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TITLE: A Phase 2 Study of Plerixafor and Cemiplimab in Metastatic Pancreatic Cancer

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1. OBJECTIVES

1.1. Primary Objective

To estimate the objective response rate (ORR) using immune RECIST (iRECIST) in patients with metastatic pancreatic cancer treated with plerixafor and cemiplimab.

1.2. Secondary Objectives

1.2.1. To estimate ORR using RECIST v.1.1.

1.2.2. To assess safety and characterize toxicities of plerixafor in combination with cemiplimab.

1.3. Exploratory Objectives

1.3.1. To assess progression free survival (PFS), time to progression (TTP), disease control rate (DCR), best overall response (BOR), duration of response (DOR), duration of clinical benefit (DCB), and time to objective response (TTOR) using, iRECIST and RECIST v.1.1.

1.3.2. To assess the overall survival (OS).

1.3.3. To measure pharmacokinetic and pharmacodynamic parameters in pancreatic cancer patients treated with plerixafor and cemiplimab including but not limited to increase numbers of CD34+ cells in the blood.

1.3.4. To collect pre- and on-treatment biopsies to explore the association of features of the tumor microenvironment in response to therapy, including but not limited to assessment of:

- T cell subset markers (CD4, CD8, FoxP3, Granzyme A/B, CD69), immune regulation (PD-L1, PD-L2, CTLA4, LAG-3, IDO1, TIM-3), and immune cell population markers (NK, DC, B cell, MDSC, etc.). Techniques used for analyses may include but are not limited to immunohistochemistry (IHC) and mass cytometry.
- Transcriptomics using single-cell RNASeq analysis. Immune cell numbers and activation state will be characterized.
- CXCR4 and CXCL12 IHC

1.3.5. To evaluate molecular determinants of response using next generation sequencing and other sequencing techniques.

1.3.6. To collect peripheral blood mononuclear cells (PBMC) and serum to identify potential therapeutic targets, biomarkers and predictors of response (OS, PFS and best overall response).

- Measure pre- and post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells, monocytes, and macrophages through cell phenotyping analysis and gene expression profiling.

- Proteomic approaches will be used on pre- and post-treatment sera to identify targets and biomarkers of response or toxicity.

1.3.7. To evaluate clonal T cell populations in the tumor and in the periphery through T cell receptor sequencing, and to functionally assess mutation associated neoantigen-specific T cells.

1.3.8. To measure serum and salivary cortisol levels and correlate with response and immune cell infiltration.

1.3.9. To use CT imaging for body composition analyses and correlate with outcomes.

1.3.10. To measure changes in cfDNA content and quantity in response to therapy.

1.4. Study Design

This is a single center, phase II trial in patients with previously-treated metastatic pancreatic cancer. There will be a safety run-in (n=6). Plerixafor will be administered at 80 mcg/kg/hr x 24 hours per day x 7 days each cycle. The cycle will be repeated every three weeks. Cemiplimab will be administered on day 1 of each cycle at a dose of 350mg by intravenous infusion. Tumor biopsies will be obtained at baseline and on either Cycle 1 Day 8 or Cycle 2 Day 1 for alternating patients. An optional biopsy may be obtained at the time of disease progression.

The primary endpoint is objective response rate (irORR: CR + PR) per iRECIST. The treatment regimen would be considered of insufficient activity for further study in this population if the irORR is 7.7% or less, and the minimum required level of efficacy that would warrant further study is an irORR of 20%. The sample size is calculated to detect an improved irORR from 7.7%[1] to 20%. A modified Simon's two-stage design is planned. A total of 21 patients will be entered in the first stage. If <=1 subject responds, the treatment will be terminated and we will conclude the regimen is ineffective. If >=2 subjects respond, then additional 18 patients will be enrolled. If a total of 5 or fewer subjects respond in stage one and two combined, we consider the regimen ineffective. If a total of 6 or more respond, we conclude the regimen is promising and warrant further study. The maximum sample size will be 39.

The study will consist of a pre-screening period, a screening period (within 28 days of the first dose), a treatment period, and a follow-up period. Subjects will receive treatment on 21 day cycles, and will come to clinic for dosing and/or assessments on Day 1 of each cycle and additional days for safety and immune monitoring follow up as per the study schedule in **Section 9.** No dose escalations or reductions of plerixafor or cemiplimab are allowed. Complete information on study drug administration, schedule, and dosing can be found in **Section 4.1.**

The study will include a safety run-in for the first six patients. If more than 1 of the first 6 patients experiences an unacceptable toxicity within the first cycle, then enrollment will be halted and the overall risk-benefit ratio of the study will be reconsidered. At any time thereafter, if more than 33% of patients are observed to experience unacceptable toxicity within the first cycle, enrollment will be halted and the safety of the combination will be re-evaluated. Complete unacceptable toxicity criteria can be found in **Section 4.7**.

Treatment may continue up to a maximum of 2 years, or until discontinuation due to toxicity, lack of clinical benefit as determined by the investigator, subject withdrawal, or termination of the study. Subjects may continue on treatment with radiographic disease progression if subject is clinically stable and investigator believes the treatment is providing benefit. Criteria for removal from treatment are found in **Section 4.10**.

Tumor biopsies, PBMC, serum and plasma collection, and computed tomography (CT) scans or magnetic resonance imaging (MRI), if CT is contraindicated, will be obtained at baseline and during treatment for clinical assessments and correlative analyses. Tumor assessments will be made using RECIST 1.1/iRECIST.

Subjects will return to the study site 30 (+/- 7) days after the final administration of study treatment for an end of treatment (EOT) evaluation. Subjects will be considered in the treatment period until 30 days after the last dose of study drug. After completion of treatment and EOT assessments, all subjects will continue to be followed per **Section 4.12**.

Information on progression-free survival and overall survival may continue to be gathered for supplementary analyses after the completion of the primary analysis.

2. BACKGROUND

2.1. Study Disease

Despite decades of basic and clinical research, effective therapy for the treatment of patients with pancreatic ductal adenocarcinoma (PAC) remains one of the greatest unmet clinical needs in oncology today. Currently, PAC accounts for approximately 7% of all cancer-related mortality and has the lowest 5-year survival rate among all cancer types in the United States. PAC is currently the 4th leading cause of death from cancer in the U.S. with estimates in 2016 for 53,070 people diagnosed and about 41,780 dying from the disease [2]. Worldwide it will claim more than 300,000 lives this year [3]. It is projected that by 2030, pancreatic cancer will become the second leading cause of cancer-related death in the US [4].

Most patients are initially diagnosed with advanced disease that is inoperable with median survival of less than 1 year. Patients with advanced disease are usually treated with chemotherapy, with the intent of prolonging survival and palliating symptoms (pain, weight loss and decrease in performance status). From 1997, gemcitabine was the standard chemotherapy for advanced pancreatic cancer after demonstrating a significant improvement in survival compared to 5-fluorouracil (5-FU) [5]. Median survival was 5.65 months for gemcitabine-treated patients and

4.41 months for 5-FU treated patients, while overall tumor response rates were 5.4% and 0%, respectively.

Until recently, only erlotinib, an oral epidermal growth factor (EGF) inhibitor, was shown in a Phase 3 study to modestly improve median OS in combination with gemcitabine over gemcitabine alone (6.24 months for the doublet versus 5.91 months for gemcitabine alone) without a significant difference in ORR between the treatments [6]. In 2011, a Phase 2/3 trial conducted by a French consortium study group demonstrated FOLFIRINOX, a combined regimen of oxaliplatin, irinotecan, fluorouracil, and leucovorin significantly increased survival in patients with pancreatic cancer over gemcitabine alone. Median OS was 11.1 months versus 6.8 months for each treatment, respectively (hazard ratio [HR] for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; $p < 0.001$). The ORR was also increased to 31.6% from 9.4% ($p < 0.001$). Adverse events were increased in the FOLFIRINOX group and 5.4% of patients in this group experienced febrile neutropenia [7]. Although FOLFIRINOX represents an efficacious regimen in pancreatic cancer, there are still concerns about its potential toxicity and it is being reserved for the most fit patients.

In the MPACT (**M**etastatic **P**ancreatic **A**denocarcinoma **C**linical **T**rial) study, *nab*-paclitaxel combined with gemcitabine demonstrated a statistically significant and clinically meaningful median OS of 8.5 versus 6.7 months (HR 0.72, $p < 0.0001$ including a 59% increase in one-year survival (35% versus 22%, $p=0.0002$) and demonstrated double the rate of survival at two years (9% versus 4%, $p=0.02$) as compared to gemcitabine alone in previously untreated patients with metastatic pancreatic cancer. *nab*-/gemcitabine also demonstrated a statistically significant improvement in key secondary endpoints compared to gemcitabine alone, including a 31% reduction in the risk of progression or death with a median PFS of 5.5 versus 3.7 months (HR 0.69, $p < 0.0001$) and an ORR of 23% compared to 7% (response rate ratio of 3.19, $p < 0.0001$)[8]. The MPACT study and regimen formed the basis for full FDA approval in September 2013 for the first-line treatment of metastatic adenocarcinoma of the pancreas.

