A PHASE 1, OPEN-LABEL, DOSE ESCALATION AND EXPANSION STUDY EVALUATING THE SAFETY AND PHARMACODYNAMICS OF PF-07263689, EITHER ALONE OR IN COMBINATION WITH AN ANTI-PD-1 ANTIBODY, IN PREVIOUSLY TREATED PARTICIPANTS WITH SELECTED LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

Study Intervention Number:	PF-07263689
Study Intervention Name:	NA
CCI [redacted]	[redacted]
EudraCT Number:	NA
ClinicalTrials.gov ID:	NA
Protocol Number:	C4651001
Phase:	1

Brief Title: Phase 1 Study of PF-07263689 in Participants with Selected Advanced Solid Tumors

Document History

Document	Version Date
Amendment 1	20 July 2021
Original protocol	03 June 2021

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ ECs and any protocol administrative clarification letter.

Amendment 1 (20-July-2021)

Overall Rationale for the Amendment: The primary purpose of this amendment is to incorporate feedback received from the FDA. In addition, clarification, administrative and typographical modifications were made.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis; Section 3.1. Dose Escalation; Section 3.2 Dose Escalation; Section 9.3.3.2. Sasanlimab Pharmacokinetic Analysis	Secondary objectives and statistical consideration were included for Part 1 and Part 2 sasanlimab's PK and immunogenicity.	Sasanlimab's PK and immunogenicity were previously omitted.
Section 1.1. Synopsis; Section 1.2. Schema; Section 2.3. Benefit/Risk Assessment; Section 4.1.1. Dose Escalation (Part 1)	Part 1B will include CCI [redacted]	Due to potential overlapping CCI [redacted] clinical safety signals and mitigate overall risk to patients.
Section 1.1. Synopsis Section 1.2. Schema, Section 2.3. Benefit/Risk Assessment; Section 4.1.1. Dose Escalation (Part 1)	In Part 1A monotherapy, CCI [redacted]	To adequately capture acute and subacute adverse events for Part 1A monotherapy and mitigate overall risk to patients.
Section 1.1. Synopsis Section 1.2. Schema; Section 4.1.1. Dose Escalation (Part 1); Section 4.3. Justification of Dose; Section 4.3.1. Starting	In Part 1A, the provisional dose for each dose level has been revised to half log dose increments. CCI [redacted] (which is one log level below	Given the MOA based on a replicative oncolytic virus and gene therapy platform, a more conservative dosing approach has been adapted.

Section # and Name	Description of Change	Brief Rationale
Dose; 4.3.2 Criteria for Dose Escalation and 9.3.2 Primary Endpoint(s)/Estimand(s)/ Analysis	the NOAEL) is included, and the dose levels above NOAEL have been removed in this amendment.	
Section 1.3. Schedule of Activities; Section 2.3.1. Risk Assessment; Section 8.2.4. Vital Signs; Section 8.2.6 Echocardiogram or MUGA; Section 10.2. Appendix 2: Clinical Laboratory Assessments; Section 10.8.3.4. Echocardiogram or MUGA	The following assessments have been added in the SOA and throughout the protocol: • Cardiac Biomarkers (CPK and troponin levels) • Echocardiogram or MUGA • Pulse oximetry	Safety assessments added as the combination of PF-07263689 and sasanlimab may potentially lead to increased CCI [redacted].
Section 1.1. Synopsis; Section 5.1. Inclusion Criteria; Section 5.2. Exclusion Criteria	The eligibility criteria were modified: • Participants with persistent non-hematologic toxicities of Grade ≥ 3 (NCI-CTCAE v5.0), including symptoms and objective findings from treatment, such as chemotherapy, kinase inhibitors, immunotherapy, experimental agents, radiation or surgery. • Creatinine clearance was increased to ≥60 mL/min except for participants with RCC in which the CrCl cut-off will be ≥30 mL/min. • In Part 1, participants who are HIV, HBV or HCV positive will be excluded. • Participants with a history of myocarditis or congestive heart failure, as well as unstable angina, serious uncontrolled cardiac arrhythmia, or myocardial infarction 6	To further ensure patient safety and to reduce any potential CCI [redacted], possible allergic reaction to antiviral agents and the safety of immunocompromised patients.

Section # and Name	Description of Change	Brief Rationale
	months prior to study entry. • Participants with active ILD/pneumonitis or a history of ILD/pneumonitis requiring treatment with systemic steroids. • Participants whose baseline pulse oximetry is less than 92% "on Room air". • Participants with an LVEF <50% by echocardiogram or MUGA. • Participants with known allergic history to antiviral agents. Duplicate inclusion criterion regarding participants compliance with study procedures was removed.	
Section 1.1., Synopsis; Section 1.3. Schedule of Activities; Section 4.3.4. Late Toxicity Definition and Management; Section 7.1 Discontinuation of Study Intervention; Section 8.3.1. Time Period and Frequency for Collection AE and SAE Information	All participants will be monitored for immune related toxicities for at least 90 days.	Clarified duration of monitoring for possible delayed toxicities from the combination treatment.
Section 4.3.3. DLT Definition; Section 4.3.3.2. Non- Hematologic DLTs;	The DLT criteria were updated to include CRS, myocarditis, as well as any grade ≥ 3 toxicity of any duration affecting vital organs.	To further mitigate risk to patients.
Section 10.3.5. Guidance for Immune-Related Adverse Events	The immune-related adverse events for checkpoint inhibitor table was updated.	This table was previously incomplete.
Section 7.1.3. Cardiac Adverse Events	Added text to indicate that participants with Grade ≥ 3	To reduce the increase risk of recurrent/serious cardiac toxicity.

Section # and Name	Description of Change	Brief Rationale
	myocarditis will be discontinued from the study.	
Section 8.3.8 Adverse Events of Special Interest	CCI [redacted]	To ensure patients safety and to reduce any potential CCI [redacted]
Section 9.3.2. Primary Endpoint(s)/Estimand(s)/ Analysis	The stopping criteria for safety were revised to pause enrollment if early experience uncovers important safety problems.	To mitigate risk to additional patients.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Phase 1 Study of PF-07263689 in Participants with Selected Advanced Solid Tumors

Rationale

PF-07263689 is an oncolytic virus that selectively grows in and kills cancer cells. In addition to its direct cytolytic activity, it has the capability to stimulate innate and adaptive immune reactions against tumor cells. PF-07263689 is also genetically engineered to express an IL-2gv therapeutic payload as a strategy to alter the tumor microenvironment to potentially reverse checkpoint refractoriness and induce killing of uninfected bystander tumor cells. It is delivered systemically for infection of disseminated disease that can stimulate systemic antitumor immune responses in patients with or without prior anti-PDx therapies.

Objectives, Endpoints, and Estimands

Dose Escalation (Part 1):

Objectives	Endpoints	Estimands
Primary:		
• Part 1A: To assess safety and tolerability at increasing dose levels of PF-07263689 in successive cohorts of participants with select locally advanced/metastatic solid tumors, until the MTD is estimated or the MFD dose is reached. • Part 1B: To assess safety and tolerability PF-07263689 in combination with sasanlimab in successive cohorts of participants with select locally advanced/metastatic solid tumors, in order to estimate and select the combination RP2D/schedule.	• First cycle DLTs. • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0, except CRS, which will be graded by ASTCT criteria), timing, seriousness, and relationship to study treatment. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	• The primary estimand for incidence of DLTs in Part 1 is DLT rate estimated based on data from DLT-evaluable participants during the DLT evaluation period, which is the first 28 days after the first dose of study intervention. The attributes of this estimand are provided in Section 9.

Objectives	Endpoints	Estimands
Secondary:		
• To evaluate preliminary antitumor activity.	• ORR, as assessed using the RECIST version 1.1. • Time to event endpoints: DOR, PFS, TTP by RECIST 1.1.	• The key secondary estimand in Part 1 is to evaluate the treatment effect of PF-07263689 assessed by ORR, based on investigator assessment per RECIST 1.1, in the response evaluable analysis population. The attributes of this estimand are provided in Section 9.
• To evaluate the viral load kinetics following first and second dose of PF-07263689. • To collect sasanlimab drug concentration data in Part 1B for evaluation of sasanlimab PK.	• Viral load kinetics parameters of PF-07263689 in blood, including C_{max}, T_{max}, and AUC_{last}. • Trough concentrations of sasanlimab for selected cycles	• NA
• To characterize the viral shedding of PF-07263689.	• Viral titers CCI [redacted] PF-07263689 dose.	• NA
• To evaluate the immunogenicity of PF-07263689 and sasanlimab following monotherapy and combination administration.	• Incidence and titers of ADA against PF-07263689 and sasanlimab. • Incidence and titers of anti-IL2 antibodies.	• NA
CCI [redacted]		
• To assess viral replication and transgene expression of PF-07263689 in both tumors and blood of participants.	• CCI [redacted]	• NA
• To explore the pharmacodynamic effect of PF-07263689 in both tumor and blood of participants.	• CCI [redacted]	• NA

Objectives	Endpoints	Estimands
	CCI [redacted]	
• To explore additional biomarkers associated with clinical response and to elucidate the potential MOA and mechanism of resistance to PF-07263689.	• CCI [redacted]	• NA

Dose Expansion (Part 2)

Objectives	Endpoints	Estimands
Primary:		
• To confirm safety and tolerability of PF-07263689 at the RP2D in combination therapy in participants with selected tumor types. • To evaluate preliminary evidence of antitumor activity of PF-07263689 in combination therapy in participants with selected tumor types.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0, except CRS, which will be graded by ASTCT criteria), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. • ORR as determined by RECIST version 1.1.	• The primary estimand in Part 2 is to evaluate the treatment effect of PF-07263689 in combination with PF-06801591 assessed by the ORR, based on investigator assessment per RECIST 1.1, in the response evaluable analysis population. The attributes of this estimand are provided in Section 9.
Secondary:		
• To further evaluate the viral load kinetics following PF-07263689 administration. • To collect sasanlimab drug concentration data in Part 2 for evaluation of sasanlimab PK.	• Viral load kinetics parameters of PF-07263689 in blood, including C_{max}, T_{max}, and AUC_{last}. • Trough concentrations of sasanlimab for selected cycles	• NA

Objectives	Endpoints	Estimands
• To characterize the viral shedding of PF-07263689.	• Viral titers CCI [redacted] PF-07263689 dose.	• NA
• To further evaluate the immunogenicity of PF-07263689 and sasanlimab.	• Incidence and titers of ADA against PF-07263689 and sasanlimab. • Incidence and titers of anti- IL-2 antibodies.	• NA
• To evaluate preliminary antitumor activity through time to event time points.	• DCR, DOR, PFS, and TTP by RECIST version 1.1.	• NA
• To assess overall survival of participants treated with PF-07263689.	• Overall survival.	• NA
CCI [redacted]		
• To assess viral replication and transgene expression of PF-07263689 in tumors of participants. • To explore the pharmacodynamic effect of PF-07263689 in both tumor and blood. • To explore additional biomarkers associated with clinical response and to elucidate the potential mode of action and mechanism of resistance to PF-07263689.	• CCI [redacted]	• NA

Overall Design

Brief Summary

The proposed Phase 1, open-label, multicenter, multiple dose, dose escalation, and dose expansion study will evaluate the safety, tolerability, viral load kinetics and shedding, PD, and anti-tumor activity of PF-07263689, either alone or in combination with sasanlimab (an investigational anti-PD-1 antibody), in participants with locally advanced or metastatic solid tumors who have exhausted all standard of care therapies available to them. The study consists of 2 parts: Part 1 dose escalation for PF-07263689 monotherapy (Part 1A) and combination with sasanlimab (Part 1B) and Part 2 dose expansion for the combination therapy.

The study will evaluate weekly IV dosing of PF-07263689 for 4 total doses, either as a monotherapy or in combination with sasanlimab administered at 300 mg SC Q4W. In the combination therapy arm, administration of sasanlimab will start concurrently with PF-07263689 and continue beyond the end of the PF-07263689 treatment course until disease progression, intolerable toxicity, withdrawal of consent, or until the study is completed. Alternative PF-07263689 regimens may also be evaluated if supported by emerging data.

