have severe infusion related hypersensitivity reactions (e.g. anaphylaxis). The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

If a patient experiences an infusion reaction with signs of anaphylaxis, stop the infusion of siltuximab. Discontinue further therapy with siltuximab.

If the patient develops a mild to moderate infusion reactions, stop the infusion. If the reaction resolves, the siltuximab infusion may be restarted at a lower infusion rate. Consider medication with antihistamines, acetaminophen, and corticosteroids. Discontinue siltuximab if the patient does not tolerate the infusion following these interventions.

6.6 Study drug preparation and dispensation

6.6.1 Spartalizumab

Spartalizumab will be provided as global clinical supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Spartalizumab will be administered intravenously as a 30 minute infusion (up to 2 hours, if clinically indicated). Infusion must take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available during the period of drug administration. Clinical monitoring during and post infusion should be performed according to local practice and institutional guidelines, and as outlined in Section 6.1. Further instructions for the preparation and dispensation of spartalizumab are described in the [Study Pharmacy Manual].

6.6.2 Siltuximab

Use aseptic technique for reconstitution and preparation of dosing solution.

1. Calculate the dose (mg), total volume (mL) of reconstituted siltuximab solution required and the number of vials needed. A 21-gauge 1-½ inch needle is recommended for preparation. Infusion bags (250 mL) must contain Dextrose 5% in Water and must be made of Polyvinyl chloride (PVC) with Di-{2-ethylhexyl}phthalate (DEHP), or Polyolefin (PO).

2. Allow the vial(s) of siltuximab to come to room temperature over approximately 30 minutes. Siltuximab should remain at room temperature for the duration of the preparation.

3. Aseptically reconstitute each siltuximab vial as instructed in Table 2.

Gently swirl the reconstituted vials to aid the dissolution of the lyophilized powder. DO NOT SHAKE or SWIRL VIGOROUSLY. Do not remove the contents until all of the solids have been completely dissolved. The lyophilized powder should dissolve in less than 60 minutes.

Once reconstituted, and prior to further dilution, inspect the vials for particulates and discoloration. Do not use if particles or solution discoloration are present or if visibly opaque. The reconstituted product should be kept for no more than two hours prior to addition into the infusion bag.

4. Dilute the reconstituted siltuximab solution dose to 250 mL with sterile Dextrose 5% in Water by withdrawing a volume equal to the total calculated volume of reconstituted siltuximab from the Dextrose 5% in Water, 250 mL bag. Slowly add the total calculated volume (mL) of reconstituted siltuximab solution to the Dextrose 5% in Water infusion bag. Gently invert the bag to mix the solution.

5. Administer the diluted siltuximab solution in 5% Dextrose in Water 250 mL by intravenous infusion over a period of 1 hour using administration sets lined with polyvinyl chloride (PVC) with di-{2-ethylhexyl}phthalate (DEHP) or polyurethane (PU), containing a 0.2micron inline polyethersulfone (PES) filter. The infusion should be completed within 4 hours of the dilution of the reconstituted solution to the infusion bag.

6. Do not infuse siltuximab concomitantly in the same intravenous line with other agents.

7. Do not store any unused portion of the reconstituted product or of the infusion solution. Waste material should be disposed of in accordance with local requirements.

6.6.3 Study treatment packaging and labeling

Study treatment, spartalizumab, will be provided as global clinical open supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment, Siltuximab, will be provided by EUSA Pharmac (UK) Ltd.

6.6.4 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the *study treatment* should be stored according to the instructions specified on the drug labels and in the latest Investigator's Brochure.

6.6.5 Study drug compliance and accountability

6.6.5.1 Study drug compliance

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

6.6.5.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

6.6.6 Disposal and destruction

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

6.7 Subject Withdrawal/Discontinuation Criteria

Patients may voluntarily discontinue from the siltuximab or spartalizumab for any reason at any time. If a patient decides to discontinue from the investigational treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue siltuximab or/and spartalizumab for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

In addition to mandatory spartalizumab and siltuximab must also be discontinued under the following circumstances:

a. Pregnancy

b. Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue either spartalizumab or siltuximab should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 14.3. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 6.7.6.