Nanoliposomal irinotecan in combination with 5-FU was recently approved for patients with previously treated pancreatic cancer. However, it is unknown if this combination is better than 5-FU and irinotecan (FOLFIRI) as 5-FU was the comparator and there was no benefit in patients who previously received irinotecan so the value of this drug is questionable in FOLFIRINOX treated patients[1, 9]. Therapies for patients with metastatic pancreatic cancer are urgently needed.

Novel approaches, such as immunotherapy, hold promise in this very difficult cancer.

2.2. Dual Blockade of PD-1 and CXCR4

[redacted]

[redacted]

2.3. Dose Selection

2.3.1. Cemiplimab

Cemiplimab is a PD-1 receptor blocking antibody. The initial US approval was in September 2018 for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. The recommended dosage is 350mg as an intravenous infusion over 30 minutes every 3 weeks and is therefore, the dose and schedule selected for this study.

2.3.2. Plerixafor

[redacted]

2.4. Rationale

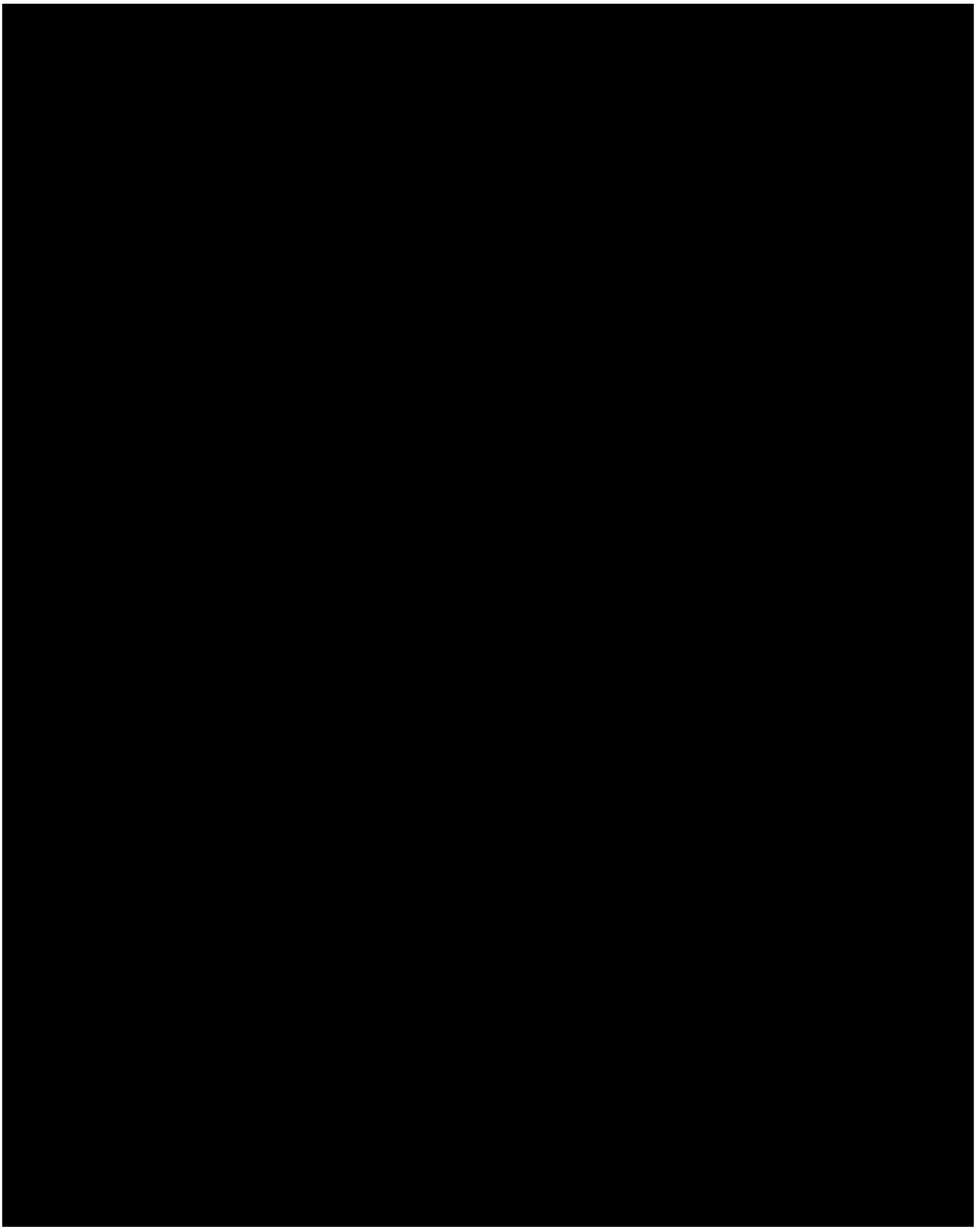
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



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This study aims to combine plerixafor and cemiplimab to synergistically improve T cell activation, proliferation, and infiltration to combat immune evasion by tumors. This study will be an open label, phase II study to evaluate ORR using iRECIST in patients with metastatic previously-treated pancreatic adenocarcinoma.

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Age ≥18 years.

3.1.2. ECOG performance status of 0-1 (**Appendix A**).

3.1.3. Have histologically- or cytologically-proven ductal adenocarcinoma of the pancreas.

3.1.4. Have metastatic disease.

3.1.5. Have documented radiographic disease progression at the time of study enrollment, after previous systemic chemotherapy given in a neoadjuvant, adjuvant, locally advanced or metastatic setting.

3.1.6. Presence of at least one lesion with measurable disease as defined by 10 mm in longest diameter for a soft tissue lesions or 15 mm in short axis for a lymph node by RECIST 1.1.

3.1.7. Patient's acceptance to have a tumor biopsy of an accessible lesion at baseline and on treatment.

3.1.8. Life expectancy of greater than 3 months.

3.1.9. Adequate organ and marrow function as defined below:

- Leukocytes ≥ 3,000/mcL
- Absolute neutrophil count ≥ 1,000/mcL
- Platelets ≥ 90 × 10^3/uL
- Hemoglobin ≥ 8.0 g/dL
- Total bilirubin ≤ 1.5 upper limit of normal (ULN) except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL
- AST(SGOT) and ALT(SGPT) ≤3.0 × ULN
- Alkaline phosphatase ≤5.0 × ULN
- Creatinine ≤1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

- Albumin ≥3.0 g/dL

3.1.10. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]). WOCBP is defined in **Section 4.8.** NOTE: If a patient has a positive or indeterminate serum or urine pregnancy test, then an ultrasound must be done to rule out pregnancy to enroll on trial.

- WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 4 weeks (duration of ovulatory cycle) for a total of 5 months post treatment completion.

- Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

- At least one barrier method of contraception must be employed by all sexually active patients (male and female), regardless of other methods, to prevent the transfer of body fluids.

3.1.11. Ability to understand and willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1. Patient has a known history or evidence of brain metastases.

3.2.2. Patient who has had chemotherapy, radiation, or biological cancer therapy within 14 days prior to the first dose of study drug.

3.2.3. Patient has received an investigational agent or used an investigational device within 28 days of the first dose of study drug.

3.2.4. Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study.

3.2.5. Patients who have had surgery within 28 days of dosing of investigational agent, excluding minor procedures (dental work, skin biopsy, etc.), celiac plexus block, and biliary stent placement.

3.2.6. Patients who have received any prophylactic vaccine within 14 days of first dose of study drug or received a live vaccine within 30 days of planned start of study therapy.

3.2.7. Patients with a history of prior treatment with an anti-CXCR4 agent.

3.2.8. Currently using any chronic systemic steroids (at doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy (steroid premedication for contrast is allowed).

3.2.9. Patients receiving growth factors including, but not limited to, granulocyte-colony stimulating factor (G-CSF), GM-CSF, erythropoietin, within 14 days of study drug administration. Use of such agents while on study is also prohibited.

3.2.10. History of severe hypersensitivity reaction to any monoclonal antibody. Exceptions may be approved by Protocol Chair if the patient has subsequently tolerated an antibody.

3.2.11. Evidence of clinical or radiographic ascites. Trace or small amounts of radiographic ascites may be approved by the Protocol Chair.

3.2.12. History of clinically significant and/or malignant pleural effusion.

3.2.13. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.14. Subjects with active autoimmune disease. Subjects with Graves or Hashimoto's disease, vitiligo, type I diabetes mellitus, psoriasis or other conditions not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects with autoimmune conditions requiring systemic treatment in the past may be approved by the Protocol Chair.