For Part 1A, participants will be assessed for radiological response on Day 43 (±5 days). Additional scans may be performed every 6 weeks (±7 days) following Day 43. For Part 1B and Part 2, all participants will be assessed for radiographic response every 6 weeks (±7 days) for up to 6 months followed by every 12 weeks (±7 days) until starting new anticancer therapy or at time of radiographic progression, whichever is earlier. Urine, saliva, and infusion site swabs will be collected to assess viral shedding during treatment and up to 60 days after last dose of PF-07263689 as indicated in the SoA. Any skin lesions that appear will be swabbed to assess for virus shedding. Participants will continue to be followed for survival and long-term safety until death, withdrawal of consent, or the end of the entire study.

Dose Escalation (Part 1)

Participants with any advanced or metastatic solid tumor indications known to have approved therapies using immune checkpoint inhibitors or anti-vascular endothelial growth factor agents are eligible for Part 1. Participants must have exhausted all standard of care therapy for the primary tumor type available to them. Participants with immune checkpoint inhibitor-sensitive tumor types (eg, NSCLC, RCC, UC, melanoma) are expected to be treated in a post-anti-PD-1/PD-L1 (hereafter referred to as anti-PDx) failure setting in Part 1. Tumor types in which anti-PDx antibody therapy is not indicated, such as ovarian and MSS CRC, may be treated in any post-standard of care setting.

Participants will be hospitalized CCI [redacted] PF-07263689 for monitoring. In Part 1A, the CCI [redacted] in each dose escalation cohort will be staggered by

CCI [redacted] mitigate against unexpected immune-related adverse reactions. In Part 1B (PF-07263689 in combination with sasanlimab), the CCI [redacted] of participants of potential overlapping adverse reactions prior to enrolling the remaining participants in Part 1B. There is no formal staggering for subsequent participants in each dose cohort.

Part 1A Monotherapy Dose Escalation: A BLRM along with EWOC will be utilized to guide dose escalation and to determine the monotherapy MTD if MFD is not reached. Dose escalation from the determined CCI [redacted]. After the last participant at the MTD or the MFD has finished all doses of PF-07263689, the monotherapy RP2D will be determined based on all available safety, efficacy, and viral load kinetics and shedding data. During the dose escalation process, intermediate doses may be tested based on BLRM.

Part 1B Combination Dose Escalation: Dose escalation of PF-07263689 in combination with sasanlimab will CCI [redacted] MTD of PF-07263689, CCI [redacted], as guided by the BLRM and EWOC criteria. If started below the monotherapy MTD, PF-07263689 may be escalated to MTD or the MFD in the combination. After completing PF-07263689 dosing, participants will remain on sasanlimab 300 mg SC Q4W until disease progression, intolerable toxicity, withdrawal of consent, or until the study is completed. The combination therapy RP2D will be determined based on all available safety, efficacy, and PK/PD data during the combination dose escalation process.

Dose Expansion (Part 2)

Part 2 will further evaluate PF-07263689 in combination with sasanlimab at the preliminary combination RP2D from Part 1B. Sasanlimab will be administered at 300 mg SC Q4W in tumor-specific arms of post-PDx failure NSCLC (Arm A), post-PDx failure RCC (Arm B), post-PDx failure melanoma (Arm C), and PDx-naïve refractory CRC (Arm D), at approximately 15 to 20 participants per arm. Initially, 3 tumor-specific arms will commence based on preliminary data from Part 1, with the option to subsequently open the fourth arm based on emerging data. For the post-PDx indications, Arms A, B, and C may be limited to participants with primary or secondary resistance to PDx inhibitors after discussion with investigators.

Number of Participants

Approximately 120 participants are expected to be enrolled in the study overall, including approximately 40 DLT evaluable participants for Part 1 and approximately 80 participants (15 to 20 per cohort) for Part 2.

Study Population and Specific Inclusion/Exclusion Criteria

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

- Histological or cytological diagnosis of locally advanced/metastatic solid tumor indications known to have approved therapies using immune checkpoint inhibitors or anti-vascular endothelial growth factor agents.
- Participants should have exhausted all available standard of care therapy or for whom no standard therapy is available for their tumor type. Participants who have actively declined available standard of care therapies are eligible upon documentation of refusal.
- Participants with solid tumors with FDA-approved anti-PDx antibody therapy should have received at least 1 prior anti-PDx therapy.
- Participants with prior anti-PDx must have documentation of primary or secondary resistance to last prior anti-PDx therapy according to Society for Immunotherapy of Cancer Immunotherapy Resistance Taskforce (Kluger et al, 2020) as follows:
    - Primary resistance: drug exposure for at least 6 weeks with best response of PD, or SD for < 6 months (including PD at any time after stopping PDx for any reason unrelated to toxicity if best response while receiving anti-PDx therapy was PD or SD < 6 months).
    - Secondary resistance: drug exposure for at least 6 months with best response of CR or PR or SD ≥ 6 months. If prior PDx was stopped prior to PD, PD must have occurred within 12 weeks after the last dose of PDx.
- Participants entering the study in the expansion cohort have at least 1 measurable lesion as defined by RECIST version 1.1 that has not been previously irradiated.
- Dose Escalation (Part 1A and 1B): Participants with any advanced or metastatic solid tumor indications known to have approved therapies using immune checkpoint inhibitors or anti-vascular endothelial growth factor agents.

- Dose Expansion (Part 2): Participants with the following indications must have exhausted all relevant available standard of care or have documented intolerability to such therapies.

  - NSCLC (≥2L): Participants with NSCLC must have received prior anti-PDx therapies. NSCLC participants with driver mutations must have received prior available targeted therapy(ies) (eg, participant with *BRAF* V600E mutation must have also received BRAF inhibitor with or without MEK inhibitor) or have documented intolerability.

  - RCC (≥2L): Participants with RCC must have received prior anti-PDx therapies. RCC participants must also have received prior anti-VEGF therapy.

  - Melanoma (≥2L): Participants with melanoma must have received prior anti-PDx therapy with or without anti-CTLA-4. Melanoma participants with driver mutations must have received prior available targeted therapies.

  - MSS CRC: Participants with CRC must have received regimen containing combinations of pyridimine analog-containing combination chemotherapy with anti-VEGF (as appropriate), anti-EGFR (as appropriate if RAS wild-type), and/or encorafenib (if *BRAF* V600E).

- Participants must have recently obtained (≤1 year prior to Day 1) archival FFPE tumor tissue sample available. If archival FFPE ≤1 year is not available a fresh tumor sample must be collected at screening. If the archival sample is older than 1 year and a biopsy during screening cannot be performed safely, the investigator must contact the sponsor to discuss eligibility prior to enrollment.

- ECOG PS 0-1.

- Adequate hematologic, renal, and liver functions.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

- Participants with any other active malignancy within 3 years prior to planned first dose, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix, Bowen's disease. Other indolent, secondary cancers may be permitted after discussion with sponsor.

- Participants sustaining recent major surgery defined as a complex procedure performed under regional or general anesthesia with a recovery period of at least 4 weeks prior to planned first dose. Exceptions include:
  - Minor surgical procedures require at least 1-week period prior to planned first dose.
  - Participants having an implantable port placed can enter the study 1 week after the port is placed, assuming no complications have occurred, and the port is functioning normally.
- Known or suspected hypersensitivity to, allergic history of, or prior treatment within the past 10 years on any vaccinia oncolytic, pox virus, or antiviral agents.
- Known or suspected hypersensitivity to any anti-PDx antibody if planned to receive combination therapy with sasanlimab.
- Participants with a history of myocarditis or congestive heart failure (as defined by New York Heart Association (NYHA) Functional Classification III or IV), as well as unstable angina, serious uncontrolled cardiac arrhythmia, or myocardial infarction 6 months prior to study entry.
- Participants with active ILD/pneumonitis or a history of ILD/pneumonitis requiring treatment with systemic steroids.
- Participants with an LVEF <50% by echocardiogram or MUGA.
- Systemic anticancer therapy and chemotherapy within 4 weeks prior to planned first dose (6 weeks for mitomycin C or nitrosoureas). Prior targeted or endocrine therapy require an interval of 2 weeks or 5 half-lives (whichever is shorter) prior to planned first dose. If the last immediate anticancer treatment contained an antibody based agent(s) (approved or investigational), then an interval of 4 weeks or 5 half-lives (whichever is shorter) of the agent(s) prior to receiving the study intervention treatment is required. With last prior anti-PDx therapy, the washout period may be extended based on emerging clinical data.
- Recent transfusion of RBCs or platelets within 4 weeks prior may be exclusionary. Discuss with the sponsor if participant had recent transfusion(s).
- Participants requiring chronic systemic immunosuppressants.
- History of Grade ≥3 immune mediated AE (including AST/ALT elevations that were considered drug-related and cytokine release syndrome) that was considered related to prior immune modulatory therapy (eg, immune checkpoint inhibitors, co-stimulatory agents, etc.) and required immunosuppressive therapy.

- Known symptomatic brain metastases requiring steroids. Participants with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable for 3 months (requires MRI confirmation).

- History of or ongoing severe inflammatory skin condition or severe eczema (as determined by the investigator) having required medical treatment.

- Any prior or planned organ transplant.

- Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis or melena in the past 6 months.

- Presence of any open, active wound requiring treatment for proper healing.

Intervention Groups and Duration

Participants in Part 1A will receive weekly IV dosing of PF-07263689 for 4 weeks. Participants will be in the study for approximately 130 days, including the Screening (≤28 days), Treatment (43 days), and Follow-up (30, 45, 60 and 90 days) Periods. Additionally, survival follow-up will occur by telephone Q12W (±7 days).

Participants in Part 1B and Part 2 will receive weekly IV dosing of PF-07263689 for 4 weeks in combination with 300 mg sasanlimab SC Q4W. In general, participants will be in the study for approximately 130 days or longer depending if the participants continue to benefit from PF-07263689 and sasanlimab. Treatment with study intervention will continue until either disease progression, unacceptable toxicity, participant refusal, or whichever is earliest, unless the investigator and medical monitor agree to treatment beyond disease progression based on individual benefit/risk assessments or agree to discontinue treatment or the study is terminated. Additional, survival follow-up will occur by telephone Q12W (±7 days).

No dose delay or dose reductions of PF-07263689 are allowed. Participants may only miss or skip one dose of PF-07263689. No dose reductions of sasanlimab are allowed, but doses of sasanlimab may be skipped or delayed for a cycle based on persisting toxicity.

The end of the study will be the date of the last visit of the last participant or 2 years after the last participant receives their first dose (whichever occurs first). The study may also be terminated at any time at the discretion of the sponsor. Any additional treatment beyond 2 years shall be discussed and approved by the sponsor.

A participant is considered to have completed the study if he/she has completed all phases of the study including the EOT visit.

Data Monitoring Committee or Other Independent Oversight Committee: No

This study will not use a DMC. However, a DLRM will convene for dose escalation decisions. The actual dose selected at each dose decision may be at or below the statistical model's (ie, BLRM) recommended dose as determined by the members of the DLRM after considering all safety information. The review team will be composed of investigator(s), Pfizer GCL, Pfizer Study Clinician, and Pfizer Study Manager. Additional members may be added as needed (eg, Clinical Pharmacologist Lead, Translational Oncology, Safety Risk Lead or designee, and Pfizer Biostatistics representative). A quorum, defined as >50% of the participating investigators or their qualified designee (ie, subinvestigator or research nurse or study coordinator possessing hard copy documentation [eg, email] of the investigator's vote regarding the dose level review), must be in attendance for the DLRM. Participating investigators are defined as those whose sites have been initiated for screening and enrollment of patients. The DLRM will be rescheduled if a quorum is not reached.

Statistical Methods

For Part 1, determination of MTD will be performed using the DLT evaluable set, if MTD is achieved prior to the maximum feasible dose.