For patients who discontinue treatment for reasons other than documented disease progression per RECIST 1.1, death, lost to follow-up, or withdrawal of consent, clinical and tumor assessments must continue to be performed every 9 weeks (+/- 1 week) until documented disease progression per RECIST 1.1, death, lost to follow-up, or withdrawal of consent.

In some circumstances patients may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1 criteria (Section 14.3). These patients will continue assessments, and will complete the EOT visit only after permanent discontinuation of study treatment.

6.7.1 Replacement policy

Escalation part:

Patients will not be replaced on study. However, if a patient is considered as non-evaluable for the DDS, enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Enrollment of new patients may be considered until at least the minimum number (1 or 3) or at most the maximum number (3 or 6) of evaluable patients is achieved within the cohort. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.2.

Expansion part:

During the dose expansion part, no replacements will be needed.

6.7.2 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Spartalizumab and siltuximab must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

6.7.3 Follow up for safety evaluations

All patients must be followed for safety up to 150 days after the last dose of spartalizumab or siltuximab. After the 30-day onsite safety follow-up visit, patients will be followed (via telephone call or onsite visit if patient happens to be visiting the site) at 60, 90, 120 and 150 days after the last dose of spartalizumab and or siltuximab. All safety assessments should be completed as per Section 7.0. However, if the patient begins post treatment antineoplastic medication before the 150-Day safety follow-up visit the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected AEs and suspected SAEs will continue to be collected up to Day 150. All irAE will collected till the end of the safety

monitoring period (i.e. 150 days as stated in the protocol). Suspected SAEs will continue to be collected beyond the 150-Day safety visit. Data collected should be added to the appropriate eCRF pages. For female patients of child bearing potential, a pregnancy test will be performed at the time points listed in Section 7.0.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

6.7.4 Follow-up for efficacy evaluations

Patients who discontinue study treatment for reasons other than disease progression as per RECIST 1.1, should continue tumor assessment until disease progression as per RECIST 1.1, withdrawal of consent, lost to follow up, or death irrespective of start of new anti-neoplastic therapy at the same intervals as per Section 7.0.

6.7.5 Survival follow-up

Patients will enter the survival follow-up period once they complete the safety follow-up and efficacy follow-up after treatment discontinuation (whichever is longer). Patients will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since the last contact date will also be collected during these phone calls along with the start/end date and date of disease progression (clinical or radiological) on subsequent therapies to assess time to progression on next-line therapy (PFS2).

6.7.6 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

6.7.7 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with spartalizumab and siltuximab and had at least two treatments with spartalizumab and siltuximab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for additional treatment with spartalizumab and siltuximab via the Second Course Phase at the discretion of the investigator as detailed in Section 6.7.

7.0 TRIAL FLOW CHART

7.1 Study Flow Chart

Trial Period:	**Treatment Cycles [a]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
						5	6	7	8				
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon		Every 12 weeks
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X		X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	
Trial Treatment Administration [c]		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X	X	
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events			X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X	X	X	X	X	X	X	X				
Directed Physical Examination										X	X	X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X[d]	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG[e]	X												
PT/INR and aPTT	X												

Trial Period:	**Treatment Cycles [a]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon		Every 12 weeks
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis screening [f]	X												
Urinalysis	X									X			
T3, FT4 and TSH	X		X			X			X	X	X		
ECG	X												
Uric Acid	X		X		X		X						
Tumor Imaging	X[g]			X[g]			X[g]						
Archival or Newly Obtained Tissue Collection [i]	X	X											
Correlative Studies Blood Collection [j]	X	X	X	X						X			

a. Treatment cycles are 3 weeks
b. Only for patients with ongoing treatment related toxicities. Details of required follow up visit are given in section 6.5.1 and 6.7.
c. Siltuximab and spartalizumab given day 1 of each cycle except cycle 1 in the expansion phase
d. ECOG performance status should be done within 10 days or less from day 1 of cycle 1
e. Pregnancy test once a month women of child bearing potential

f. HBV-DNA, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), Hepatitis B surface antibody (HBsAb), HCV RNA- PCR

g. Baseline imaging with 8 weeks of day 1 is acceptable
h. Scans will be done every 3 cycles between day 15 and day 21 of that cycle
i. Paired biopsies will only be obtained from patients on the dose expansion cohort at baseline and between days 14 and 21 of cycle 1. Archival tissue will be tested for MSI status.