3.2.15. Presence of any tissue or organ allograft, regardless of need for immunosuppression, including corneal allograft. Exceptions can be approved by the Protocol Chair if loss of the graft is not a clinical concern. Patients with a history of allogeneic hematopoietic stem cell transplant will be excluded.

3.2.16. All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 5) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long-lasting sequelae, such as neuropathy after chemotherapy, are permitted to enroll.

3.2.17. Have received a diagnosis of human immunodeficiency virus (HIV), hepatitis B (Hep B sAg negative permitted) or hepatitis C (patients who are hepatitis C antibody positive may be enrolled if they are confirmed with negative viral load at screening)

3.2.18. Patient has a pulse oximetry of <92% on room air.

3.2.19. Patient is on supplemental home oxygen.

3.2.20. Patient has clinically significant heart disease (such as uncontrolled angina, myocardial infarction within the last 3 months or congestive heart failure of New York Heart Association III or IV).

3.2.21. Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or other substance abuse (including alcohol) that could potentially interfere with adherence to study procedures or requirements.

3.2.22. Patient is unwilling or unable to follow the study schedule for any reason.

3.2.23. Patient is pregnant or breastfeeding.

3.2.24. Have rapidly progressing disease, as judged by the investigator (e.g., rapid progression through prior treatment[s]).

3.2.25. History of significant, recurrent, unexplained postural hypotension in the last 6 months.

3.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. TREATMENT PLAN

4.1. Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dosing delays are described in **Section 5.** No investigational or commercial agents or therapies other than those described below in **Table 1** may be administered with the intent to treat the patient's malignancy.

Table 1: Regimen Description

REGIMEN DESCRIPTION					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Cemiplimab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section 4.2**	350mg	IV infusion over 30 (+/-15) min*	Day 1	21 days
Plerixafor		80mcg/kg/hr (1920mcg/kg/24hrs)	Continuous IV infusion over 7 days**	Days 1-7	21 days

*Infusion times are approximate and may be adjusted based on subject tolerability.
** Plerixafor formulation for infusion is stable for 5 days at room temperature. Therefore, patients will return to clinic on day 4 to exchange the infusion bag and on day 8 to discontinue their plerixafor infusion. The bag exchange on Day 4 should occur within 1 hour of completion of the first infusion bag.

Subjects should be observed for a minimum of 30 minutes between the administration of cemiplimab and plerixafor.

Please see **Section 5.2** for guidance regarding dosing delays.

Antiemetic medications should not be routinely administered prior to dosing of drugs. See **Section 4.2.1** for subsequent premedication recommendations following an infusion reaction.

4.2. General Concomitant Medication and Supportive Care Guidelines

Cemiplimab and plerixafor can cause hypersensitivity reactions. Subjects should be closely monitored for potential AEs during infusion and potential AEs throughout the study.

4.2.1. Infusion Reactions

If an infusion reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other allergic-like reactions. All grade 3 or 4 infusion reactions should be reported to the Protocol Chair and reported as an SAE if criteria are met. Infusion reactions should be graded according to CTCAE (version 5.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

> Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional co-administrations.

For grade 2 symptoms (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours):

> Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the

subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before study drug infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For grade 3 or grade 4 symptoms (severe reaction, grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]; grade 4: (life threatening; pressor or ventilator support indicated):

Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. All study drugs will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

4.2.2. Cemiplimab and Plerixafor-Related Adverse Events

4.2.2.1 Cemiplimab Related Adverse Events

Blocking PD-1 may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/pruritus, diarrhea/colitis, pneumonitis, hepatitis, and hypothyroidism were drug-related, presumptive autoimmune events noted in previous anti-PD-1 studies.

For the purposes of this study, a cemiplimab-related AE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with its known toxicity profile. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected AEs must be documented on an AE or SAE CRF. Identification and treatment of cemiplimab-related AEs can be found in the NCCN's guidelines for the management of immunotherapy-related toxicities. Additional guidance can be found in the cemiplimab Investigator's Brochures (IB).

Subjects who experience a grade 3 or higher related AE should be discussed with the Protocol Chair immediately.

4.2.2.2 Plerixafor Related Adverse Events

[redacted]

4.3. Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents unless they are utilized to treat an AE or as specified in **Sections 4.2** and **4.5**.
- Concurrent administration of any anticancer therapies (investigational or approved) with the exception of subjects in the survival period of the study.
- Use of growth factors unless prior discussion and agreement with the Protocol Chair.
- Use of allergen hyposensitization therapy

Palliative radiotherapy is permitted only under certain conditions as described in **Section 4.5.**

4.4. Other Restrictions and Precautions

Any vaccination containing attenuated or inactivated virus may be permitted if clinically indicated. However, this must be discussed and documented with the Protocol Chair prior to administration and may require a study drug washout period prior to and after administration of the vaccine. Inactivated influenza vaccination will be permitted on study without restriction.

It is the local imaging facility's responsibility to determine, based on subject attributes (e.g., allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (i.e., estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2) are at increased risk of nephrogenic systemic fibrosis.

4.5. Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs, prophylaxis prior to a diagnostic procedure (e.g., contrast MRI/CT scans) or as specified in **Section 4.2**. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) is permitted.

Subjects may continue to receive hormone replacement therapy (HRT).

Palliative and supportive care for disease-related symptoms may be offered to all subjects on the trial.

The potential for overlapping toxicities with radiotherapy and cemiplimab and plerixafor is currently not known. Therefore, palliative radiotherapy is not recommended while receiving any of these drugs, alone or in combination. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms, then drug administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study drug treatment, radiotherapy-related AEs should resolve to ≤Grade 1 or baseline and subjects must meet relevant dosing eligibility criteria The Protocol Chair must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Subjects receiving palliative radiation of target lesions will have the evaluation of ORR just prior to radiotherapy but such subjects will no longer be evaluable for determination of response subsequent to the date palliative radiation occurs.

For subjects who need to undergo elective surgery (not tumor-related) during the study, it is recommended to hold study drug(s) for at least 2 weeks before and 2 weeks after surgery, or until the subject recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically-related AEs should resolve to ≤Grade 1 or baseline and subjects must meet relevant dosing eligibility criteria. The Protocol Chair must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

4.6. Definition of an Overdose for this Protocol

Overdose of cemiplimab or plerixafor is defined as:

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Appropriate supportive treatment should be provided if clinically indicated.

All reports of overdose (with and without an AE) must be reported within 24 hours to the Protocol Chair and Sanofi as an SAE per **Section 6**.

4.7. Unacceptable Toxicity

Unacceptable toxicities are defined as any adverse event requiring permanent discontinuation per **Section 4.10.2** (exceptions for permanent discontinuation must be approved by the Protocol Chair).

If more than 1 of the first 6 patients experiences an unacceptable toxicity within the first cycle, then enrollment will be halted, and the overall risk-benefit ratio of the study will be reconsidered. At any time thereafter, if more than 33% of patients are observed to experience unacceptable toxicity within the first cycle, enrollment will be suspended until further review and consideration by the Protocol Chair. There will be no dose reductions for cemiplimab or plerixafor.

4.8. WOCBP, Contraception, Use in Pregnancy, Use in Nursing

4.8.1. Definition of Women of Childbearing Potential

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (e.g., rings, creams, gels)
- 4 weeks minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can considered postmenopausal.

4.8.2. Contraception

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 24 weeks after the end of study treatment.*****

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*

- Sexual abstinence

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in **Section 9**.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 33 weeks after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 33 weeks after the end of study treatment.

Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

4.8.3. Use in Pregnancy

The investigational agents used in this protocol may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

Pregnancy in female subjects throughout the study or within 24 weeks of completing treatment as well as any pregnancy in partners of male subjects throughout the study or within 33 weeks of completing the study should be reported initially as a serious adverse event (see SAE reporting procedures in **Section 6.5.1** and **6.5.4**) by the investigator within 24 hours of learning of its occurrence. Pregnancy information must be reported on the Pregnancy Form.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including any voluntary or spontaneous termination, perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Follow-up Form. Pregnancy outcomes must also be collected for the female partners of any males in this trial. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

4.8.4. Use in Nursing Women

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

4.9. Duration of Therapy

Subjects who are clinically stable and meet dosing requirements (per **Section 5.2**) may continue to receive treatment for up to a maximum of 2 years.

4.10. Criteria for Removal from Treatment

The reason for study removal and the date the subject was removed will be documented in the CRF. A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as parent or legal guardian) withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment,
- Disease progression as defined in **Section 4.10.1**. If there are no signs of disease stabilization after 18 weeks of therapy, subjects should be discontinued,
- Intercurrent illness that prevents further administration of treatment,
- Severe or life-threatening cemiplimab- or plerixafor-related AE(s) (see **Section 4.10.2**),
- Need for >2 dose delays due to the same related toxicity as per the dose delay guidelines (see **Section 5.2**)
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient,
- Noncompliance with trial treatment or procedure requirements,
- Patient is lost to follow-up,
- Patient becomes pregnant, or
- Completed 24 months of treatment with cemiplimab and plerixafor. Note: 24 months of study medication is calculated from the date of the first dose.