The dose escalation in the Part 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07263689 using a 2-parameter BLRM (Part 1A) or for the combination of PF-07263689 and sasanlimab using a 5-parameter BLRM (Part 1B). Weakly informative prior distributions based on preclinical/expert opinion information will be chosen for the logistic parameters in Part 1A; the observed DLT data in Part 1A and DLT data of sasanlimab will be used to form prior distribution for the BLRM in Part 1B. Dosing decisions are guided by the EWOC principle (Rogatko 2007). CCI [redacted], which satisfies the EWOC criterion.

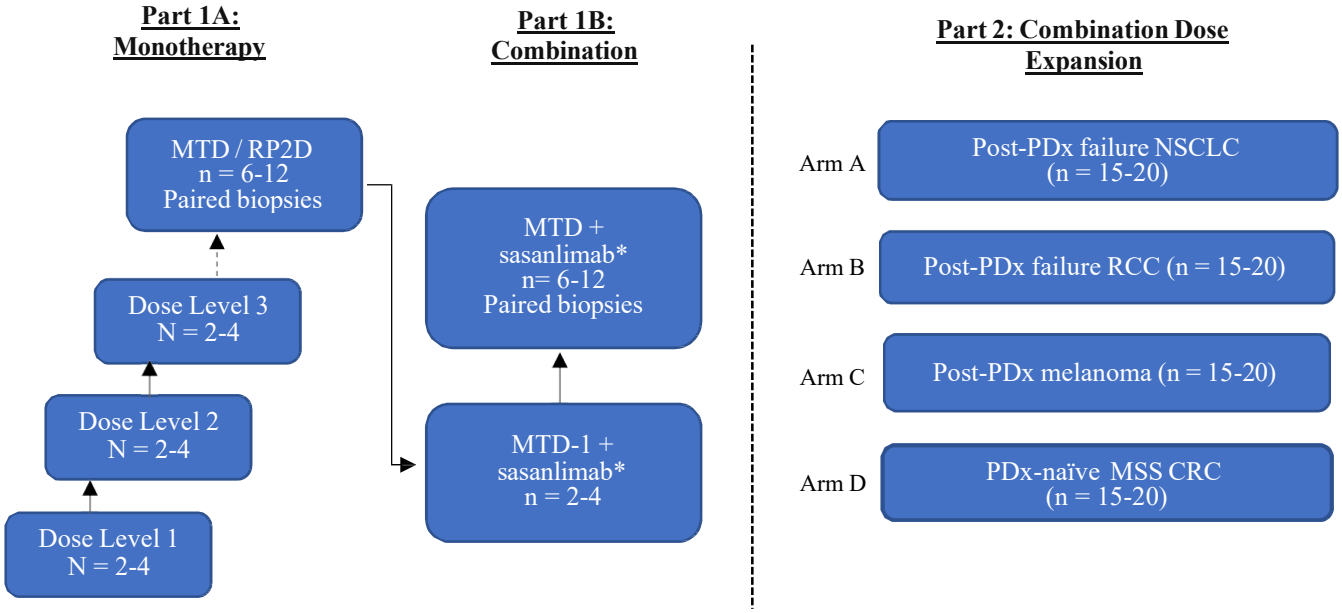
For Part 2, ORR will be a primary endpoint, along with safety and tolerability assessment. ORR evaluation, as well as other secondary efficacy endpoints.

1.2. Schema

Part 2: Dose Expansion

- Indications: Any advanced/metastatic solid tumor known to have approved therapies using immune checkpoint inhibitors or anti-VEGF agents
- Primary Objective: Safety, MTD (Part 1A)/RP2D (Part 1B)

- Indications: Post-PDx failure NSCLC, post-PDx RCC, post-PDx melanoma; PDX-naïve MSS CRC tumor-specific arms will open based on emerging data
- Primary Objective: Safety, Efficacy



PF-07263689 regimen: IV once weekly for 4 doses (Q1W x 4)
PF-07263689 dose range: CCI [redacted]
Sasanlimab: 300mg SC Q4W; Each SC cycle = 28 days
Paired biopsies: In Part 1, paired de novo tumor biopsy samples pre-treatment and on-treatment (C1D8 ± 1 day) will be required from 5 participants each in Part 1 at or below MTD and Part 1B at or below MTD + sasanlimab. In Part 2, paired de novo tumor biopsy samples will be collected from 5-8 participants in each arm unless biopsy samples cannot be obtained safely.
* The starting dose of PF-07263689 for Part 1B will be at or one dose lower than the MTD from Part 1A.

Part 1A, dosing of initial participants CCI [redacted] **against unexpected adverse drug reaction as follows:** Each dose level: CCI [redacted]

Part 1B, dosing of the CCI [redacted] **against possible overlapping adverse drug reaction as follows prior to enrolling the remaining participants in Part 1B.**

Part 2 Dose Expansion: Initially, 3 tumor-specific arms will commence based on preliminary data from Part 1, with the option to open the fourth arm based on emerging data. For the post-PDx indications, Arms A, B, and C may be limited to participants with primary or secondary resistance after discussion with investigators.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Schedule of Assessments – Monotherapy (Part 1A)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	**SCREENING**	**TREATMENT**											**NOTES**
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±1d**	**±1d**	**±5d**	**±5d**	***±4h is relative to the most current dosing**
General Assessments													
Informed Consent	**X**												• Informed consent must be obtained prior to undergoing any study-specific procedures.
Registration	**X**												• Participant enrollment number and dose level allocation assigned by Pfizer Inc.
Demographics and Medical History	**X**												• Includes tumor histology and other medical history.
Complete Physical Examination	**X**												• Includes height only at screening. • Includes skin assessment.
Brief Physical Examination		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• Daily while hospitalized. • Includes skin assessments for any lesions.
Overall Skin Monitoring	**X**	**X**				**X**			**X**	**X**			• Participants should be monitored not only for infusion site reactions but also any skin

Table 1. Schedule of Assessments – Monotherapy (Part 1A)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	**SCREENING**	**TREATMENT**											**NOTES**
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±1d**	**±1d**	**±5d**	**±5d**	***±4h is relative to the most current dosing**
													lesions in whole body following PF-07263689 administration. • Refer to Section 8.2.3.
ECOG Performance Status	**X**	**X**				**X**			**X**	**X**	**X**		
Weight	**X**					**X**			**X**		**X**		
Vital Signs	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• Measure vitals prior to the PF-07263689 treatment. • Daily while hospitalized; collect temperature (oral preferred), pulse rate, BP every 6 hrs (±10 min) and as needed during inpatient monitoring.
Pulse Oximetry (SpO2)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Triplicate 12-lead ECGs	**X**	**Refer to** Table 4.Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)										**X**	• Perform prior to dosing. • Additional triplicate ECGs may be performed as clinically indicated. • See Section 8.2.5.
Echocardiogram or MUGA	**X**	Assess as baseline. Additional testing as clinically indicated.											• Echocardiogram or MUGA; imaging methods must be consistent throughout the study for individual participants.
AE Assessments	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• Document AEs as described in Section 8.3 and Appendix 3.

Table 1. Schedule of Assessments – Monotherapy (Part 1A)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	**SCREENING**	**TREATMENT**											**NOTES**
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±1d**	**±1d**	**±5d**	**±5d**	***±4h is relative to the most current dosing**
													• SAEs identified during LTFU will be reported to Pfizer Safety only if considered reasonably related to study intervention.
Concomitant Treatment(s)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• All concomitant treatment and Non-Drug Supportive Interventions should be recorded on the CRF through the treatment period. Only subsequent anti-cancer therapy initiated after end of study treatment(s) will be reported at the follow-up visits.
Laboratory Assessments													
Hematology	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Blood Chemistry	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Coagulation	**X**	**X**				**X**			**X**	**X**	**X**	**X**	• PT or INR and PTT/aPTT.
Endocrinology	**X**					**X**					**X**	**X**	• TSH, ACTH, Free T4.
Cardiac biomarkers	**X**	**X**				**X**			**X**	**X**	**X**	**X**	• CPK and troponin
Hepatitis Serology	**X**												• HbsAg, anti-HCV antibody • If anti-HCV Ab test is positive, perform HCV RNA test.

Table 1. Schedule of Assessments – Monotherapy (Part 1A)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	**SCREENING**	**TREATMENT**											**NOTES**
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h ***	**±4h ***	**±1d**	**±1d**	**±5d**	**±5d**	***±4h is relative to the most current dosing**
Tumor Markers	**X**										**X**		• CA125 for OvCA; CEA for CRC; CA 15-3 for BRCA; PSA for prostate cancer.
Pregnancy Testing/ Contraception Check	**X**	**X**											• See Section 5.3.1 and Section 8.2.8.
Urinalysis	**X**	**X**											• No need to repeat on Day 1 if baseline assessment performed within 7 days of Day 1 • Dipstick is acceptable at minimum at screening and EOT. • Samples analyzed locally.
Viral Shedding Assessments													
Whole Blood Sample for Viral Load Kinetics of PF-07263689		**Refer to** Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)											
Injection Site Swab for Viral Shedding		**Refer to** Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)											
Saliva and Urine Sample for Viral Shedding		**Refer to** Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)											
Immunogenicity Assessments													
Blood for Serum Sample for PF-07263689 Immunogenicity (anti-vaccinia virus neutralizing antibody, anti-IL-2 antibodies)		**Refer to** Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)											

Table 1. Schedule of Assessments – Monotherapy (Part 1A)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	**SCREENING**	**TREATMENT**											**NOTES**
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±1d**	**±1d**	**±5d**	**±5d**	***±4h is relative to the most current dosing**
Pharmacodynamic Assessments													
Blood for Germline DNA Sequencing		**Refer to** Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)											
Blood for pSTAT5		**Refer to** Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)											
Blood for Serum IL-2gv Evaluation (Serum)		**Refer to** Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)											
Treatment Administration													
PF-07263689 Administration		**X**				**X**			**X**	**X**			• Participants should remain at the investigational site for observation and labs for at least 4-hour postdose on D15 and D22. Additional monitoring may be required based on individual toxicities.
Inpatient Monitoring (Hospitalization)		**X**	**X**	**X**	**X**	**X**	**X**	**X**					• Participants will be admitted for inpatient monitoring (per local standard of practice) CCI [redacted] • Hospitalization period may be extended if the participant experiences abnormal laboratory findings or ongoing AEs that require further hospitalization.

Table 1. Schedule of Assessments – Monotherapy (Part 1A)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	**SCREENING**	**TREATMENT**											**NOTES**
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h ***	**±4h ***	**±1d**	**±1d**	**±5d**	**±5d**	***±4h is relative to the most current dosing**
Clinical & Radiographic Tumor/Response Assessments													
CT or MRI Scans of Chest, Abdomen, Pelvis, Any Clinically Indicated Sites of Disease, and of Bone Lesions; Clinical Evaluation of Superficial Disease	**X**											**X** D43 then Q6W (±7 days)	• If allergic to contrast agents for imaging, a non-contrast CT of the chest with contrast enhanced abdominal and pelvic MRI can be used • Brain and/or bone scans to be performed at screening if disease is suspected and during study as appropriate. • Q6W until disease progression. • Confirmatory scan may be done 4 weeks later if needed.
Optional Photographs of Skin Pox Lesions		**ANYTIME**											• See Section 8.2.11.
Archival Tumor Tissue	**X**												• See Section 8.7.1.
De Novo (Fresh) Tumor Biopsies	**X**					**X**							• See Section 8.7.1.
Reporting Exposure to PF-07263689													
Exposure of Participant's Close Contact		**ANYTIME**											• See Section 5.3.2.
Exposure of Subject's Healthcare Provider		**ANYTIME**											• See Section 5.3.2.