j. Samples will be collected at baseline, cycle1 days 1,8,15, cycle 2 day 1 and cycle 3 day 1. Blood will also be collected at EOT and disease progression. Analysis will include proportion of T, B, NK, memory and effector T cell subsets and expression of PD-1, PD-L1 and B7 family members.

8.0 TRIAL PROCEDURES

8.1 Trial Procedures

The Trial Flow Chart - Section 7.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

8.1.1 Tumor Tissue Collection and Correlative Studies Blood Sampling

Biomarker analyses will be used to investigate the effect of the spartalizumab and siltuximab at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. In addition, potential predictive markers of efficacy, as well as mechanisms of resistance to spartalizumab and siltuximab treatment will also be explored.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of the PI.

The sample collection information must be entered on the appropriate sample collection log eCRF page(s) and requisition form(s). Detailed instructions for the collection, handling, and shipment of tumor samples are outlined in the laboratory manual for the study.

Samples collected for research purposes include blood and tissue. Blood is not optional. The samples will be used to evaluate correlative markers for this study and will be stored and may be used for other research in the future. Tissue biopsies performed as part of the trial will only be done in a subset of patients and are optional. Tissue biopsies will only be performed during the expansion phase. Tissue will used to evaluate correlative markers for this study and will be stored and may be used for other research in the future.

All correlative samples will be de-identified. A study specific subject number will used to identify the samples. The study specific subject number will be linked to the patient information only in our HIPPA compliant electronic CRF.

Samples will be handled and stored in Dr. Lesinski's lab (Winship Bldg. C 3rd floor).

During the study, both blood and tumor samples will be collected to perform exploratory biomarker assessments. These are summarized in Table 10

Table 10 Biomarker sample collection plan

Sample type	**Volume**	***Visit***	***Time point***
Optional: **Paired biopsies pre and post treatment for patients on the expansion phase** Core, excisional and incisional biopsies are acceptable.		*Pretreatment* *And days 14-21 of cycle 1*	*pretreatment* *days 14 to 21 of cycle 1*
Blood samples as detailed in study calendar			

8.1.1.1 Biomarker assessments *in tumor samples*

Pre- and post- treatment tumor biopsies will be obtained from 24 patients enrolled on the expansion phase. Patients will sign the optional biopsy consent prior to starting treatment and will be assigned to either start spartalizumab or spartalizumab / siltuximab for the first cycle. Biopsies will be obtained within 4 weeks prior to the first dose of study therapy (biopsy #1) and then during the third week between Day 14 and Day 20. At least three core biopsies will be obtained at the time of the biopsy (unless limited for technical/safety reasons). The obtained tissues will be handled in the following way:

1) RNAlater for RNA stabilization and tissue storage

2) Formalin-fixed paraffin block with one cut H&E stained slide

3) Liquid nitrogen frozen tissue in cryo-preservation vials

All collected tissues are stabilized and stored in -80°C freezers (RNAlater stabilized, OCT embedded, short term storage) or the vapor phase of a liquid nitrogen freezer (long term storage) in single use aliquots. All FFPE tissue blocks are stored in a climate controlled storage room that is temperature (less than 27ºC) and humidity controlled.

Tissue will be evaluated using IHC for CD3, CD4, CD8, CD163, PD-1, PD-2, PDL-1, MIF, TAM and stromal/ vascular markers. Tissue will also be dissociated and flow cytometry will be used to determine the characteristics of macrophages and lymphocytes. Genomic (transcriptome) profiling will be performed on tissue and lymphocytes.