4.10.1. Disease Progression

Immunotherapy is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some subjects may have objective volume increase of tumor lesions or other disease parameters within weeks following the start of immunotherapy. Such subjects may not have had sufficient time to

develop the required immune activation or, in some subjects, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 2-4 months of the study would constitute disease progression and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response [11].

Subjects will be permitted to continue with treatment beyond RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and
- Subject is tolerating study drug.

If there are no signs of disease stabilization after 18 weeks of therapy, subjects should be discontinued.

All decisions to continue treatment beyond PD must be discussed with the Protocol Chair and documented in the study records.

Tumor assessments will be made using RECIST 1.1 and iRECIST (**Appendix B and C**).

4.10.2. Cemiplimab- and Plerixafor-Related Adverse Events

Permanent discontinuation of all study treatment should be considered for any of the following (exceptions for permanent discontinuation must be approved by the Protocol Chair):

1. Severe or life-threatening related AEs, including, but not limited to, any of the following (the Protocol Chair must be notified in the event of these AEs):
    - Any grade 2 treatment-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within the re-treatment period OR requires systemic treatment
    - Any grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions:
        - Grade 3 treatment-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
        - Grade 3 treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
        - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:

- Grade 3 treatment-related thrombocytopenia > 7 days OR that is associated with bleeding requires discontinuation

- Any treatment-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - ALT or AST > 8 x ULN, regardless of duration, or
  - ALT or AST > 5 x and ≤ 8 x ULN, that fails to return to ≤ Grade 1 within 2 weeks despite medical intervention, or
  - Total bilirubin > 5 × ULN, or
  - Potential drug-induced liver injury (DILI) event **(Section 6.5.5)**

- Any grade 4 treatment-related AE or laboratory abnormality, except for the following events which do not require discontinuation:

  - Grade 4 neutropenia ≤ 7 days

  - Grade 4 lymphopenia and leukopenia.

  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations.

  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

  - Grade 4 treatment-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Protocol Chair.

- Any dosing interruption lasting > 6 weeks with the following exceptions:

  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Protocol Chair must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Protocol Chair. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Protocol Chair

must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued dosing.

In order to standardize the management of irAEs for all subjects, treatment management algorithms can be found in the NCCN's guidelines for the management of immunotherapy-related toxicities. Additional AE treatment management guidance included in the IBs might be considered for individual cases.

4.11. End of Treatment (EOT)

All subjects will return to the study site 30 days (± 7 days) after the last dose of study drug (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first) for an EOT evaluation. Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **Sections 4.12 and 9** as appropriate.

4.12. Duration of Follow Up

4.12.1. Safety Follow-up

Subjects who discontinue treatment should be contacted by telephone or email at 100 days (+ 14 day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.

Subjects who are discontinued from the study treatment due to an unacceptable drug-related AE will be monitored for safety until the resolution of the AE to ≤ grade 1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

4.12.2. Clinical Follow-up

All enrolled subjects who discontinue treatment without disease progression will enter the clinical follow-up portion of the trial. Subjects will begin the clinical follow-up period after they complete the EOT visit. Clinical follow-up visits will occur every 12 weeks (± 2 weeks) until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first. Refer to **Section 9** for the schedule of assessments that should be performed at each visit. After disease progression or start of a new antineoplastic therapy, subjects will enter the survival follow-up portion of the trial (**Section 4.12.3**).

4.12.3. Survival Follow-up

Subjects who discontinue treatment and have disease progression will enter the survival follow-up portion of the trial. Subjects should be contacted every 12 weeks (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1. Dose Modifications

Subjects will be monitored continuously for AEs while on study drug. Subjects will be instructed to notify their physician immediately for any and all AEs. Dose escalations or reductions of cemiplimab or plerixafor will not be allowed.

5.2. Dose Delays

In some cases, the natural history of select AEs associated with immunotherapy can differ from and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity.

Guidance for Investigators is provided in the current cemiplimab and plerixafor Investigator's Brochures. Additionally, management algorithms have been developed to assist Investigators with select toxicities and can be found in the NCCN's guidelines for the management of immunotherapy-related toxicities**.**

Subjects who experience the following must have all study drugs held:

- Select drug-related AEs and drug-related laboratory abnormalities:
  - Grade ≥ 2 pneumonitis
  - AST/ALT > 3 x ULN
  - Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
  - Creatinine > 1.5 x ULN
  - Grade ≥3 diarrhea or colitis
  - Grade ≥ 2 neurological AE
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study drug.

Subjects not meeting guidelines for permanent discontinuation will be permitted to resume therapy when the treatment-related AE(s) resolve to grade ≤1 or baseline value, with the following exceptions:

- If the toxicity resolves to ≤ Grade 1 or baseline > 6 weeks after last dose, but the subject does not otherwise meet criteria for permanent discontinuation, and the Investigator

believes that the subject is deriving clinical benefit, then the subject may be eligible to resume the study drugs following the approval of the Protocol Chair.

- Subjects with grade 4 drug-related amylase and/or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis can continue on therapy.
- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects with baseline normal or grade 1 AST, ALT or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resumed treatment in the presence of grade 2 AST, ALT or total bilirubin elevation.
- Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE grade or normal, provided the criteria for permanent discontinuation are not met.
- Treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

Subjects eligible to resume study drug will resume study drug at the treatment visit following their last received study drug dose.

The on treatment tumor assessments (i.e., CT/MRI, positron emission tomography [PET], etc.) will continue on an every 9-week schedule relative to the subject's first dose regardless of any treatment delay incurred. Subjects who are required to permanently discontinue both study drugs are listed in **Section 4.10.**

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised CTCAE version 5.0 for AE reporting.

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

6.1. Definitions

6.1.1. Adverse Event

An AE is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered AEs if they worsen after starting the study treatment (any procedures specified in the protocol). New medical conditions / diseases occurring before starting the study treatment but after signing the informed consent form will not be recorded as AEs. Additionally, expected progression of the disease being studied will not be recorded as an adverse event.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as AEs. A grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator (induce clinical signs or symptoms or require corrective therapy), meets the definition of an SAE, or requires the participant to have study drug discontinued or interrupted. It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

6.1.2. Serious Adverse Event

A SAE is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) for >24 hours
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Form)
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.

Events **not** considered to be SAEs are hospitalizations for:

- a visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life-threatening event)

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.1.3. Adverse Event of Special Interest (AESI)

An adverse event of special interest (AESI) is an adverse event (serious or non-serious) of scientific and medical concern specific to the investigational product, for which ongoing monitoring and rapid communication by the Investigator to the Protocol Chair and Sanofi may be appropriate. Such events may require further investigation in order to characterize and understand them.

6.2. Relationship

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Assessment of Grade:

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0) and graded as shown below:

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

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the subject.

6.3. Expectedness

Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE that is not included in the IB, package insert, safety reports or informed consent is considered "unexpected". An expected AE with a fatal outcome should be considered unexpected unless the IB specifically states that the AE might be associated with a fatal outcome.

Expected (known) AE: An AE, which has been reported in the IB, package insert or safety reports. An AE is considered "expected", only if it is included in the IB document as a risk.

6.4. Handling of Expedited Safety Reports

In accordance with local regulations, Sanofi will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to plerixafor and cemiplimab. An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report that is to be e-mailed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the SUSAR to the appropriate IRB. The investigator and IRB will

determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

6.5. Reporting

6.5.1. Adverse Events (AEs) and Serious Adverse Events (SAEs)

All AEs (both expected and unexpected) occurring from the first dose of study drug will be captured on the appropriate study-specific case report forms (CRFs).

All AEs (both related and unrelated) will be captured on the appropriate study-specific CRFs. All AEs experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will be followed for 28 days after last dose of study drug unless related to the investigational agent.

Subjects who experience a grade 3 or higher cemiplimab or plerixafor-related AE should be discussed with the Protocol Chair.

Report AEs to the Protocol Chair within 24 hours once identified as an unacceptable toxicity (defined in Section 4.7).

Dung Le (Protocol Chair): [redacted]

Report AESIs to the Protocol Chair and Sanofi within 24 hours once identified (defined in Section 6.1.3) using the form found in Appendix E.

Dung Le (Protocol Chair): [redacted]
Sanofi: [redacted]
Regeneron: [redacted]

All SAEs (including deaths) occurring from the first dose of study drug, throughout the study, and 100 days (+14 day reporting window) after the last dose of study drug or before initiation of a new antineoplastic treatment (whichever comes first) must be reported. All SAEs that the investigator considers related to the study drug occurring after the follow-up periods must be reported.