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
General Assessments												
Informed Consent	**X**											• Informed consent must be obtained prior to undergoing any study-specific procedures.
Registration	**X**											• Participant enrollment number and dose level allocation assigned by Pfizer Inc.
Demographics and Medical History	**X**											• Includes tumor histology and other medical history.
Complete Physical Examination	**X**											• Includes height at screening • Includes skin assessments.
Brief Physical Examination		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• Daily while hospitalized. • Includes skin assessments for any lesions.
Overall Skin Monitoring	**X**	**X**				**X**			**X**	**X**	**X**	• Participants should be monitored not only for infusion site reactions but also any skin lesions in whole body following PF-07268689 administration (Parts 1B, and 2), as well as injection site reactions following administration of sasanlimab (in Parts 1B and 2). • Refer to Section 8.2.3.
ECOG Performance Status	**X**	**X**				**X**			**X**	**X**	**X**	

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
Weight	**X**					**X**			**X**		**X**	
Vital Signs	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• Measure vitals prior to study drug(s) administration on day of dosing. • Daily while hospitalized; collect temperature (oral preferred), pulse rate, BP every 6 hrs (± 10 min) and as needed during inpatient monitoring.
Pulse Oximetry (SpO2)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Triplicate 12-lead ECGs	**X**	**Refer to** Table 5. PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)**.**									**Every other cycle beginning with Cycle 2**	• Perform prior to dosing. • Additional triplicate ECGs may be performed as clinically indicated. • See Section 8.2.5.
Echocardiogram or MUGA	**X**	**Assess at baseline. Additional testing as clinically indicated.**										• Echocardiogram or MUGA; imaging method must be consistent throughout the study for individual participants.
AE Assessments		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• Document AEs as described in Section 8.3 and Appendix 3. • SAEs identified during LTFU will be reported to Pfizer Safety only if considered reasonably related to study intervention.

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
Concomitant Treatment(s)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	• All concomitant treatment and Non-Drug Supportive Interventions should be recorded on the CRF through the treatment period. Only subsequent anti-cancer therapy initiated after end of study treatment(s) will be reported at the follow-up visits.
Laboratory Assessments												
Hematology	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Blood Chemistry	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Coagulation	**X**	**X**				**X**			**X**	**X**	**X**	• PT or INR and PTT/aPTT.
Endocrinology	**X**					**X**			**X**	**X**	**X**	• TSH, ACTH, Free T4. • Every cycle for the first 3 cycles followed by every 4 cycles starting at Cycle 4 Day 1.
Cardiac Biomarker	**X**	**X**				**X**			**X**	**X**	**X**	• CPK and troponin
Hepatitis Serology	**X**											• HbsAg, anti-HCV antibody. • If anti-HCV antibody test is positive, HCV RNA test must be performed.

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
CCI [redacted]	[redacted]										[redacted]	[redacted]
Pregnancy Testing/ Contraception Check	**X**	**X**										• See Section 5.3.1 and Section 8.2.8.
Urinalysis	**X**	**X**									**X**	• No need to repeat on Day 1 if baseline assessment performed within 7 days prior to Day 1. • Dipstick is acceptable at minimum at screening and EOT. • Samples will be analyzed locally.
Pharmacokinetics and Viral Shedding Assessments												
Whole Blood Sample for Viral Load Kinetics of PF-07263689		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										
Blood Serum PK Sample for Sasanlimab		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										
Injection Site Swab for Viral Shedding		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										
Saliva and Urine Sample for Viral Shedding[c]		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
Immunogenicity Assessments												
Blood Serum Sample for Sasanlimab Immunogenicity		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										
Blood Serum Sample for PF-07263689 Immunogenicity Anti-VV Neutralizing Antibody, Anti-IL-2 Antibodies		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										
Pharmacodynamic Assessments												
Blood for Germline DNA Sequencing		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										
Blood for Serum IL-2gv Evaluation (Serum)		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										
Immune Cell Profiling and pSTAT5 (Flow Cytometry)		**Refer to** Table 5.PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)										
Treatment Administration												

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
PF-07263689 Administration		**X**				**X**			**X**	**X**		• Participants should remain at the investigational site for observation and labs for at least 4-hour post dose for Day 15 and Day 22. • Additional monitoring may be required based on individual toxicities.
Sasanlimab Administration		**X**									**X**	• Must be administered after PF-07263689 on Cycle 1 Day 1.
Inpatient Monitoring (Hospitalization)		**X**	**X**	**X**	**X**	**X**	**X**	**X**				• Part 1B participants will be admitted for inpatient monitoring (per local standard of practice) C [redacted] CI • Length of hospitalization will be re-assessed based on safety data prior to starting Part 2. • Hospitalization period may be extended if the participant experiences abnormal laboratory findings or ongoing AEs that require further hospitalization.
Clinical & Radiographic Tumor/Response Assessments												

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
CT or MRI Scans of Chest, Abdomen, Pelvis, Any Clinically Indicated Sites of Disease, and of Bone Lesions; Clinical Evaluation of Superficial Disease	**X**	**Imaging visits will occur Q6W (±7 days) through Week 24 followed by Q12W (±7 days) until starting new anticancer therapy or at time of radiographic progression, whichever is earlier.**										• If allergic to contrast agents for imaging, a non-contrast computed tomography of the chest with contrast enhanced abdominal and pelvic MRI can be used. • Brain and/or bone scans to be performed at screening if disease is suspected and during study as appropriate to follow disease. • Confirmatory scan may be done 4 weeks later as needed. For participants who discontinue treatment before confirmed disease progression, tumor imaging will continue per standard of care until progression of disease.
Optional Photographs of Skin Pox Lesions		**ANYTIME**										• See Section 8.2.11.
Archival Tumor Tissue	**X**											• An archival sample collected ≤1 year prior to study start should be submitted per laboratory manual. • If archival FFPE ≤1 yr is not available a fresh tumor sample must be collected at screening. • If the archival sample is >1 yr and a biopsy during screening cannot

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
												be performed safely, the investigator must contact the sponsor to discuss eligibility prior to enrollment.
De Novo (Fresh) Tumor Biopsies	**X**					**X**						• Request 5 pre-/on-treatment fresh biopsy pairs at or below one dose level from MTD in both Part 1A monotherapy and Part 1B in combination with sasanlimab cohorts. • Request 5-8 pre-/on-treatment fresh biopsy pairs in each arm of Part 2 dose expansion study unless biopsy cannot be performed safely. • An archival sample collected prior to study start may not be substituted for the mandatory pre-treatment paired biopsy in Part 1 and Part 2. • Participants who provide fresh pre- and on-treatment tumor biopsy pairs may also provide archival samples.
Reporting Exposure to PF-07263689												

Table 2. Schedule of Assessments – Combination Therapy (Part 1B and Part 2)

Visit Identifier Abbreviations used in this table may be found in Appendix 12.		**TREATMENT**										**NOTES**
	SCREENING	**Cycle 1 (1 cycle = 28 days)**									**Cycle ≥2**	
Days	**≤28**	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**15**	**22**	**1**	• **See Table 3 for EOT and follow-up visit schedules**
Visit Window		**0**	**±4h***	**±4h***	**±4h***	**±1d**	**±4h***	**±4h***	**±2d**	**±24h**	**±2 day**	***±4h is relative to the most current dosing**
Exposure of Participant's Close Contact		**ANYTIME**										• See Section 5.3.2.
Exposure of Subject's Healthcare Provider		**ANYTIME**										• See Section 5.3.2.

Table 3. Schedule of Activities: EOT, Post-Treatment, and Survival Follow-up (Parts 1A, 1B, and 2)

	EOT[1]/ Withdrawal	30 Day Follow-up[2]	45 Day Follow-up[3]	60 Day Follow-up[4]	90 Day Follow-up[5]	Survival Follow-up[6]	Notes For detailed notes refer to main schedule of assessment
		28 days after last dose				Every 3 months after 30 Day Follow-up	
Visit Window (days)		± 7 days	± 2 days	± 7 days	± 7 days	± 7 days	
Physical Examination							
Complete Physical Examination	X						
Brief Physical Examination		X					
ECOG Performance Status	X	X					
Vital Signs	X	X					
ECG	X						
Pulse Oximetry	X						
Echocardiogram or MUGA	X						• Assessment of LVEF using echocardiogram or MUGA.
Blood draw for Laboratory Assessment							
Hematology	X	X					
Blood Chemistry	X	X					
Coagulation	X	X					• PT or INR, PTT/aPTT.
Endocrinology	X	X					• TSH, ACTH, Free T4.
Cardiac Biomarkers	X	X					• CPK and troponin
Tumor Markers	X						• After EOT, continue to report standard or care tumor marker assessments until start of new therapy or EOS. • CA125 for OvCA; CEA for CRC; CA15-3 for BRCA; PSA for prostate cancer.
Pregnancy Test/Contraception Check		X					• See Section 5.3.1 and Section 8.2.8.
Urinalysis	X	X					• Dipstick is acceptable at minimum.
Tumor Response Assessment							

Table 3. Schedule of Activities: EOT, Post-Treatment, and Survival Follow-up (Parts 1A, 1B, and 2)

	EOT[1]/ Withdrawal	30 Day Follow-up[2]	45 Day Follow-up[3]	60 Day Follow-up[4]	90 Day Follow-up[5]	Survival Follow-up[6]	Notes For detailed notes refer to main schedule of assessment
		28 days after last dose				Every 3 months after 30 Day Follow-up	
Visit Window (days)		± 7 days	± 2 days	± 7 days	± 7 days	± 7 days	
CT or MRI Scans of Chest, Abdomen, Pelvis, Any Clinically Indicated Sites of Disease, and of Bone Lesions; Clinical Evaluation of Superficial Disease	X					X	• Tumor assessment should be repeated at the EOT visit if >6 weeks have passed since the last evaluation. • After EOT, continue to report standard of care imaging until start of new therapy or EOS.
Subsequent Anti-cancer Therapy		X				X	
AE Assessment	X	X	X	X	X	X	• All AEs and SAEs must be collected until a minimum of 90 days after the last administration of the study intervention. • The SAEs identified during long-term follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study intervention.
Whole Blood Sample for Viral Load Kinetics of PF-07263689	X	X					
Blood for Serum Sample for PF-07263689 Immunogenicity (anti-VV neutralizing antibody, anti-IL-2 antibodies)	X	X (if suspected ADA-related AE)		X (if suspected ADA-related AE)			
Injection Site Swab for Viral Shedding	X	X					
Saliva and Urine Sample for Viral Shedding	X	X	X	X			

Table 3. Schedule of Activities: EOT, Post-Treatment, and Survival Follow-up (Parts 1A, 1B, and 2)

	EOT[1]/ Withdrawal	30 Day Follow-up[2]	45 Day Follow-up[3]	60 Day Follow-up[4]	90 Day Follow-up[5]	Survival Follow-up[6]	Notes For detailed notes refer to main schedule of assessment
		28 days after last dose				Every 3 months after 30 Day Follow-up	
Visit Window (days)		± 7 days	± 2 days	± 7 days	± 7 days	± 7 days	

1. **EOT/Withdrawal:** Visit to be performed as soon as possible but no later than 28 days from the last dose of study intervention and prior to initiation of any new anticancer therapy. Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
2. **30 Day Follow-up:** At least 28 calendar days, and no more than 35 calendar days, after discontinuation of study intervention, participants will return to undergo the procedures listed above. If EOT occurs at the same time of the 30 Day Follow-up, then the 30 Day Follow-up do not need to be completed.
3. **45 Day Follow-up:** 45 days after last dose of PF-07263689.
4. **60-Day Follow-up**: 60 days after last dose of PF-07263689.
5. **90-Day Follow-up:** 90 days after last dose of PF-07263689.
6. **Survival Follow-up:** Subsequent to the 1-month follow-up visit, participants survival status will be collected by telephone every 12 weeks (±7 days) to obtain information on subsequent anticancer treatment and overall survival until the end of the study. If the participant is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call. Any standard of care tumor response assessments including CT/MRI imaging and/or tumor-specific markers (ie, CEA and CA125) obtained between EOT and subsequent anti-cancer therapy will also be collected.

Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)

Visit Identifier	Screen	Day 1					Day 2	Day 3	Day 4	Day 8					Day 9	Day 10	Day 15		Day 22[e] (±2 days)	
		Pre-dose	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	72h* (±4h)	Pre-dose	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	Pre-dose	4h*	Pre-dose	4h*
Whole Blood Sample for Viral Load Kinetics of PF-07263689[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for Serum Sample for PF-07263689 Immunogenicity (anti-Vaccinia Virus Neutralizing antibody, anti-IL-2 Antibodies[b]		X								X							X		X	
Injection Site Swab for Viral Shedding				X						X							X		X	
Saliva and Urine Sample for Viral Shedding[c]		X			X		X	X	X	X			X		X	X	X		X	
CCI																				
Blood for Cytokines Evaluation (Serum)		X				X	X	X	X	X				X	X	X	X		X	

Table 4. Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments (Part 1A)

Visit Identifier	Screen	Day 1					Day 2	Day 3	Day 4	Day 8					Day 9	Day 10	Day 15		Day 22[e] (±2 days)	
		Pre-dose	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	72h* (±4h)	Pre-dose	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	Pre-dose	4h*	Pre-dose	4h*
Triplicate 12-Lead ECG[f]	X	X		X			X			X		X			X		X		X	

* All sampling times are relative to the most recent dose. Samples collected on day of dosing (ie, on Day 1, Day 8, Day 15, and Day 22) will be collected ±10% of nominal time. Therefore, 0.5, 1, 4, and 8 hr samples will have a ±3, ±6, ±24, ±48 minutes collection window, respectively. On all other days, sampling windows are indicated ie, 24 hr ± 4hrs.

a. Blood samples for determination of viral genomes: Blood samples will be collectedly at each time point for determination of viral load kinetics after PF-07263689 administration.

b. Blood samples for anti-vaccinia virus neutralizing antibody and anti-IL2 IgG measurement: Blood samples will be collected at each time point for neutralizing antibody and anti-IL2 IgG assessment.

c. Samples for viral shedding assessment: Indicated samples will be collected at each time point for assessment of viral shedding. Samples will be collected 60 days post last dose of PF-07263689 (see Table 3).

C [redacted]
C

Ie. Refer to Table 3 for EOT and follow-up visit schedules.

f. Screening ECGs should be performed < 14 days from Day 1. When ECGs are obtained with PK sampling, ECGs must be completed before the PK samples is taken.

Table 5. PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)

Visit Identifier	Screen	Day 1					Day 2	Day 3	Day 4	Day 8					Day 9	Day 10	Day 15		Day 22		Cycle ≥ 2[h]
		Pre-dose*	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	72h* (± 4h)	Pre-dose*	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	Pre-dose*	4h*	Pre-dose*	4h*	(±3 days)
Whole Blood Sample for Viral Load Kinetics of PF-07263689[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Serum PK Sample for Sasanlimab[d]		X								X							X		X		X
Blood Serum Sample for Sasanlimab Immunogenicity		X																	X		X[f]
Blood Serum Sample for PF-07263689 Immunogenicity Anti-VV Neutralizing Antibody, Anti-IL-2 Antibodies[b]		X								X							X		X		
Injection Site Swab for Viral Shedding				X						X							X		X		
Saliva and Urine Sample for Viral Shedding[c]		X			X		X	X	X	X			X		X	X	X		X		
CCI [redacted]																					

Table 5. PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)

Visit Identifier	Screen	Day 1					Day 2	Day 3	Day 4	Day 8					Day 9	Day 10	Day 15		Day 22		Cycle ≥ 2[h]
		Pre-dose*	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	72h* (± 4h)	Pre-dose*	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	Pre-dose*	4h*	Pre-dose*	4h*	(±3 days)
CCI [redacted]																					
Triplicate 12-lead ECG[i]	X	X		X			X			X		X			X		X		X		

Table 5. PK, Viral Shedding, ECG, Immunogenicity, and Biomarker Schedule of Assessments: PF-07263689 Combination with Sasanlimab (Part 1B and Part 2)

Visit Identifier	Screen	Day 1					Day 2	Day 3	Day 4	Day 8					Day 9	Day 10	Day 15		Day 22		Cycle ≥ 2[h]
		Pre-dose*	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	72h* (± 4h)	Pre-dose*	0.5h*	1h*	4h*	8h*	24h* (±4h)	48h* (±4h)	Pre-dose*	4h*	Pre-dose*	4h*	(±3 days)

* All sampling times are related to start of dosing. Samples collected on day of dosing (ie, on Day 1, Day 8, Day 15, and Day 22) will be collected ±10% of nominal time. Therefore, 0.5, 1, 4, and 8 hr samples will have a ±3, ±6, ±24, ±48 minutes collection window, respectively. On all other days, sampling windows are indicated ie, 24 hr ± 4hrs.

a. Blood samples for determination of viral genomes: Blood samples will be collectedly at each time point for determination of viral load kinetics after PF-07263689 administration.
b. Blood for serum samples for anti-vaccinia virus neutralizing antibody and anti-IL2 measurement: Blood samples will be collected at each time point for anti-VV neutralizing antibody assessment.
c. Samples for viral shedding assessment: Indicated samples will be collected at each time point for assessment of viral shedding. Samples will be collected 60 days post last dose of PF-07263689 (see Table 3).
d. Blood sample for determination of sasanlimab concentration: Blood samples will be collected at each time point for PK analysis of sasanlimab.
e. Blood sample for sasanlimab immunogenicity: Blood samples will be collected at each time point for ADA/NAb assessment.
f. Blood sample for sasanlimab immunogenicity to be collected every 3rd cycle starting with Cycle 5, as well as 30 days post last dose of sasanlimab.
C [redacted]
C .
h. Refer to Table 3 for EOT and follow-up visit schedules.
i. Screening ECGs should be performed < 14 days from Day 1. When ECGs are obtained at the same time as a PK sample, the ECGs must be completed before the PK samples is taken.

2. INTRODUCTION

PF-07263689 is a genetically engineered oncolytic vaccinia virus being developed for the treatment of solid tumors following IV administration.

2.1. Study Rationale

The purpose of this FIH study is to evaluate the safety, tolerability, viral load kinetics and shedding, and PD of repeat IV dosing of PF-07263689 as a monotherapy (Part 1A) and in combination with sasanlimab, an investigational anti-PD-1 antibody (Part 1B), in participants with locally advanced or metastatic solid tumors who have exhausted all standard of care therapy available to them. Participants with any advanced or metastatic solid tumor indications known to have approved therapies using immune checkpoint inhibitors or anti-vascular endothelial growth factor agents are eligible for Part 1, including but not limited to NSCLC, RCC, UC, melanoma, sarcoma, ovarian, and CRC. Part 2 is to evaluate the efficacy and safety of PF-07263689 as combination therapy with sasanlimab in selected PDx-naïve or refractory solid tumors.

2.2. Background

2.2.1. Oncolytic Viruses

OVs have been widely investigated as cancer immunotherapy platforms and are represented by a diverse group of DNA and RNA viruses. Almost all OVs have the properties of being replication-competent, selectively replicating in tumor cells while sparing normal cells, causing tumor-selective cell killing (oncolysis) and tumor debulking, acting as in situ vaccines, and inducing both innate and adaptive anti-tumor immune responses (Lawler et al, 2017; Russell et al, 2012). Most OVs have been genetically engineered for additional tumor selectivity, and a common strategy used is to alter or delete viral genes (eg, viral TK^-) to enhance safety by greatly limiting replication in normal cells by taking advantage of high endogenous TK levels in tumors compared with normal resting cells (Twumasi-Boateng et al, 2018). In addition to harnessing the oncolytic efficacy of OVs, there are considerable efforts and opportunities to “arm” these viruses with transgenes that work to counter the immunosuppressive TME allowing for immunogenic tumor cell death, DC recruitment and activation, and tumor cell killing mediated by infiltrating tumor antigen specific T cells (Bommareddy et al, 2018; Kirn et al, 2009).

Vaccinia viruses are double-stranded DNA viruses and an attractive OV platform because of the proven potential for systemic delivery, rapid replication in permissive tissues, broad tumor tropism, and robust tumor cell lysis. Additionally, the large DNA genome enables insertion of foreign transgenes, including immunomodulatory transgenes, under the control of natural or synthetic promoters to better control [redacted]. An example of this approach using vaccinia virus is JX-594 or pexastimogene devacirepvec (Pexa-Vec), a TK^- oncolytic vaccinia virus derived from the Wyeth strain containing GM-CSF and LacZ transgene insertions. JX-594 has been evaluated both as an IT injection in HCC (Park et al 2008; Heo et al 2013) as well as via IV dosing to achieve oncolysis and antitumor responses in less accessible primary and/or more widespread metastatic tumors, such as refractory CRC

(Brietbach et al 2011; Park et al. 2015). JX-594 has also been evaluated in combination with sorafenib as well as ongoing trials with immune checkpoint inhibitors.

2.2.2. PF-07263689

PF-07263689 is an oncolytic vaccinia virus based on VV-Cop that has been genetically modified for safety and anti-tumor efficacy following IV administration. Unmodified, wild-type VV-Cop was used as a vaccine strain during the smallpox eradication campaign in Europe (Kretzschmar et al, 2006). It was selected for its superior oncolytic activity in human tumor cell lines compared to other strains (eg, Wyeth, WR; Ricordel et al, 2018). [redacted] A foreign transgene encoding a variant of herpes simplex virus type 1 TK (HSV TK.007, Preuss et al, 2010) [redacted] PF-07263689 sensitive to readily available antiviral drugs (eg, GCV, ACV) to enable treatment of spontaneous skin lesions that can occur in some patients following vaccinia virus treatment (Breitbach et al, 2015; Kung et al, 2015) with topical antivirals, thus reducing the risk of secondary transmission of infectious virus. A third genetic modification is a mutation in the viral A34R gene to encode a K151E variant that enhances release of virus from infected cells (Blasco et al, 1993) in the early stages of virus infection, thus expediting progeny virus spread and enhancing IV efficacy. [redacted] designed to enhance immune-mediated tumor cell killing by activation of CD8+ T cells and NK cells, while avoiding the activation and immunosuppressive effects of Treg cells and the systemic toxicities associated with clinical use of recombinant wild-type IL-2.

IL-2 is a potent cytokine and an approved immunotherapy for the treatment of metastatic RCC and metastatic melanoma (Proleukin® USPI). While very effective, the high doses of recombinant IL-2 required to achieve antitumor efficacy are associated with significant but reversible systemic toxicities (eg, capillary leak syndrome) as a result of IL2Rα receptor binding on vascular endothelial cells (Rosenberg, 2014). Researchers have sought to develop IL-2 variants with modified receptor binding properties in an effort to avoid these IL2Rα-mediated toxicities and bias activity of the IL-2 variant towards immunostimulatory activity (via the IL2Rβ/ɣ present on CD8+ T cells and NK cells) and away from immunosuppressive activity (via the α/β/ɣ receptor complex present on Treg cells). Examples of such IL-2 variants that have advanced to Phase 2/3 clinical studies and shown promising anti-tumor activity and safety in multiple indications include NKTR-214 (Bentebibel et al, 2019) and FAP-IL-2v (Soerensen et al, 2018). [redacted]

2.2.3. Sasanlimab

Sasanlimab is a humanized, hinge region-stabilized IgG4 monoclonal antibody, with antagonistic activities specific for human PD-1. PD-1 is a member of the CD-28 superfamily that is mainly, but not exclusively, expressed on activated T-cells. Engagement of PD-1 with its ligands, PD-L1 and PD-L2, delivers negative signals that limit T-cell proliferation and cytokine production; thereby, regulating peripheral immune tolerance. Activation of PD-1 also attenuates tumor immunity and facilitates tumor progression. Therefore, inhibition of PD-1 signaling reveals a mechanism of action that may enhance tumor immune surveillance and anti-tumor immune responses (Francisco et al, 2010; Jin et al, 2011; Pico de Coaña et al, 2015). Agents targeting PD-1 and PD-L1 specifically are currently showing promise in multiple tumor types, including Opdivo® (nivolumab), Keytruda® (pembrolizumab), Imfinzi® (durvalumab), Tecentriq® (atezolizumab), Bavencio® (avelumab), and Libtayo® (cemiplimab) (Opdivdo package insert, 2018; Keytruda package insert, 2018).