8.1.1.2 Biomarker assessments in plasma

All patients participating in the study will be requested to provide a mandatory whole blood samples (approximately 20 mL each), collected at study treatment baseline (Pre-dose) and at specific time points during treatment (Table 7.6). The plasma will be used to measure cytokines levels (and/or other circulating markers) to correlate with antitumor activity of spartalizumab. The changes of cytokines (or other markers) related to immune response will

be assessed to explore spartalizumab activity (e.g. assessing interferon gamma response cytokines).

Approximately 20 mL of peripheral blood samples will be collected prior to initiation of study therapy, on day 1 of the first 3 cycles. The peripheral blood mononuclear cells will be isolated from these samples and stored in -80°C freezers until analysis. Samples will be evaluated for:

i. Determine whether there is an increase in expression of T-cell co-stimulatory markers in PBMCs after treatment. Samples will be collected at baseline and every other week for the first 9 weeks. Analysis will include proportion of T, B, NK, memory and effector T cell subsets and expression of PD-1, PD-L1 and B7 family members.

ii. Determine whether changes in ex vivo functional assays for PBMCs post treatment correlate with response. Samples will be collected at baseline and on weeks 6 and 9. This will be performed using interferon- gamma and CD107.

8.1.1.3 Biomarker Germline DNA analysis

A mandatory blood sample will be obtained from all patients participating in the study. One whole blood (6mL) sample will be collected at any time during screening. The 6mL sample will be used for germline DNA analysis. The germline DNA will be used to compare with genetic sequences found in tumor DNA of the same patients that differ from reference genes sequences; the goal is to determine if any difference of tumor DNA, from reference gene sequences is of somatic or germline origin. In addition eventual polymorphism of PD1, PD-L1 and PD-L2 may be assessed in germline DNA.

8.1.2 Screening

A patient who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the re-test result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within approximately 3 weeks of the original screening visit date. In this case, the subject will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 3 weeks of the original screening visit, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however, the patient ID number will remain the same. All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

All subjects must sign an informed consent document prior to the initiation of any study related procedures. The informed consent document must be signed within 28 days of Cycle 1 Day 1. Screening procedures (with the exception of the scans) are to be conducted within 28 days of Cycle 1 Day 1.

- Review of study eligibility criteria
- Medical History
- Record concomitant medications taken up to 28 days prior to day 1 cycle 1
- Vitals [temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR)]
- Physical Examination, including height and weight
- ECOG Performance Status evaluation (within 10 days or less of cycle 1 day 1)
- Laboratory Assessments
    - Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
    - Serum chemistry: sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, total bilirubin, LDH, total protein, ALP, ALT, AST, uric acid and albumin. Fasting glucose.
    - Serum or urine pregnancy test for women of childbearing potential
    - Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
    - Urinalysis
    - Tumor markers(when applicable such as known elevated tumor markers): CA19-9

- T3, FT4, TSH
- HBV-DNA, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), Hepatitis B surface antibody (HBsAb), HCV RNA-PCR
- HIV, if clinically indicated

- 12-lead ECG
- Radiologic imaging studies to evaluate tumor status. contrast computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen and pelvis. Additional imaging may be obtained as clinically indicated. Baseline scans may be done within 8 weeks prior to cycle 1 day 1.
- Baseline fresh biopsy (in selected group) will be obtained with 28 days of day1 cycle 1 and after consent is signed.

8.1.2.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered in the patient's electronic research records. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

8.1.2.2 Patient demographics and other baseline characteristics

Baseline demographic data will be collected on all patients include: gender, race, and age. Past medical history, concomitant medications, family history and prior treatments for pancreatic cancer will be collected at baseline.

8.1.3 Treatment period

Day 1 (±3 days) of each cycle

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Toxicity assessment
- Laboratory Assessments
  - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count

  - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
  - Tumor markers - when applicable
  - T3, FT4, TSH cycle 2 and then after every 3 cycle
  - Uric acid every other cycle
  - For the cycle1 day 1 labs, blood samples from the screening tests maybe used if completed within 1 week of day 1
- Blood sample 20 cc for correlative work (only cycle 1, 2, 3)
- Spartalizumab and siltuximab will be administered as IV infusion every 3 weeks. Given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted.
- **In selected case in patients receiving paired biopsies siltuximab maybe held in cycle 1**