SAEs will be reported promptly to the Protocol Chair and Sanofi within 24 hours of recognition of the adverse event using the form found in **Appendix D**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports and any other relevant safety information are to be sent to:

Dung Le (Protocol Chair): [redacted]
Sanofi: [redacted]
Regeneron: [redacted]

6.5.2. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department concerning the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

As soon as relevant information is available, a follow-up SAE report will be submitted to the Protocol Chair and Sanofi.

6.5.3. Reconciliation of SAEs

The Principal Investigator will reconcile the clinical database SAE cases (case level only) transmitted to the Protocol Chair, Sanofi [redacted] Frequency of reconciliation should be approximately every 3 months and prior to the database lock or final data summary. Sanofi will email, upon request from the Principal Investigator (or representative), the reconciliation report. Requests for reconciliation should be sent to [redacted] The data elements listed on the Sanofi reconciliation report will be used for case identification purposes. If the Principal Investigator determines a case was not transmitted to the Protocol Chair and Sanofi, the case should be sent immediately to the Protocol Chair and Sanofi.

6.5.4. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

6.5.5. Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs under the seriousness category checked as 'other medically important event'. Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)
   AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
AND
3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.5.6. Pregnancy Reporting

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 24 weeks following cessation of the study drugs, or pregnancy of a partner of a male subject within 33 weeks of cessation of the study drugs, must be reported by the investigator using the Pregnancy Surveillance Form. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Protocol Chair and Sanofi.

Any SAE occurring during pregnancy (pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth) must be recorded on the SAE report form and submitted to the Protocol Chair and Sanofi.

6.5.7. Institutional Review Board (IRB)

SAEs will be reported to the IRB per institutional guidelines. Follow-up information will be submitted to the IRB as soon as relevant information is available.

7. PHARMACEUTICAL INFORMATION

Detailed instructions will be provided in the pharmacy manual.

7.1. Cemiplimab

7.1.1. Agent Accountability

The Protocol Chair or the Protocol Chair's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

At the end of the study period, Sanofi will not continue to supply study drug to subjects/investigators unless the Protocol Chair chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care

or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

7.1.2. Mode of Action

Cemiplimab is human monoclonal immunoglobulin (Ig) antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self-antigens.

7.1.3. Description

[redacted]

7.1.4. Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1.5. Preparation

[redacted]

7.1.6. Storage

[redacted]

7.1.7. Stability

[redacted]

[redacted]

7.1.8. Route of Administration

[redacted]

7.1.9. Subject Care Implications

[redacted]

7.1.10. Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Sanofi or designee, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

7.2. Plerixafor

7.2.1. Agent Accountability

The Protocol Chair or the Protocol Chair's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

At the end of the study period, Sanofi will not continue to supply study drug to subjects/investigators unless the Protocol Chair chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care

or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

7.2.2. Mode of Action

Plerixafor is approved by the US FDA in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients. Plerixafor is a bicyclam derivative, a selective reversible antagonist of CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell derived factor-1a (SDF-1a), also known as CXCL12. Plerixafor is used in this protocol as a CXCR4 antagonist.

7.2.3. Description

[redacted]

7.2.4. Packaging and Labeling Information

[redacted]

7.2.5. Preparation

[redacted]

7.2.6. Calculation of Dose

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.7. Storage

[redacted]

[redacted]

7.2.8. Stability

[redacted]

7.2.9. Route of Administration

[redacted]

[redacted]

7.2.10. Subject Care Implications

[redacted]

7.2.11. Returns or Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Sanofi, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8. CORRELATIVE/SPECIAL STUDIES

Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. Sample collection, processing, storage, and shipment instructions will be provided in the Laboratory Manual.

8.1. Tumor Tissue Studies

Blocks or slides (twenty five unstained slides) will be collected from archived tissue. These slides will also be used for the evaluation of additional immune and tumor markers. See the Laboratory Manual for additional details regarding tissue collection, processing, storage, and shipment.

Tumor biopsies will be collected per **Section 9**. Fine needle aspiration samples do not contain sufficient tissue contextual information and will not be obtained. Additional biopsies may be obtained during the course of therapy or at progression.

To explore the association of the tumor microenvironment and clinical responses, archived tumor tissue and tumor tissue obtained at baseline and during treatment will be compared. PD-L1 expression may predict response to anti-PD-1 therapy [12]; however, PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Pre- and post-treatment tumor biopsies will also be analyzed with immunohistochemistry and gene expression analysis for expression of T cell subset markers (CD3, CD4, CD8, FoxP3, Granzyme A/B, CD69), immune regulation (PD-L1, PD-L2, CTLA4, LAG-3, IDO1, TIM-3), and immune cell population markers (NK, DC, B cell, MDSC, M1/M2 macrophages).

To explore genetic determinants of response, whole-exome sequencing will be performed on DNA from tumors and matched normal tissue. We will characterize the tumor mutational landscape through exomic sequencing for mutation analysis and neoantigen prediction.

TCR sequencing will be undertaken to evaluate the T cell repertoire through next-generation sequencing in the tumor tissue and to characterize peripheral immune responses. Gene expression

profiling will also be employed to identify gene signatures within the tumor microenvironment (TME) associated with response and survival.

Results from the sequencing studies will not be released to the patients. These studies are for research purposes only, and the sequencing studies are not using a clinically validated platform.

8.2. Whole Blood

Whole blood will be collected to assess the baseline characteristic of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and toxicity. DNA will be extracted from whole blood and used to evaluate for any germline mutations that may correlate with response or toxicity.

Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.3. Peripheral Blood Mononuclear Cells (PBMCs)

PBMCs will be collected per the study calendar. Post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells and macrophages through cell phenotyping analysis and gene expression profiling will be measured. Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS.

T cells will be isolated and co-cultured with synthetic peptide neoantigens and will undergo TCR sequencing to assess for clonal expansion as previously described[13]. Gene expression will also be conducted on pre- and on-treatment PBMCs.

Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.4. Serum and Plasma Marker Studies

Sera and plasma will be collected per the study calendar to elucidate plerixafor exposure in this patient population, identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity through proteomic approaches. DNA will be extracted from plasma samples and ctDNA levels commonly mutated genes may be assessed.

Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.5. Serum and Salivary Cortisol

Abnormalities in the diurnal variation of salivary cortisol in patients with advanced cancer have been associated with adverse prognosis[14, 15] and impaired immune cell function[16]. The most likely mechanism is a direct reduction in tumor infiltrating lymphocytes, in particular CD3 positive T cells (manuscript currently under review).

Serum and salivary cortisol levels will be collected per the study calendar if available. Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.6. CT Scans for Body Composition

Deidentified CT images will be sent to collaborators for evaluation of body composition for correlation with outcomes. No additional imaging will be required.

8.7. Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnoses immune related toxicities. Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.8. Genomic Analysis

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed. Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

Clinical analysis

Several CLIA-certified laboratories now offer molecular profiling of cancer specimens in commercial and noncommercial settings and provide these results to patients and their physicians (e.g. Foundation Medicine, PGDx, Michigan Center for Translational Pathology, or JHU CLIA Laboratories). It is possible, therefore, that some of our research analyses will be conducted in these CLIA-certified environments. If tissue or cells are evaluated with next generation sequencing strategies to provide a molecular profile of individual cancer specimens in a CLIA-certified facility, these results will be made available to the patient and their physician. Patient confidentiality will be maintained, and the patient's identity will not be publicly linked to any study results. Researchers may use the data set generated in the CLIA assay setting to study genetic alterations across a large number of genes important in cancer. Germline mutations are only identified in punitive cancer genes. Researchers will use the data set for exploratory research to study cancer cell heterogeneity. Some of the sequencing data obtained from the NGS strategies will be uploaded to government sponsored databases, such as GEO and dbGAP. The results of the research studies may be published but subjects will not be identified in any publication.

If a germline alteration of clinical importance (as judged by the Investigator) to the subject and his or her family members is identified by a CLIA-certified test in the course of this analysis, attempts will be made in writing to contact the subject and/or family members for genetic counseling referral.