Sasanlimab can selectively and reversibly bind to human PD-1 and block the interaction between PD-1 and PD-L1/PD-L2. Sasanlimab has shown to increase human T-cell proliferation and cytokine secretion (IFN-g and IL-2), when PD-L1 is highly expressed in both in-vitro and in-vivo systems. Sasanlimab blockade of the interaction between PD-1 on T-cells and its ligands on tumor cells is expected to restore antitumor immunity and form the basis for an immunotherapeutic approach to treat cancer.

2.2.3.1. Sasanlimab, an Anti-PD-1 Antibody: Clinical Experience in Study B8011001 (NCT02573259)

B8011001 is an ongoing Phase 1, open-label, multicenter, multiple dose, dose escalation and expansion, safety, PK, and PD study of sasanlimab. The primary purpose of this study is to evaluate safety and early signs of efficacy. This clinical study was divided into a dose escalation (Part 1) phase and a dose expansion (Part 2) phase.

Study enrollment was completed and a total of CCI [redacted]. The available clinical data indicate sasanlimab has an acceptable safety profile and evidence of efficacy, both highly consistent with other approved PD-1 agents. Refer to Appendix 14 for Preliminary Clinical Summary and the sasanlimab IB for more details.

2.2.4. Nonclinical Pharmacology

2.2.4.1. In vitro and In vivo Pharmacology

CCI [redacted]
studies demonstrate the in vitro and in vivo oncolytic mechanism of action of PF-07263689 in human tumor models. VV-Cop, and by inference PF-07263689, demonstrated stronger activity in a human tumor cell line xenograft tumor model than VV-Wyeth. CCI [redacted]

CCI

[redacted]

2.2.5. Nonclinical Pharmacokinetics and Metabolism

No nonclinical methods of analysis, absorption, PK, toxicokinetic, metabolism, excretion, or drug interaction studies have been conducted for PF-07263689. Traditional pharmacokinetic studies are not considered relevant for oncolytic viruses/cancer vaccines (WHO, 2005). Nonclinical biodistribution study results are discussed in Section 2.2.4.

2.2.6. Nonclinical Safety

Toxicity studies of PF-07263689 were conducted in cynomolgus monkeys, which were CCI [redacted]

Overall, the nonclinical profile of PF-07263689 has been adequately characterized and supports its exploration in patients with advanced cancer.

2.2.7. Clinical Overview

This is a FIH study for PF-07263689; therefore, no clinical data are available.

This study will be conducted in solid tumor indications known to have approved therapies using immune checkpoint inhibitors or anti-vascular endothelial growth factor agents, or known to be susceptible to oncolytic virus. The study will enroll participants with locally advanced or metastatic solid tumors who have exhausted all relevant standard of care therapy including PDx treatment if approved or accepted per local standard for such indications. Therefore, the target populations represent unmet needs having no or very limited alternative therapeutic options for their advanced disease.

2.3. Benefit/Risk Assessment

Since this is the FIH study for selected disease indications where participants in late line settings have exhausted standard of care treatment options, the benefit/risk relationship has been considered in the planning of this study based on preclinical efficacy data, toxicology studies, and nonclinical safety profiles of PF-07263689.

Safety findings that were observed in the nonclinical studies with PF-07263689 include: CCI [redacted], and

CCI [redacted]. The potential overlapping toxicities with the combination therapy based on clinical data with sasanlimab to date include CCI [redacted]. Injection site reactions and skin changes with sasanlimab SC administration may affect or impact spontaneous skin lesions with PF-07263689. In this Phase 1 study, risks are being mitigated through eligibility criteria and clinical assessments via appropriate and frequent safety monitoring (see Section 2.3.1). Notably, participants in dose escalation will be hospitalized for at least CCI [redacted] In Part 1A monotherapy, the dosing CCI [redacted] to mitigate against unexpected immune-related adverse reactions. In Part 1B (combination with sasanlimab), the CCI [redacted] to mitigate against possible overlapping adverse reactions. There is no formal staggering for subsequent participants in each dose cohort. The requirements of inpatient hospitalization and stagger will be re-evaluated based on totality of the safety data prior to initiating dose expansion cohorts.

Combination treatment with sasanlimab, which belongs to a class of drugs where the benefit/risk ratio is well known as a single agent, is also expected to have a favorable benefit/risk ratio. Sasanlimab may potentiate the effects of oncolytic vaccinia virus (Liu et al, 2017) without significant overlapping toxicity, resulting in a similar or better benefit/risk profile compared with PF-07263689 as a monotherapy.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07263689 and sasanlimab may be found in the respective IBs, which are the SRSDs for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention with PF-07263689		
Skin lesions	The potential risks are based on non-clinical studies for PF-07263689.	*Skin Lesions:* Supportive care including non-occlusive dressing or bandage and topical treatment will be applied to the skin lesions. Refer to Section 5.3.2 and Section 6.8.3.1.
CCI [redacted]		[redacted]
[redacted]		
[redacted]		
Study Intervention with PF-07263689 and Sasanlimab		
irAE	The potential overlapping risks are based on the investigator's brochure for sasanlimab and nonclinical studies for PF-07263689.	Guidelines for treatment interruption and discontinuation in case toxicities, and guidelines for steroid treatment implementation are incorporated in Appendix 3. Participants must have a LVEF ≥50% by echocardiogram or MUGA to be eligible. Cardiac biomarkers such as troponin and CPK will be performed throughout the study. Participants with active ILD/pneumonitis or history of ILD/pneumonitis requiring systemic steroids are excluded. Participants with a baseline pulse oximetry of < 92% "on Room air" are excluded. CCI [redacted]

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI [redacted]		[redacted]
Injection site reactions and skin changes		Participants should be monitored not only for infusion site reactions but also any skin lesions in whole body following PF-07263689 administration (Parts 1A, 1B, and 2), as well as injection site reactions following administration of sasanlimab (in Parts 1B and 2). Refer to Section 5.3.2, Section 6.8.3.1 and Section 8.2.3.

Study Procedures		
De novo (fresh) tumor biopsy • Mandatory pre-/on-treatment paired biopsies for at least 5 participants at or below 1 dose level from MTD in Part 1A, Part 1B, and in Part 2 dose expansion (~5-8 participants in each arm unless biopsy cannot be performed safely)	There is a risk associated with any tumor biopsy: • Stinging pain from injection of local anesthetic; • Pain or discomfort from the biopsy procedure; • Discomfort from lying still for an extended time; • Bleeding, swelling, scarring, soreness, or bruising at the biopsy site; • Infection of wound; • Contamination of cancer cells to unaffected tissue when removing biopsy needle.	• Local anesthetic will be administered. • Sterile techniques will be used. • Procedures will be performed by qualified medical practitioners. • Participants should not be subjected to a significant risk procedure to obtain the biopsies (ie, the absolute risk of mortality or major morbidity in the participant's clinical setting and at the institution completing the procedure should be <2%).
CT or MRI procedures for tumor assessments	CT scans expose the participant to a small dose of radiation. The contrast dye used with the CT scan may cause pain or burning when injected. The dye may worsen kidney function for those with kidney disease or are dehydrated. The dye may cause an allergic reaction. MRI risks include possible reactions to metals due to magnets, loud noises from the machine causing hearing issues, increase in body temperature during long MRIs, and claustrophobia.	• Only experienced professionals will conduct the CT or MRI procedures. The participant will be asked about allergies to the contrast dye. Medical history will be reviewed for kidney disease, and information will be provided to minimize dehydration. If possible, an open MRI can be used for those experiencing claustrophobia. The participant may be offered earplugs and/or headphones to minimize the noise.

2.3.2. Benefit Assessment

In the animal studies, toxicity from PF-07263689 has been observed only at a much higher dose per weight or body surface area in the mouse than the equivalent maximum dose that will be tested in humans in the Phase 1 study. As a class, vaccinia viruses have been safely administered to humans across vaccine and oncology studies, and there is a potential for therapeutic benefit to the administration of PF-07263689 given the antitumor effects seen in preclinical data, even with single-agent PF-07263689. Given that the prognosis in metastatic cancers is quite poor following standard of care therapies in solid tumor malignancies in general, and given that patients in this study do not have alternative treatment options with proven efficacy, the benefit/risk remains favorable for clinical evaluation of PF-07263689 in the proposed setting. Combination treatment with sasanlimab, a PD-1 inhibitor, which as a class has an established and favorable benefit/risk ratio in multiple tumor types and in addition may potentiate the effects of oncolytic vaccinia virus (Liu et al, 2017), is also expected to have a favorable benefit/risk ratio.

Close medical monitoring will occur during the participant's time on study, including identification of AEs through evaluations and assessments by the site and sponsor teams, which will further mitigate participant risk.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with PF-07263689 and sasanlimab are justified by the anticipated benefits that may be afforded to participants with locally advanced or metastatic solid tumors who have exhausted all standard of care therapy.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Dose Escalation (Part 1)

Objectives	Endpoints	Estimands
Primary:		
• Part 1A: To assess safety and tolerability at increasing dose levels of PF-07263689 in successive cohorts of participants with select locally advanced/metastatic solid tumors, until the MTD is estimated or the MFD dose is reached. • Part 1B: To assess safety and tolerability PF-07263689 in combination with sasanlimab in successive cohorts of participants with select locally advanced/metastatic solid tumors,	• First cycle DLTs. • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0, except CRS, which will be graded by ASTCT criteria), timing, seriousness, and relationship to study treatment. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	• The primary estimand for incidence of DLTs in Part 1 is DLT rate estimated based on data from DLT-evaluable participants during the DLT evaluation period, which is the first 28 days after the first dose of study intervention. The attributes of this estimand are provided in Section 9.

Objectives	Endpoints	Estimands
in order to estimate and select the combination RP2D/schedule.		
Secondary:		
• To evaluate preliminary antitumor activity.	• ORR, as assessed using the RECIST version 1.1. • Time to event endpoints: DOR, PFS, TTP by RECIST 1.1.	• The key secondary estimand in Part 1 is to evaluate the treatment effect of PF-07263689 assessed by ORR, based on investigator assessment per RECIST 1.1, in the response evaluable analysis population. The attributes of this estimand are provided in Section 9.
• To evaluate the viral load kinetics following first and second dose of PF-07263689. • To collect sasanlimab drug concentration data in Part 1B for evaluation of sasanlimab PK.	• Viral load kinetics parameters of PF-07263689 in blood, including C_{max}, T_{max} and AUC_{last}. • Trough concentrations of sasanlimab for selected cycles	• NA
• To characterize the viral shedding of PF-07263689.	• Viral titers during 30, 45, and 60 days after the last PF-07263689 dose.	• NA
• To evaluate the immunogenicity of PF-07263689 and sasanlimab following monotherapy and combination administration.	• Incidence and titers of ADA against PF-07263689 and sasanlimab. • Incidence and titers of anti-IL2 antibodies.	• NA
CCI [redacted]		
• To assess viral replication and transgene expression of PF-07263689 in both tumors and blood of participants.	• CCI [redacted]	• NA
• To explore the pharmacodynamic effect of PF-07263689 in both tumor and blood of participants.	• CCI [redacted]	• NA

Objectives	Endpoints	Estimands
	• CCI [redacted]	
• To explore additional biomarkers associated with clinical response and to elucidate the potential MOA and mechanism of resistance to PF-07263689.	• CCI [redacted]	• NA

3.2. Dose Expansion (Part 2)

Objectives	Endpoints	Estimands
Primary:		
• To confirm safety and tolerability of PF-07263689 at the RP2D in combination therapy in participants with selected tumor types. • To evaluate preliminary evidence of antitumor activity of PF-07263689 in combination therapy in participants with selected tumor types.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0, except CRS, which will be graded by ASTCT criteria), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. • ORR as determined by RECIST version 1.1.	• The primary estimand in Part 2 is to evaluate the treatment effect of PF-07263689 in combination with PF-06801591 assessed by the ORR, based on investigator assessment per RECIST 1.1, in the response evaluable analysis population. The attributes of this estimand are provided in Section 9.
Secondary:		
• To further evaluate the viral load kinetics following PF-07263689 administration. • To collect sasanlimab drug concentration data in Part 2 for evaluation of sasanlimab PK.	• Viral load kinetics parameters of PF-07263689 in blood, including C_{max}, T_{max}, and AUC_{last}. • Trough concentrations of sasanlimab for selected cycles.	• NA
• To characterize the viral shedding of PF-07263689.	• Viral titers during 30, 45, and 60 days after the last PF-07263689 dose.	• NA
• To further evaluate the immunogenicity of PF-07263689 and sasanlimab.	• Incidence and titers of ADA against PF-07263689 and sasanlimab. • Incidence and titers of anti- IL-2 antibodies.	• NA

Objectives	Endpoints	Estimands
• To evaluate preliminary antitumor activity through time to event time points.	• DCR, DOR, PFS, and TTP by RECIST version 1.1.	• NA
• To assess overall survival of participants treated with PF-07263689.	• Overall survival	• NA
CCI [redacted]		
• To assess viral replication and transgene expression of PF-07263689 in tumors of participants. • To explore the pharmacodynamic effect of PF-07263689 in both tumor and blood. • To explore additional biomarkers associated with clinical response and to elucidate the potential mode of action and mechanism of resistance to PF-07263689.	• CCI [redacted]	• NA

4. STUDY DESIGN

4.1. Overall Design

The proposed Phase 1, open-label, multicenter, multiple dose, dose escalation, and dose expansion study will evaluate the safety, tolerability, viral load kinetics and shedding, PD, and antitumor activity of PF-07263689, either alone or in combination with sasanlimab (an investigational anti-PD-1 antibody), in participants with locally advanced or metastatic solid tumors who have exhausted all standard of care therapies available to them. The study consists of 2 parts: Part 1 dose escalation for PF-07263689 monotherapy (Part 1A) and combination with sasanlimab (Part 1B) and Part 2 dose expansion for the combination therapy.