Days 8 and 15 (±1 day) in cycle 1 and 2 ONLY

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Toxicity assessment
- Blood sample 20 cc for correlative work (only cycle1)
- Laboratory Assessments
  - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin

Between days 14-21 cycle 1

- **Repeat biopsy in selected cases.**

Every Month

- **Pregnancy test for women of child bearing potential**

Every 3 cycles between day 15 and 21

- **Repeat cross sectional imaging (CT or MRI)**

End of treatment visit

- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Toxicity assessment
- Laboratory Assessments
  - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
  - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
  - Tumor markers - when applicable
  - T3, FT4, TSH cycle 2 and then after every 3 cycle
  - Blood sample 20 cc for correlative work

8.1.3.1 Second Course Phase (Retreatment Period)

Subjects who stop siltuximab and spartalizumab with SD or better may be eligible for up to one year of additional siltuximab and spartalizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with siltuximab and spartalizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 24 weeks with siltuximab and spartalizumab before discontinuing therapy
    - Received at least two treatments with siltuximab and spartalizumab beyond the date when the initial CR was declared

OR

  - Had SD, PR or CR and stopped siltuximab and spartalizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with siltuximab and spartalizumab
- Did not receive any anti-cancer treatment since the last dose of siltuximab and spartalizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Patients should not be restarted on the study treatments if urgent treatment of the tumor(s) is needed to avoid risk to organ function or physical function (e.g. visceral crisis or spinal cord compression).
- Meet all the eligibility criteria as detailed in Section 6.1

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received siltuximab and spartalizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 7.0 – Trial Flow Chart.

9.0 SAFETY MONITORING AND REPORTING-NOVARTIS

9.1 Adverse events

9.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least:

- 150 days following the last dose of spartalizumab (or all patients in a double blind study) OR
- until the start of a new post treatment antineoplastic medication if sooner than the 150 days mentioned above. If a patient starts a post treatment antineoplastic therapy, then

only adverse events suspected to be related to study treatment should be collected out to 150 days after discontinuation of spartalizumab.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version

Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form *(or EOT/SEC/Survival Information in NOVDD)*.

The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
   or
   Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials)

Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement

to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

For phase I studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (*for example, as per RECIST criteria for solid tumors*), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

9.1.2 Laboratory test abnormalities

9.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

9.1.3 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 product or 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. AESIs are discussed in detail in the latest Investigator Brochure for ***spartalizumab*** are:

- Endocrinopathies (Hypothyroidism, hyperthyroidism, diabetes, hypophysitis and hypopituitarism, adrenal insufficiency)
- Pneumonitis
- Colitis
- Hepatitis
- Nephritis
- Encephalitis
- Rash
- Other immune-mediated events
- Infusion reactions

9.2 Serious adverse events

9.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

9.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent must be reported to Novartis within 24 hours of learning of its occurrence and until:

- at least 150 days following the last dose of spartalizumab (or all patients in a double blind study) OR
- the start of a new post treatment antineoplastic medication if sooner than the 150 days mentioned above.

If a patient starts a post treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment should be collected out to 150 days after discontinuation of spartalizumab. SAEs suspected to be related to spartalizumab will continue to be collected beyond the 150-Day safety visit.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported by Dr Alese as sponsor to the FDA and to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

9.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of

the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office, and Patient Safety (CMO&PS).

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

The newborn will be followed up at birth only. Further advice on the length of post-natal follow up will be sought from Novartis Pediatric Advisory Group.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

10.0 SAFETY MONITORING AND REPORTING-EUSA PHARMA

10.1 Overview

As the sponsor of the Study, the SPONSOR INVESTIGATOR (SI) shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The SI will provide safety information to EUSA Pharmacovigilance on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

10.2 Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to a EUSA Pharma Medicinal Product and product quality complaints with or without an adverse event as described in this section will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the EUSA Pharma medicinal product is: SILTUXIMAB™ (Siltuximab)

10.3 Definitions

10.3.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

10.3.2 Adverse Events of Special Interest

Adverse events of special interest are events that EUSA Pharmacovigilance is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- All-Grade Infections and Infestations
- Hepatotoxicity
- Gastrointestinal Perforations
- Hemoglobin Increases above the ULN
- QT Interval Prolongation

Any Adverse Event of Special Interest that is to be reported to EUSA medicinal product should be recorded on a Serious Adverse Event Report Form and be reported to EUSA Pharmacovigilance **within 24 hours of knowledge of the event.**

10.4 Individual Case Safety Report (ICSR)

A valid ICSR must
requirements.