9. STUDY CALENDAR

Study Procedures	Screen	Cycle (21 days)									EOT[21]	Safety FU[22]	Clinical FU[23]	Survival FU[24]
		D1[20]	D2	D3	D4	D5	D6	D7	D8	D15				
Visit Windows (days)[1]	-28 to D1	± 3	-	-	-	-	-	-	-	+3/-2	± 7	+14	± 14	± 14
Plerixafor[2]		X												
Cemiplimab[2]		X												
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics	X													
Medical, Cancer, & Con Med Hx[3]	X													
Con Meds, Adverse Events[4]		X			X				X	X[25]	X	X	X	
Physical Exam, ECOG PS[4]	X	X							X[25]	X[25]	X		X	
Vitals[5]	X	X			X				X	X[25]	X		X	
Height[6]	X													
Weight	X	X							X[25]	X[25]	X		X	
Hematology, Chemistry[7,13]	X	X			X[27]				X	X	X		X	
Endocrine[8,13]	X	X									X			
CD34[9]		X			X									
APTT/PTT	X													
Urinalysis[10]	X													
Virology[11]	X													
Pregnancy Test[12,13]	X	X												
CA19-9[13]	X	X									X		X	
C-reactive protein (CRP)[13]	X	X									X		X	
Serum Cortisol, ACTH[14, 26]	X								X[25]					
Salivary Cortisol[15, 26]	X								X[25]					
12-lead ECG	X													
CT/MRI, RECIST/iRECIST[16]	X	X									X		X	
Whole Blood (up to 10cc)[17, 26]		X												
PBMC (up to 120cc)[18, 26]		X							X[25]	X[25]				
Plasma (up to 20cc) [18, 26]		X							X[25]	X[25]				
Serum (up to 5cc) [18, 26]		X							X[25]	X[25]				
Plerixafor PK (up to 12 cc)[28]		X			X				X					
Tumor Biopsies[19, 26]	X								X[25]					
Archival Tissue[26]	X													

Study Procedures	Screen	Cycle (21 days)									EOT[21]	Safety FU[22]	Clinical FU[23]	Survival FU[24]
		D1[20]	D2	D3	D4	D5	D6	D7	D8	D15				
Survival Follow-up														X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the Protocol Chair.
2: Order of administration is Cemiplimab followed by Plerixafor. Subjects should be observed for a minimum of 30 minutes between each infusion. Plerixafor will be administered as a continuous 7-day IV infusion. Prepared plerixafor formulation is stable for 5 days at room temperature. Therefore, patients will return to clinic on day 4 to exchange the infusion bag and on day 8 to discontinue their plerixafor infusion.
3: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens, MSI testing, and tumor mutation testing. If MSI testing has not been previously done, MSI testing may be done retrospectively if tissue is available.
4: Complete physical examination and assessment of ECOG PS will be completed at baseline; focused physical examinations and assessment of ECOG PS will be conducted thereafter. Exams, concomitant medication, AE assessments, and ECOG PS can be evaluated up to 3 days prior to infusion on Day 1 of each cycle.
5: Blood pressure, pulse, and temperature. On Day 1 of each cycle, vitals should be collected prior to both the Cemiplimab and Plerixafor administrations. On Cycle 1 Day 1, patients will have a 6 hour observation period with hourly vital sign assessment.
6: Height will be obtained at or prior to baseline only.
7: Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count; serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, calcium, magnesium, and phosphorus. Calculated creatinine clearance (Cockcroft-Gault) is required at screening and on Day 1 of every cycle.
8: TSH (Total T3 and free T4 if TSH abnormal and clinically indicated).
9: Day 1 and 4 of Cycle 1 and 2 only
10: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.
11: HIV antibody, hepatitis B surface antigen and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll.

12: Pregnancy tests will be administered to WOCBP: serum pregnancy test is required at screening; serum or urine pregnancy tests are required before doses on Day 1 of each cycle.
13: Labs may be collected within a window of up to 3 days prior to Day 1 of each cycle.
14: ACTH collected at baseline only. Serum cortisol measured as scheduled with the exact record of time of sample acquisition (not time of sample processing) at baseline (any time prior to the first dose after eligibility is met), disconnection of plerixafor infusion (Cycle 1 Day 8) and Cycle 2 Day 1. Ideally this should be a fixed time, i.e. either 0800 or 1200. Collection will commence with saliva samples.
15: Baseline saliva samples should be collected (if available) over 2 days (any time prior to the first dose after eligibility is met, D-7 to D-1), preferably when no other trial related procedures or visits are performed. On study saliva samples (if available) will be collected on Cycle 1 Day 7 and Cycle 1 Day 21 (i.e. one day prior to Cycle 2 Day 1 with a -1 day window for collection). The following five samples should be collected at each timepoint: 1. on awakening (right away, before breakfast), 2. 30 minutes after the first sample (still before breakfast), 3. 11:00am, 4. 4:00pm, and 5. just before bedtime (prior to brushing teeth). Collection of these samples will begin once kit and vendor are identified.
16: Spiral CT of thorax, abdomen and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. On study radiologic evaluations and tumor measurements (RECIST/iRECIST per **Appendix B and C**) will be at baseline, every 9 weeks (+/- 2 week), and the EOT evaluation (± 4 weeks). The EOT scans do not need to be repeated if one has been done within the past 6 weeks. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.
17: Baseline only (any time prior to the first dose after eligibility is met)
18: Whole blood for PBMC, plasma, and serum will be collected at baseline (any time prior to the first dose after eligibility is met), Cycle 1 Days 8 and 15, Cycle 2 Days 1 and 8, Cycle 4 Day 1, and Cycle 7 Day 1. Plasma and serum samples will also be collected on Day 8 of Cycles 4 and 7. Additional optional blood samples may be obtained later in the course of study treatment if patients have a response of interest. Detailed instructions for sample collection, processing, and shipment are provided in the Laboratory Manual.
19: Tumor biopsies to be taken (4-6 cores per time point, if a subject's tumor is thought to be reasonably safe and easy to biopsy) at the following timepoints: 1. Baseline (any time prior to the first dose after eligibility is met), 2. Prior to dosing on either Cycle 1 Day 8 (-1 day) or Cycle 2 Day 1 (-3 day) for alternating patients, and 3. Optional biopsy may be obtained at the time of disease progression or if there is a response of interest. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing, and shipment are provided in the Laboratory Manual.
20: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations.
21: EOT visit will occur 30 (±7) days after the final dose (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). NOTE: CT scan assessment at EOT will occur 30 days (± 4 weeks) after the final dose. If the EOT visit occurs early, an assessment for AEs should be made by telephone or email on day 30 (±1) after last study dose.

22: Subjects who discontinue treatment should be contacted by telephone or email at 100 days (+ 14 day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, related SAEs occurring during this time should be reported as well.

23: Subjects who discontinue treatment without disease progression will enter the clinical follow-up portion of the trial (**Section 4.12.2**). Clinical follow-up visits will occur every 12 weeks (± 2 weeks) until progression. After disease progression, subjects will enter the survival follow-up portion of the trial.

24: Subjects who discontinue treatment and have disease progression will enter the survival follow-up portion of the trial (**Section 4.12.3**). Subjects should be contacted every 12 weeks (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

25: Cycle 1 only.

26: Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

27: Cycle 1 and 2 only

28: Whole blood for plerixafor plasma PK will be collected at baseline (any time prior to the first dose after eligibility is met), Cycle 1 Days 4 prior to changing the infusion bag and Day 8 prior to stopping the infusion. Documentation of the infusion start/stop times along with the exact timing of the specimen is necessary to interpret the results. Detailed instructions for sample collection, processing, and shipment are provided in the Laboratory Manual.

10. STUDY ENDPOINTS

10.1. Primary Endpoint

The primary endpoint is ORR using iRECIST, which is defined as the proportion of subjects with PR or CR according to iRECIST. Subjects who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders. Subjects who discontinue for reasons other than toxicity or clinical progression prior to the post-baseline tumor assessments or for other reasons prior to their first dose of study drug will be replaced and not included in the primary efficacy analysis.

10.2. Secondary Endpoints

The secondary endpoints are as follows:

- ORR by RECIST v.1.1.
- Safety assessed by the following measures:
  - Number of patients who have grade 3 or above drug-related toxicities
  - Frequency of drug-related toxicity by grade
  - Plerixafor- and cemiplimab-related infusion reactions
  - Immune-related AEs
  - Unacceptable toxicities
  - Vital signs: BP, pulse, respiratory rate, temperature
  - Physical examination
  - Changes in ECG readings
  - Clinical hematology: complete blood count (CBC) with differential ANC, ALC, AEC, and platelet count
  - Clinical serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, lipase, total protein, albumin, calcium, magnesium, and phosphorus
  - TSH, T3, Free T4

10.3. Exploratory Endpoints

The exploratory endpoints are as follows:

- Overall survival (OS), progression free survival (PFS), time to-progression (TTP), disease control rate (DCR), best overall response (BOR), duration of response (DOR), duration of clinical benefit (DCB), and time to objective response (TTOR) measured by iRECIST and RECIST 1.1 (**Appendix B**).
  - Overall survival (OS) is defined as the number of months from the date of first treatment until death or end of follow-up (OS will be censored on the date the subject was last known to be alive for subjects without documentation of death at the time of analysis).
  - Progression-free survival (PFS) is defined as the number of months from the date of first treatment to disease progression (PD or relapse from CR as assessed using

RECIST 1.1 criteria) or death due to any cause. PFS will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis. iPFS is defined as the time to iUPD if the next scan (4-8 weeks later) confirms PD (state change from iUPD to iCPD, time to progression defined in this instance as iUPD).
    - Disease Control Rate (DCR) is defined as the percentage of subjects achieving stable disease or better (SD + PR + CR).
    - Best Overall Response (BOR) is defined in **Appendix B.**
    - Duration of Response (DOR) is defined as the number of months from the first documentation of a response to date of disease progression.
    - Duration of Clinical Benefit (DCB) is defined as the number of months from the date of first treatment to date of disease progression in those achieving a PR or CR.
    - Time to Objective Response (TTOR) is defined as the number of months from the date of first treatment to the date of documented partial or complete response.
    - Time to-progression (TTP) is defined as the number of months from the date of first treatment to the date of documented disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria). It differs from PFS in that it does not include death in the definition of an event. TTP will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis.
- Immune subset analysis by IHC and gene expression profiling of the tumor
- Sequencing of tumor
- Immune subset analyses in PBMCs including effector, helper, and regulatory T cells, NK cells and macrophages
- T cell receptor (TCR) repertoire analysis in PBMCs and tumors
- Gene expression analysis
- cfDNA analysis
- Steady-state plerixafor concentrations to correlate with pharmacodyanmic endpoints (e.g., safety, response, and correlative studies).