The study will evaluate weekly IV dosing of PF-07263689 for 4 total doses, either as a monotherapy or in combination with sasanlimab administered at 300 mg SC Q4W. In the combination therapy arm, administration of sasanlimab will start concurrently with PF-07263689 and continue beyond the end of the PF-07263689 treatment course until disease progression, intolerable toxicity, withdrawal of consent, or until the study is

completed. Alternative PF-07263689 regimens may be evaluated if supported by emerging data.

Approximately 120 participants are expected to be enrolled in the study overall, including approximately 40 DLT evaluable participants for Part 1 and approximately 80 participants (15 to 20 per cohort) for Part 2.

For Part 1A, participants will be assessed for radiological response on Day 43 (±5 days). Additional scans may be performed every 6 weeks (±7 days) following Day 43. For Part 1B and Part 2, all participants will be assessed for radiographic response every 6 weeks (±7 days) for up to 6 months followed by every 12 weeks (±7 days) until starting new anticancer therapy or at time of radiographic progression, whichever is earlier. Urine, saliva, and infusion site swabs will be collected to assess viral shedding during treatment and up to 60 days after last dose of PF-07263689 as indicated in the SoA. Any skin lesions that appear will be swabbed to assess for virus shedding. Additionally, survival follow-up will occur by telephone Q12W (±7 days). Participants will continue to be followed for survival and long-term safety until death, withdrawal of consent, or the end of the entire study (see Section 4.3).

4.1.1. Dose Escalation (Part 1)

Participants with any advanced or metastatic solid tumor indications known to have approved therapies using immune checkpoint inhibitors or anti-vascular endothelial growth factor agents are eligible for Part 1. Participants must have exhausted all standard of care therapy for the primary tumor type available to them. Participants with immune checkpoint inhibitor-sensitive tumor types (eg, NSCLC, RCC, UC, melanoma) are expected to be treated in a post-anti-PD-1/PD-L1 (hereafter referred to as anti-PDx) failure setting in Part 1. Tumor types in which anti-PDx antibody therapy is not indicated, such as ovarian and MSS CRC, may be treated in any post-standard of care setting.

Participants will be hospitalized for at least [redacted]. In Part 1A monotherapy, the dosing of the first [redacted] to mitigate against unexpected immune-related adverse reactions. In Part 1B (PF-07263689 in combination with sasanlimab), the dosing of the first [redacted] to mitigate against possible overlapping adverse reactions. There is no formal staggering for subsequent participants in each dose cohort.

Part 1A Monotherapy Dose Escalation: A BLRM along with EWOC will be utilized to guide dose escalation and to determine the monotherapy MTD if MFD is not reached. Dose escalation from the determined starting dose (at one log level CCI [redacted] After the last participant at the MTD or the MFD has finished all doses of PF-07263689, the monotherapy RP2D will be determined based on all available safety, efficacy, and viral load kinetics and shedding data. During the dose escalation process, intermediate doses may be tested based on BLRM.

Part 1B Combination Dose Escalation: Dose escalation of PF-07263689 in combination with sasanlimab will start at equal to or one dose level lower than the monotherapy MTD of PF-07263689, or any intermediate dose between MTD and the next lower dose of MTD, as guided by the BLRM and EWOC criteria. If started below the monotherapy MTD, PF-07263689 may be escalated to MTD or the MFD in the combination. After completing PF-07263689 dosing, participants will remain on sasanlimab 300 mg SC Q4W until disease progression, intolerable toxicity, withdrawal of consent, or until the study is completed. The combination therapy RP2D will be determined based on all available safety, efficacy, and PK/PD data during the combination dose escalation process.

4.1.2. Dose Expansion (Part 2)

Part 2 will further evaluate PF-07263689 in combination with sasanlimab at the preliminary combination RP2D from Part 1B. Sasanlimab will be administered at 300 mg SC Q4W in tumor-specific arms of post-PDx failure NSCLC (Arm A), post-PDx failure RCC (Arm B), post-PDx failure melanoma (Arm C), and PDx-naïve refractory CRC (Arm D), at approximately 15 to 20 participants per arm. Initially, 3 tumor-specific arms will commence based on preliminary data from Part 1, with the option to subsequently open the fourth arm based on emerging data. For the post-PDx indications, Arms A, B, and C may be limited to participants with primary or secondary resistance to PDx inhibitors after discussion with investigators.

4.2. Scientific Rationale for Study Design

PF-07263689 is an oncolytic virus that selectively grows in and kills cancer cells. In addition to its direct cytolytic activity, it has the capability to stimulate innate and adaptive immune reactions against tumor cells. PF-07263689 is also genetically engineered to express an IL-2gv therapeutic payload as a strategy to alter the tumor immune microenvironment to potentially reverse checkpoint refractoriness and induce killing of uninfected bystander tumor cells. It is delivered systemically for infection of disseminated disease that can stimulate systemic antitumor immune responses in patients with or without prior anti-PDx therapies. As demonstrated in preclinical studies with PF-07263689 in which antitumor efficacy was further enhanced by coadministration of an anti-PD-1 antibody, combination therapy of sasanlimab with PF-07263689 is expected to maintain the oncolytic virus induced antitumor T-cell immune response long-term.

4.2.1. Dose Level Review Committee

This study will not use a DMC. However, a DLRM will convene for dose escalation decisions. The actual dose selected at each dose decision may be at or below the statistical model's (ie, BLRM) recommended dose as determined by the members of the DLRM after considering all safety information. The review team will be composed of investigator(s), Pfizer GCL, Pfizer Study Clinician, and Pfizer Study Manager. Additional members may be added as needed (eg, Clinical Pharmacology Lead, Translational Oncology, Safety Risk Lead or designee, and Pfizer Biostatistics representative). A quorum, defined as >50% of the participating investigators or their qualified designee (ie, subinvestigator or research nurse or study coordinator possessing hard copy documentation [eg, email] of the investigator's vote

regarding the dose level review), must be in attendance for the DLRM. Participating investigators are defined as those whose sites have been initiated for screening and enrollment of patients. The DLRM will be rescheduled if a quorum is not reached.

Voting members of the DLRM will include the Pfizer Medical Monitor and all participating investigators or their qualified medical doctor designee(s). The team may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion or a cohort, de-escalation at a lower dose, or termination of the study.

All available study data including demographics, medical history (including tumor history), concomitant medications, AEs, ECGs, vital signs, laboratory results, and emerging PK or PD data will be reviewed.

4.2.2. Choice of Contraception/Barrier Requirements

Studies to evaluate the development toxicity of PF-07263689 and sasanlimab have not been conducted. On the basis of the mechanism of action of sasanlimab and data from approved drugs of the same class, sasanlimab may cause a risk for severe manifestations of developmental toxicity in humans. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.3. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification of Dose

The selection of starting dose and regimen for this FIH study was based on the nonclinical toxicology and pharmacology studies. Results from nonclinical toxicological studies indicate that monkey is the most relevant species. In the pivotal GLP toxicological study in monkeys, the CCI [redacted]. The key findings in this study were the expected skin lesions and immune system findings consistent with viral infection. The human equivalent dose for the HNSTD/NOAEL dose CCI [redacted]

The proposed starting dose CCI [redacted] is one log level below the human equivalent dose of NOAEL in monkey, and is predicted to be in the lower range of biologically active dose based on preclinical data. In nonclinical pharmacology studies CCI [redacted] of PF-07263689 CCI [redacted], a CCI [redacted] was shown to be effective in tumor growth inhibition. This dose is CCI [redacted] (assuming a 60 kg body weight) and represents a conservative biologic active dose based on the preclinical data.

PF-07263689 will be administered using flat dosing. Both flat dosing and body weight-based dosing have been employed in clinical trials with other oncolytic viruses with lack of

evidence favoring body weight-based dosing (Streby et al, 2019; García M et al, 2018; Small et al, 2006; Mell et al, 2017; Downs-Canner et al, 2016; Freeman et al, 2006; Comins et al, 2010; Rudin et al, 2011; Breitbach et al, 2011; Karapanagiotou et al, 2012; Kolb et al, 2015; Park et al, 2015; Machiels et al, 2019). In addition, flat dosing would be more convenient and could reduce potential dosing errors associated with body weight-based dosing.

Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and viral load kinetic data.

4.3.1. Starting Dose

The starting dose for Part 1A will [redacted] given once weekly for 4 weeks.

4.3.2. Criteria for Dose Escalation

The objective of Part 1 of the study is to establish the MTD before the pre-specified MFD using the BLRM approach and the EWOC principle. The use of the EWOC principle limits the risk that a potential next dose will be toxic. A 2-parameter BLRM will be used to guide the dose escalation process of the monotherapy of PF-07263689, and a 5-parameter BLRM will be used to guide the dose escalation of PF-07263689 in combination with sasanlimab. See Section 9.3.2 and Appendix 9 for more details on the Bayesian logistic regression model. Using DLT data at all tested dose levels and pre-specified prior distribution of model parameters, posterior probabilities of probability of having a DLT falling into 3 dosing intervals (underdosing, target dosing, overdosing) will be calculated for all dose levels. A dose may only be used for newly enrolled participants if the risk of excessive toxicity, ie, toxicity higher than 0.33 at that dose is less than 25%.

The provisional maximum dose for each dose level to be evaluated are listed in Table 6.

Table 6. Provisional Dose Levels in Dose Escalation

Dose Level/Cohort	Dose (PFU)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Intermediate doses that may be explored will be within the dose range listed in the table above. The [redacted]; the dose preparation and handling time required to [redacted] DP presentation would present significant microbial and safety risks.

Dose escalation will stop when stopping criteria are met (see Section 9.3.2).

4.3.3. DLT Definition

In Part 1A and Part 1B , a participant is classified as DLT evaluable if he/she either 1) receives 3 of the 4 doses of PF-07263689 and has completed the scheduled safety assessments during the DLT observation period or 2) has experienced a DLT. Participants may miss a single dose, but the first dose and the last dose must occur within the 22-day window. Participants who withdraw from the study during the DLT evaluable period for reasons other than a DLT may be replaced with a new participant at the same dose level. The sole exception to criterion 1) is if the participant has missed a minority of safety assessments due to emergency situations (eg, site accessibility issues, inability to go to an external lab, etc.). In such cases, the DLRM Committee may judge the participant evaluable, depending on the abundance of the available data. Participants that experience any DLT at any dose level in Part 1 and Part 2 of the study will not be replaced.