Instructions *(Remove Instruction Box prior to finalization)*

Include this text where applicable, to clarify for which Janssen medicinal product(s) adverse even
reporting is solicited

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a EUSA Pharma medicinal product
- an adverse event, outcome, or certain special situations
-

The minimum information required is:

- suspected EUSA medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- protocol ID

10.5 Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

10.6 Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

10.6.1 Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided. Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)

- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

10.6.2 Life-Threatening Conditions

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

10.7 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.siltuximab.com/shared/product/siltuximab/siltuximab-prescribing-information.pdf

10.8 Special Reporting Situations

Safety events of interest for a medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a EUSA medicinal product
- Exposure to a EUSA medicinal product from breastfeeding
- Suspected abuse/misuse of a EUSA medicinal product
- Inadvertent or accidental exposure to a EUSA medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of an EUSA medicinal product
- Medication error involving a EUSA medicinal product (with or without patient exposure to the EUSA medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a EUSA medicinal product

These safety events may not meet the definition of an adverse event; however, from a EUSA Pharmacovigilance perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to EUSA Pharmacovigilance **within 24 hours of becoming aware of the event.**

10.9 Pregnancy

All initial reports of pregnancy must be reported to EUSA Pharmacovigilance by the SI **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

If a subject becomes pregnant during the study, a determination regarding study drug discontinuation must be made by the investigator in consultation with the reference safety information.

Because the effect of the EUSA medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a EUSA medicinal product will be reported by the SI **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.10 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at EUSA Pharmacovigilance request.

10.11 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for EUSA Medicinal Products to EUSA Pharmacovigilance

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a EUSA medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a EUSA medicinal product.

All (serious and non-serious) adverse events reported for a EUSA medicinal product should be followed-up in accordance with clinical practice.

10.12 SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The SI will transmit all SAEs and special situations following exposure to a EUSA Pharma product under study in a form provided by EUSA Pharmacovigilance in accordance with Section 10.16, Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the SI will submit an unblinded SAE or pregnancy exposure report to EUSA Pharmacovigilance.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the SPONSOR INVESTIGATOR (SI), **within 24 hours becoming aware**, to EUSA Pharmacovigilance. using EUSA's Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, serious ADR or special situation is required.

- The SI is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the EUSA Product under study, are to be provided to EUSA Pharmacovigilance using a transmission method in Section 10.16 within **24 hours of such report or correspondence being sent to applicable health authorities.**

10.13 Non-Serious AEs

All non-serious adverse events where causality cannot be excluded should be reported to EUSA Pharmacovigilance within 10 days of becoming aware.

10.14 Product Quality Complaint Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and EUSA Pharmacovigilance, and are mandated by regulatory agencies worldwide. EUSA Pharmacovigilance has established procedures in conformity with

regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a EUSA medicinal product under study must be reported to EUSA Pharmacovigilance by the SI **within 24 hours after being made aware of the event.** The EUSA contact will provide additional information/form to be completed.

If the defect for a EUSA medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the SI must report the PQC to EUSA Pharmacovigilance according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by EUSA Pharmacovigilance.

10.15 Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-EUSA Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-EUSA medicinal product under study, the SI should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

10.16 Transmission Methods

The following methods are acceptable for transmission of safety information to EUSA Pharmacovigilance:

- Electronically via Email service (preferred)
  safety@eusapharma.com

- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report on Fax +44 (0) 33 0500 1167
- Telephone (if fax is non-functional) +1 888 255 9029.

Please use the contact information and process information provided by EUSA Pharmacovigilance.