11. DATA REPORTING/ REGULATORY REQUIREMENTS

AE guidelines and instructions for AE reporting can be found in **Section 6 (Adverse Events: List and Reporting Requirements)**.

Each Principal Investigator will comply with all regulated local reporting requirements and regulations, including ICH E6 guidelines for Good Clinical Practices.

11.1. Data Collection and Processing

All information will be collected on study-specific CRFs by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator.

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto eCRFs. Before or between visits, the Protocol Chair, or designee may request copies of the CRFs for preliminary medical review.

Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF.

11.2. Safety Meetings

Scheduled meetings will take place weekly (or as needed based on enrollment) and will include the protocol principal investigator, study coordinator(s), research nurse(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings, matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

11.3. Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring. The PI shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. The protocol will be monitored externally by the SKCCC CRO QA Office. Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP).

11.4. Study Documentation

11.4.1. Informed Consent and Authorization for use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information (PHI) must be obtained from each subject (or the subject's legally authorized representative) before performing any study-specific screening/baseline period evaluations. The ICF and authorization for use and disclosure of PHI, which is prepared by the investigator or the site, must be reviewed and approved by the Protocol Chair (or designee), the study monitor (if applicable), and the site's IRB before the initiation of the study.

11.4.2. Investigator Study Files

Documentation about the investigator and study staff, the IRB and the institution, is required before study site initiation. A list of required documents will be provided by the Protocol Chair designee to each participating investigator. Copies of these documents as well as supplemental information, such as the investigator's obligations, IB, clinical study protocol and amendments, safety information, investigational agent information, biological samples and laboratory procedures, SRM, study logs, and Protocol

Chair/investigator/study monitor correspondence will be kept on-site in study site-specific files.

The Protocol Chair or designee will be responsible for maintaining original and backup of all CRF data. The investigator is responsible for maintaining backup of all electronic data systems used for primary documentation or source documentation. Backup of electronic data will be performed periodically as described in the site-specific SOPs. Backup records must be stored at a secure location on site and backup and recovery logs must be maintained to facilitate data recovery. If an electronic medical records system that is not supported by the Protocol Chair or designee (or is discontinued or decommissioned) is used, the investigator must maintain a system to retrieve these records or arrange for the transfer of these records to an alternate electronic format or to paper.

Changes to any electronic records require an audit trail, in accordance with 21 CFR 11.10(e), and should include who made the changes and when and why the changes were made. An audit trail is defined as a secure, computer-generated, time-stamped electronic record that will allow reconstruction of the course of events relating to the creation, modification and deletion of an electronic record. Audit trails must be created incrementally, in chronological order and in a manner that does not allow new audit trail information to overwrite existing data. Audit trails should be in a readable format and readily available at the study site and any other location where electronic study records are maintained.

Audit trails are generated automatically for eCRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for primary documentation or source documentation.

11.4.3. Case Report Forms and Source Documentation

The investigator must make study data accessible to the site monitor, to other authorized representatives of the Protocol Chair (or designee) and to the appropriate regulatory authority inspectors. The original CRF for each subject will be checked against source documents at the study site by the site monitor.

11.4.4. Retention of Study Documents

According to ICH E6, all CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of an individual product. Longer retention periods may apply. The Protocol Chair (or designee) will notify investigators as to when documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the Protocol Chair (or designee). If the investigator relocates, retires or withdraws from the clinical study for any reason, all records required to be maintained

for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The investigator must retain either the original or a certified copy of audit trails.

11.4.5. Data Confidentiality and Subject Anonymity

All information about the nature of the proposed investigation provided by the Protocol Chair or their representative to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents retrieved from the site or sent to the Protocol Chair, study monitor, Sanofi, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, Protocol Chair or their representative.

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

Sample Size

This is an open-label, two stage, phase 2 study to evaluate the safety and clinical activity of plerixafor and cemiplimab in patients with metastatic pancreatic adenocarcinoma. The primary endpoint is objective response rate (ORR) assessed using iRECIST.

The treatment regimen would be considered of insufficient activity for further study in this population if response rate (irORR) is 7.7% or less[1], and the minimum required level of efficacy that would warrant further study is an irORR of 20%. The sample size is calculated to detect an improved irORR from 7.7% to 20%. A modified Simon's two-stage design is planned. A total of 21 patients will be entered in the first stage. If <=1 subject responds, the treatment will be terminated and we will conclude the regimen is ineffective. If >=2 subjects respond, then additional 18 patients will be enrolled. If a total of 5 or fewer subjects respond in stage one and two combined, we consider the regimen ineffective. If a total of 6 or more respond, we conclude the regimen is promising and warrant further study. The maximum sample size will be 39.

The design provides 80% power to detect the difference between the null hypothesis irORR of 7.7%[1] to the alternative rate of 20% with one-sided type I error 0.07 (target type I error 0.1). The probability of early stopping at first stage is 0.51 if the true irORR is 7.7%.

Statistical Analyses

The primary endpoint is objective response, defined as complete response (CR) or partial response (PR) per iRECIST. Objective response rate (irORR) will be estimated as the proportion of subjects whose best overall response is either a CR or PR with corresponding 95% CI. The evaluable population for the analysis is all subjects who receive at least one dose of study drug, and have at least one post-baseline tumor assessments or discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments.

Exploratory endpoints include progression-free survival (PFS), overall survival (OS), and objective response per RECISIT 1.1, duration of response (DOR), disease control (DCR), time to progression (TTP). PFS is defined as the time from the first day of study treatment to the date of the first documented tumor progression or death due to any cause, whichever occurs first. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Overall survival (OS) is the time from the first day of study treatment to the date of death due to any cause. A subject who has not died will be censored at last known date alive. Kaplan-Meier curves will be used to summarize OS. Time to-progression (TTP) is defined as the number of months from the date of first treatment to the date of documented disease progression (PD or relapse from CR).Among patients with an objective response, DOR is defined as the time between the date of initial complete or partial response to the date of the first documented tumor progression or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last tumor assessment. Summary statistics will be presented for DOR. Kaplan-Meier method will be used to summarize time-to-event outcomes PFS, OS, TTP and DOR. Rate of OR and DOR will be estimated along with 95% confidence intervals. The outcomes will be assessed using RECIST 1.1 and also iRECIST unless otherwise defined.

For biomarkers, potential relationships between biomarker data and efficacy or safety endpoints will be investigated aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond to the treatment and to identify subjects who may be predisposed to having adverse reactions to treatment. Steady-state plerixafor concentrations will be correlative with response using appropriate non-parametric analysis. These exploratory biomarker analyses will be completed with biomarkers measured in blood and in tumor samples.

12.2. Safety Analysis

The safety analysis will be performed in all treated subjects. AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each cohort. When calculating the incidence of AEs, each AE (based on preferred terminology defined by CTCAE version 5.0) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be

characterized according to the CTCAE version 5.0. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

The study will include a safety run-in for the first six patients. If more than 1 of the first 6 patients experiences an unacceptable toxicity within the first cycle, then enrollment will be halted and the overall risk-benefit ratio of the study will be reconsidered. At any time thereafter, if more than 33% of patients are observed to experience unacceptable toxicity within the first cycle, enrollment will be halted and the safety of the combination will be re-evaluated. Complete unacceptable toxicity criteria can be found in **Section 4.7.** The enrollment stops if:

Number of Patients with AE > 33%	2	3	4	5	6	7	8	9	10	11	12	13
In number of patients between	6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39

The operating characteristics of this stopping rule for toxicity, starting from the 6th patient, are shown below and based on 5000 simulations.