11.0 DATA MONITORING COMMITTEE

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being

conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Dose escalation decisions will be done at the GI working group. The PI or designee must obtain approval from the DSMC for dose escalation. The PI will provide an update on all relevant safety data of patients entered to a dose level to the DSMC when dose escalation is planned.

Dr. Alese and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet to review and discuss study data to ensure subject safety. During the meetings the PI or co-I will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, random checks of case report form completion and roadmap for each patient on the trial. All study personnel will be trained on the protocol by the PI or co-I. Study personnel will sign training log prior to being included on delegation of authority log. All AE and SAE will be handled according to Section 7.2 which provides detailed instructions on reporting requirements.

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar

days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, copied to EUSA Pharmacovigilance. The Emory University IRB will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

12.0STATISTICAL ANALYSIS PLAN

12.1 Determination of Sample Size

This is a 3+3 standard phase I trial design. The plan is to evaluate two dose cohorts- 6 mg/Kg and 11 mg/Kg of siltuximab. An intermediate dose cohort (9 mg/Kg) will be evaluated only if we observe 2 or more DLT's in the 3 or 6 patients enrolled on the 11 mg/kg dose. If we observe 2 dose limiting toxicities on dose level 1, then the study will be completed with three patients (minimal number of patients). If we observe two DLT in the first three patients on dose level 1, the study will stop and the principal investigator will discuss at that point whether a lower dose level of siltuximab should be tested. If we do not observe any dose limiting toxicities the study will require 9 patients. If we observe one dose limiting toxicity per dose level (maximum number of patient), then the study would require 18 patients. Therefore the phase part sample size can range from 3 to 18 patients.

Expansion phase will be started once the recommended phase II dose (RP2D) is determined. Given minimal activity of checkpoint inhibitors in pancreatic cancer (Response rate less than 5%) , an overall response rate of the combination of PD-1 plus IL-6 inhibitor of 20% would be considered clinically significant. With an alpha of 0.1, and power of 90% a total of 24 patients should be sufficient to make this determination. We will also obtain biologic endpoints with the paired biopsy samples that can help further develop the combination and understand its role in pancreatic cancers. We plan to enroll 24 patients on the RP2D level. Patients in the expansion phase will be assigned to treatment arms by PI (spartalizumab or spartalizumab plus siltuximab). After the first 3 weeks all patients will receive the combination therapy. There is no planned comparison between the two arms. The aim of the expansion phase is to confirm the safety profile and tolerability of the regimen in patients with pancreatic cancer.

Early stopping for safety: If we observe more than 3 dose limiting toxicities as defined in Section 6.3.2 and Table 7 (excluding death since a single death will fulfil the stopping rule) during the first 8 weeks of treatment in the first 12 patients in the expansion cohort, study enrollment be halted pending a safety review by the safety monitoring committee for a single death. Consideration for lower dose regimen will be discussed with DSMC and sponsors. If the plan is to test additional dose levels, the protocol and informed consent will be amended and re-submitted for review by the IRB.

The total number of patients who will undergo treatment will range from 27 to 42 patients. In order to have 42 patients undergo treatment, we plan to enroll up to 70 patients to account for screen failures.

12.2 Statistical and Analytical Plans

Summary statistics will be presented for all safety, efficacy and biomarker parameter analyses. The purpose of these analyses is hypothesis generating and therefore, formal statistical testing will not be performed. Various exploratory statistical tests may be applied to data generated from this trial to generate hypotheses to be tested in subsequent trials. In general, data for continuous parameters will be presented using descriptive statistics including sample size, mean, and median; standard deviation; and minimum and maximum. Categorical parameters (such as pathologic response rate) will be displayed using counts and percentages. Toxicities will be presented as worst toxicity per patient and will be reported as percent toxicity.

12.3 Analysis Sets

All subjects who receive any amount of study drug will be included in the evaluation of safety and efficacy, except for patients who take less than 80% of their prescribed dose of siltuximab and spartalizumab since they will be considered in-evaluable for the primary endpoint of toxicity.

12.4 Subject Disposition and Baseline Characteristics

The number and percentage of subjects who enrolled, were treated, and who discontinued will be tabulated. The reasons for treatment and study discontinuation will be presented. Demographic and other baseline characteristics will be summarized using descriptive statistics or counts and percentages, as appropriate.

12.5 Safety Analysis

12.5.1.1 Adverse Events

Adverse events will be classified using MedDRA System Organ Classes and Preferred Terms. Furthermore, SAEs, AEs with a severity grade of 3 or above using NCI CTCAE version 4.0, AEs deemed related to study drug, AEs leading to discontinuation of study drug, and AEs leading to death will also be summarized in preferred term by system organ class and listed on an individual subject basis.

12.5.1.2 Laboratory Data

Descriptive statistics for worst grade of each laboratory parameter by the NCI CTCAE scale version4.0 at baseline and follow-up will be presented along with change from Baseline. Additionally, laboratory values ≥ Grade 3 severity will be tabulated and listed on an individual subject basis.

12.5.1.3 Dose Modifications and Reasons

The number of subjects with skipped doses, dose delays and dose reductions as well as major reasons for dose modifications will be summarized.

13.0 ADMINISTRATIVE AND REGULATORY DETAILS

13.1 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

13.2 Prestudy Documentation

The Sponsor-Investigator must provide EUSA Pharma, and Novartis with the following documents prior to the enrollment of any subjects:

- Copy of the IRB/IEC approval letter for protocol, informed consent, Investigator and site
- Signed and dated current curricula vitae of the investigator
- Copy of approved informed consent document
- Copy of the FDA letter and IND receipt and number assignment
- Signed Clinical Trial Agreement

13.3 Protocol Adherence

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

13.4 Retention of Study Documents

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

14.0 APPENDICES

14.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

14.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

14.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

Efficacy assessments

Tumor response is the primary efficacy endpoint. Please refer to RECIST 1.1 criteria.

- Radiologic assessment will be performed at baseline and until disease progression or withdrawal of consent as defined in section 8.1.2 and study calendar (section 7).
- Patients who discontinue study treatment for reasons other than disease progression as per RECIST 1.1 should continue tumor assessment until disease progression as per RECIST 1.1.
- Each lesion that is measured at baseline must be measured by the same method (either same radiologic/nuclear method or by physical exam) throughout the study so that the comparison is consistent. The same is true for any new lesions that occur after start of treatment. They should be imaged using the same modality at each subsequent time point. Criteria required for determining partial or complete response should be present for at least 4 weeks.

  If treatment beyond initial disease progression as per RECIST 1.1 criteria (or other criteria) is planned, patients should continue to have imaging every 9 weeks after continuation of study treatment beyond PD. Patients who develop progressive disease after cessation of study treatments should not be restarted on the study treatments if urgent treatment of the tumor(s) is needed to avoid risk to organ function or physical function (e.g. visceral crisis or spinal cord compression).
- Local imaging radiology evaluations will be used for endpoints determination.

Table 7-2 Imaging Assessment Collection Plan.

Procedure	**Screening/Baseline**	**During Treatment/Follow-up**
Chest, abdomen and pelvis CT or MRI(with intravenous contrast enhancement)	Mandated	Mandated, every 3 cycles between day 15 and 21
Brain CT or MRI	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole body bone scan	If clinically indicated	If clinically indicated
Localized bone CT, MRI or x-ray	For any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 8 weeks of start of treatment (prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain CT or MRI, if clinically indicated
- Whole body bone scan, if clinically indicated
- Localized bone CT, MRI or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

If a patient is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

If brain metastases are suspected at baseline, brain MRI or CT must be completed. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

If clinically indicated, a whole body bone scan Fluorodeoxyglucose positron emission tomography (FDG-PET) will be performed. Localized CT, MRI or X-rays must be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.

If clinically indicated, CT or MRI of other areas (e.g., neck) of disease as appropriate should be performed.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments as described in Table 7-2 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1). Imaging assessments for response evaluation will be performed every 3 cycles between days 15 and 21 until disease progression per RECIST 1.1 , death, lost to follow-up or withdrawal of consent.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a patient, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. The same is true for any new lesions that occur after start of treatment. They should be imaged using the same modality at each subsequent time point. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

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