Risk of AE	0.10	0.20	0.25	0.30	0.33	0.40	0.45	0.50	0.55	0.60
% of time study stops	12.4%	45.8%	63%	78.7%	85%	96.3%	99%	99.7%	100%	100%
Expected sample size	34.98	24.64	19.62	15.25	13.02	9.04	7.69	6.81	6.41	6.19

13. REFERENCES

1. *ONIVYDE™ Prescribing Information*
2. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2016.* CA Cancer J Clin, 2016. **66**(1): p. 7-30.
3. Torre, L.A., et al., *Global cancer statistics, 2012.* CA Cancer J Clin, 2015. **65**(2): p. 87-108.
4. Rahib, L., et al., *Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States.* Cancer Res, 2014. **74**(11): p. 2913-21.
5. Burris, H.A., 3rd, et al., *Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial.* J Clin Oncol, 1997. **15**(6): p. 2403-13.
6. Moore, M.J., et al., *Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group.* J Clin Oncol, 2007. **25**(15): p. 1960-6.
7. Conroy, T., et al., *FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.* N Engl J Med, 2011. **364**(19): p. 1817-25.
8. Von Hoff, D.D., et al., *Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.* N Engl J Med, 2013. **369**(18): p. 1691-703.
9. Wang-Gillam, A., et al., *Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial.* Lancet, 2016. **387**(10018): p. 545-57.
10. Biasci, D., et al., *CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response.* Proc Natl Acad Sci U S A, 2020. **117**(46): p. 28960-28970.
11. Wolchok, J.D., et al., *Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.* Clin Cancer Res, 2009. **15**(23): p. 7412-20.
12. Taube, J.M., et al., *Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy.* Clin Cancer Res, 2014. **20**(19): p. 5064-74.
13. Le, D.T., et al., *Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade.* Science, 2017.
14. Cohen, L., et al., *Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: role of inflammatory signaling.* PLoS One, 2012. **7**(8): p. e42324.
15. Sephton, S.E., et al., *Diurnal cortisol rhythm as a predictor of lung cancer survival.* Brain Behav Immun, 2013. **30 Suppl**: p. S163-70.
16. Sephton, S.E., et al., *Diurnal cortisol rhythm as a predictor of breast cancer survival.* J Natl Cancer Inst, 2000. **92**(12): p. 994-1000.
17. Seymour, L., et al., *iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics.* Lancet Oncol, 2017. **18**(3): p. e143-e152.

APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

Disease Parameters

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

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

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

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

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements

recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Reference

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX C: DESCRIPTION OF THE IRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using the criteria outlined in **Section 4.10.1**.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including **iUPD** (unconfirmed progressive disease) and **iCPD** (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression,

whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [17].

Table 2: Comparison between RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of disease: numbers, sites and target or non	Measurable are diameters greater than 10 mm (15 for nodes maximum of 5 (2 per organ)	No change from RECIST 1.1
CR, PR or SD	Cannot have met criteria for progression	Can have had iUPD (more than once) but not iCPD before iCR, iPR or iSD
Confirmation of CR or PR	Only in non-randomized studies	As per RECIST 1.1
Confirmation of SD	Not required	As per RECIST 1.1
New lesions	Progression: recorded but not measured	iUPD but only becomes iCPD if on the next scan there are new lesions or the size increases by greater than 5 mm
Confirmation of progression	Not required	Required
Consideration of clinical status	Not required	Clinical stability considered at iUPD to decide treatment continuation

Table 3: Trajectory of progression in iRECIST

Target Lesions: iCR, Non-target: iCR, no new lesions	iCR	iCR
Target lesions: iCR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target Lesions: iPR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target lesions: iSD, Non-target: non iCR/non iUPD, no new lesions	iSD	iSD
Target lesions: iUPD with no change or with a decrease from the last time point, Non-target: iUPD with no change or decrease from last time point, new lesions	NA	New lesions confirm iCPD if new lesions previously identified and increased in size (≥ 5 mm in sum of measures for new lesions or any increase for new lesion non-target) or increase in number. If no change is seen in new lesions assignment remains iUPD

Target lesions: iSD, iPR, iCR, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD is confirmed by increase in the size of non-targets (does not need to meet RECIST 1.1 criteria)
Target lesions: iUPD, non-target: non iCR/non iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on the basis of further increase ≥ 5 mm; otherwise stays as iUPD
Target lesions: iUPD, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on previously identified targets iUPD ≥ 5 mm or non-target iUPD
Target lesions: iUPD, non-targets: iUPD, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase of ≥ 5 mm previously identified target, or non-target or an increase in size or number of new lesions
Target lesions non iUPD or progression, non-targets: non iUPD or progression, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase in size or number of new lesions previously identified.

Target lesions, non-target lesions and new lesions are defined according to RECIST 1.1 criteria: if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD are the same. * Previously identified in the assessment prior to this time point. 'I' indicates immune responses assigned using iRECIST

APPENDIX D: SAE REPORTING FORM

Serious Adverse Event Reporting Form

Please notify: Dr. Le within 24 hours [redacted]
Sanofi within 24 hours [redacted]
Regeneron within 24 hours [redacted]

Protocol Title:	**A Phase 2 Study of Plerixafor and Cemiplimab in Metastatic Pancreatic Cancer**		
Protocol Number: SGZ- 2018-12345 J19113	**Signature of PI:**	**Principal Investigator:**	**Date of Report:**
Report Type: ☐Initial ☐Follow-up ☐Final Follow-up ☐Death ☐Addendum to:	**Serious Criteria (check all that apply):** ☐Death ☐Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Other Important Medical Event ☐ Cancer ☐ Overdose ☐ Other:_____	**Hospital Admission Date:**	**Date Event Discovered:**
		Hospital Discharge Date:	**SAE ID:**

Section A: Subject Information		
Subject ID:	**Subject Gender:** ☐Male ☐Female	**Subject Age:**

Section B: Event Information			
Event diagnosis or symptoms:	**Event Grade:**	**Cause of death (if applicable):**	**Event Outcome:** ☐ Not Recovered ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Death ☐ Unknown
Event Onset Date (or Date of Death):		**Event End Date:**	

Section C: Study Drug Information

Investigational Product: Plerixafor (80mcg/kg/hr, Days 1-7) and Cemiplimab (350mg, Day 1) IV every 21 days

Indication: Metastatic pancreatic ductal adenocarcinoma

Number of Total Cycles:		**Action taken with the study drug:** ☐None ☐ Interrupted ☐ Delayed ☐ Discontinued Drug(s) discontinued:
Date of First Dose:	**Date of Last Dose prior to Event:**	

Relationship to:	**Plerixafor**	**Cemiplimab**	**Underlying Disease**
Unrelated	☐	☐	☐
Related	☐	☐	☐

Section D: Brief Description of the Event:

Section E: Relevant Tests/Laboratory Data

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

Name of the Drug	**Start Date**	**Stop Date**	**Route**	**Dose**	**Frequency**

Section H: Comments

Additional Documents: ☐ Please specify

APPENDIX E: AESI REPORTING FORM

Adverse Event of Special Interest Reporting Form

Please notify: Dr. Le within 24 hours [redacted]
Sanofi within 24 hours [redacted]
Regeneron within 24 hours [redacted]

Protocol Title:	**A Phase 2 Study of Plerixafor and Cemiplimab in Metastatic Pancreatic Cancer**		
Protocol Number: SGZ- 2018-12345 J19113	**Signature of PI:**	**Principal Investigator:**	**Date of Report:**
Report Type: ☐ Initial ☐ Follow-up ☐ Final Follow-up ☐ Addendum to:	**Event Onset Date:** **Event End Date:**	**AESI ID:**	**Date Event Discovered:**

Section A: Subject Information		
Subject ID:	**Subject Gender:** ☐ Male ☐ Female	**Subject Age:**

Section B: Event Information		
Event diagnosis or symptoms:	**Event Grade:**	**Event Outcome:** ☐ Not Recovered ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Death ☐ Unknown

Section C: Study Drug Information

Investigational Product: Plerixafor (80mcg/kg/hr, Days 1-7) and Cemiplimab (350mg, Day 1) IV every 21 days

Indication: Metastatic pancreatic ductal adenocarcinoma

Number of Total Cycles:		**Action taken with the study drug:** ☐ None ☐ Interrupted ☐ Delayed ☐ Discontinued Drug(s) discontinued:
Date of First Dose:	**Date of Last Dose prior to Event:**	

Relationship to:	**Plerixafor**	**Cemiplimab**	**Underlying Disease**
Unrelated	☐	☐	☐
Related	☐	☐	☐

Section D: Brief Description of the Event:

Section E: Relevant Tests/Laboratory Data

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

Name of the Drug	**Start Date**	**Stop Date**	**Route**	**Dose**	**Frequency**

Section H: Comments

Additional Documents: ☐ Please specify