For the purpose of dose escalation, the DLT observation period will be during the first cycle (28 days after the start of PF-07263689 monotherapy [Part 1A] and PF-07263689 combination with sasanlimab [Part 1B]) in each participant.

Significant AEs considered to be related to study intervention that occur after the DLT observation period will be reviewed in context of all safety data available. That review may result in re-evaluation of the dosing level or regimen. Severity of AEs will be graded according to CTCAE version 5.0 except CRS, which will be graded by ASTCT criteria.

For the purpose of dose escalation, any of the following AEs occurring in the DLT observation period that are considered at least possibly related to PF-07263689 and/or sasanlimab will be classified as DLTs:

4.3.3.1 Hematological DLTs

- Grade 4 neutropenia lasting >5 days from initiation of granulocyte-colony stimulating factor;
- Febrile neutropenia defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F), or a sustained temperature of >38°C (100.4°F) for more than 1 hour;
- Grade 3 neutropenia with infection;
- Grade 3 thrombocytopenia with any bleeding;
- Grade 4 thrombocytopenia.

4.3.3.2. Non-Hematologic DLTs

- Any treatment-related Grade ≥3 non-hematologic toxicity (see below for specifications applying to special circumstances);

- Clinical events consistent with Hy's Law;
- Any Grade 3 CRS as per ASTCT that does not improve to Grade ≤2 within 72 hours despite medical management;
- Any Grade 4 CRS;
- Grade ≥3 toxicity of any duration affecting vital organs (eg, heart, lung and CNS) should also be considered as DLT and be reviewed with the Sponsor.
- Grade 4 vaccinia infection lasting ≥6 days;
- Grade ≥3 nausea, vomiting, diarrhea, or fatigue that cannot be controlled to Grade ≤2 with or without medical therapy within 3 days;
- Grade ≥3 rash that does not resolve to Grade ≤2 within 21 days with supportive measures (including anti-viral therapy);
- Grade ≥3 laboratory abnormalities with a clinical correlate that cannot be controlled to Grade ≤2 with or without appropriate medical management within 3 days;
- A treatment-related AE inducing a delay by 2 weeks in receiving the next scheduled dose due to persisting toxicities attributable to study drug will be considered a DLT;
- Clinically important or persistent toxicities (eg, toxicities responsible for significant dose delay or missed doses) that are not included in the above criteria may also be considered a DLT following review by the investigators and the sponsor.

4.3.3.3. Other DLTs (Part 1B Only)

In addition, for combination therapy, irAEs that meet the following criteria will be considered DLTs:

- Grade 4 irAE regardless of duration (for laboratory abnormalities without clinical correlate and do not require medical intervention please refer to criteria above);
- Grade ≥3 colitis regardless of duration (must be supported by diagnostic testing);
- Grade ≥3 non-infectious pneumonitis regardless of duration;
- Grade 2 non-infectious pneumonitis that does not resolve to Grade 1 or less within 3 days of the initiation of maximal supportive care;

- Any grade immune-mediated myocarditis. Participants with Grade ≥3 myocarditis will be permanently discontinued;

- Grade 3 irAE, excluding colitis and pneumonitis, that does not improve to Grade ≤2 within 3 days after onset of the AE despite maximal supportive care including systemic corticosteroids or downgrade to ≤ Grade 1 or baseline within 14 days;

- Grade ≥3 immune-related endocrinopathies (eg, thyroid disorders, diabetes mellitus, adrenal insufficiency) that require treatment discontinuation or are not managed successfully with hormonal replacement therapy.

The following AEs <u>will not be</u> adjudicated as DLTs in Part 1A or Part 1B:

- Grade 3 IRR, allergic reaction, or anaphylaxis will not be considered as DLTs but may be a reason for study discontinuation and will be reviewed with the sponsor.

4.3.4. Late Toxicity Definition and Management

Significant AEs considered to be related to the PF-07263689 as monotherapy or in combination treatment under investigation that occur after the DLT observation period will be reviewed in the context of all available safety data. That review may result in re-evaluation of the dosing level or regimen.

The details of the potential late onset toxicity will be reviewed during dose level review meetings to inform decisions about enrollment and dosing (eg, dose level increments, determination of the dose(s) used beyond dose escalation, regimen). Late onset toxicities that meet the definition of DLT will be considered in the evaluation of the MTD, Phase 1 Expansion Dose, and/or RP2D, as appropriate.

All participants will be monitored for at least 90 days after treatment discontinuation for immune-related toxicities.

4.3.5. MTD Definition

MTD is defined as the highest dose with true DLT rate within the target toxicity interval. The target interval for the DLT rate is defined as [0.16, 0.33].

The safety of each cohort will be assessed by a Dose Level Review Committee, which is composed of Sponsor representatives and the Investigators. The Committee will consider all relevant clinical data, including safety, PK, efficacy, and PD in making decisions such as whether to dose escalate, dose de-escalate, dose level increments, expand cohorts, and declare MTD.

4.3.6. Recommended Phase 2 Dose Definition

The MTD is identified based on acute toxicities observed during the DLT evaluation period and defines the limit of acceptable dose escalation in a small sample size. The RP2D, on the

other hand, identifies a dose that can be used in further large-scale testing and its determination is based on an overall assessment of feasibility, tolerability, and perhaps efficacy, based on a larger patient exposure to the agent, both in number and duration, and may be the same as the MTD or the MFD, or may be lower. The RP2D will be determined in this study after the expansion cohort(s) have provided sufficient data on which to make such a determination. The final determination of the RP2D will be made by the sponsor based on a recommendation from the investigators and study team.

The dose(s) selected for use in the expansion cohorts will be referred to as the Phase 1 Expansion Dose(s). Participants enrolled to Part 1B dosed at the same dose(s) selected for the expansion cohorts and meeting the same requirements will be counted toward such data analyses.

4.4. End of Study Definition

The end of the study will be the date of the last visit of the last participant or 2 years after the last participant receives their first dose (whichever occurs first). The study may also be terminated at any time at the discretion of the sponsor. Any additional treatment beyond 2 years shall be discussed and approved by the sponsor.

A participant is considered to have completed the study if he/she has completed all phases of the study including the EOT visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Participants age ≥18 years.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Histological or cytological diagnosis of locally advanced/metastatic solid tumor indications known to have approved therapies using immune checkpoint inhibitors or anti-vascular endothelial growth factor agents.

3. Participants should have exhausted all available standard of care therapy or for whom no standard therapy is available for their tumor type. Participants who have actively declined available standard of care therapies are eligible upon documentation of refusal.

4. Participants with solid tumors with FDA-approved anti-PDx antibody therapy should have received at least 1 prior anti-PDx therapy.

5. Participants with prior anti-PDx therapy must have documentation of primary or secondary resistance to last prior anti-PDx therapy according to Society for Immunotherapy of Cancer Immunotherapy Resistance Taskforce (Kluger et al, 2020) as follows:

    a. Primary resistance: drug exposure for at least 6 weeks with best response of PD, or SD for < 6 months (including PD at any time after stopping PDx for any reason unrelated to toxicity if best response while receiving anti-PDx therapy was PD or SD < 6 months).

    b. Secondary resistance: drug exposure for at least 6 months with best response of CR or PR or SD for ≥ 6 months. If prior PDx was stopped prior to PD, PD must have occurred within 12 weeks after the last dose of PDx.

6. Participants entering the study in the expansion cohort have at least 1 measurable lesion as defined by RECIST version 1.1 that has not been previously irradiated.

7. Dose Escalation (Part 1A and 1B): Participants with any advanced or metastatic solid tumor indications known to have approved therapies using immune checkpoint inhibitors or anti-vascular endothelial growth factor agents.

8. Dose Expansion (Part 2): Participants with the following indications must have exhausted all relevant available standard of care or have documented intolerability to such therapies.

    a. NSCLC (≥2L): Participants with NSCLC must have received prior anti-PDx therapies. NSCLC participants with driver mutation(s) must have received prior available targeted therapy(ies) (eg, participant with *BRAF* V600E mutation must have also received BRAF inhibitor with or without MEK inhibitor) or have documented intolerability.

b. RCC (≥2L): Participants with RCC must have received prior anti-PDx therapies. RCC participants must also have received prior anti-VEGF therapy.

c. Melanoma (≥2L): Participants with melanoma must have received prior anti-PDx therapy with or without anti-CTLA-4. Melanoma participants with driver mutations must have received prior available targeted therapies.

d. MSS CRC: Participants with CRC must have received regimen containing combinations of pyrimidine analog-containing combination chemotherapy with anti-VEGF (as appropriate), anti-EGFR (as appropriate if RAS wild-type), and/or encorafenib (if *BRAF* V600E).

9. Participants must have recently obtained (≤1 year prior to Day 1) archival FFPE tumor tissue sample available; details are provided in the Laboratory Manual. If archival FFPE ≤1 year is not available a fresh tumor sample must be collected at screening. If the archival sample is older than 1 year and a biopsy during screening cannot be performed safely, the investigator must contact the sponsor to discuss eligibility prior to enrollment.

Informed Consent:

10. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Other Inclusion Criteria:

11. ECOG PS 0 or 1.

12. Adequate Bone Marrow Function within 14 days of the planned first dose, defined as:

- ANC ≥1,250/mm^3 or 125 x 10^9/L;
- Platelets ≥75,000/mm^3 or 75 x10^9/L;
- Hemoglobin ≥9 g/dL. Limited transfusions to reach this value are allowed, after discussion with the sponsor's medical monitor. There should not be a chronic need for transfusions (>1 per month) in the recent (approximately 3 months) past.

13. Adequate Renal Function within 14 days of the planned first dose, defined as an estimated creatinine clearance ≥60 mL/min (≥30 mL/min for RCC participants) as calculated by Cockcroft-Gault method. In equivocal cases, a 24-hour urine collection test can be used to estimate the creatinine clearance more accurately.

14. Adequate Liver Function within 14 days of the planned first dose, defined as:

    - Total bilirubin ≤1.5 x ULN unless the participant has documented Gilbert's syndrome;
    - AST and ALT ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor;
    - AP ≤2.5 x ULN (≤5 x ULN in case of bone metastasis or liver metastasis).

15. Participants with brain metastases must meet all the following conditions:

    - Have completed their planned course of local treatment;
    - Have recovered from the acute effects of radiation therapy or surgery prior to planned first dose;
    - Have discontinued corticosteroid treatment for these metastases for at least 4 weeks;
    - Have been on stable doses of anti-seizure medications (if applicable) for at least 3 months. Antiseizure medications must meet any eligibility criteria outlined for concomitant medications.
    - Are neurologically stable for 3 months since the conclusion of therapy, as documented by both neurologic and MRI examinations.
    - Participants who are diagnosed with a CNS metastasis during the screening period must also meet these criteria.

16. Resolution of acute effects of any prior therapy to either baseline severity or CTCAE version 5 Grade ≤1 (except for AEs not constituting a safety risk in the investigator's judgment unless the AEs represent persistent non-hematological toxicities of Grade ≥3).

17. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Participants with any other active malignancy within 3 years prior to planned first dose, except for adequately treated basal cell or squamous cell skin cancer, or

carcinoma in situ of the cervix, Bowen's disease. Other indolent, secondary cancers may be permitted after discussion with sponsor.

2. Participants sustaining recent major surgery defined as a complex procedure performed under regional or general anesthesia with a recovery period of at least 4 weeks prior to planned first dose. Exceptions include:

    - Minor surgical procedures require at least 1-week period prior to planned first dose.
    - Participants having an implantable port placed can enter the study 1 week after the port is placed, assuming no complications have occurred, and the port is functioning normally.

3. Participants with persistent non-hematological toxicities of ≥ Grade 3 (NCI-CTCAE v5.0), including symptoms and objective findings from treatment such as chemotherapy, kinase inhibitors, immunotherapy, experimental agents, radiation, or surgery.

4. Participants with a history of myocarditis or congestive heart failure (as defined by New York Heart Association (NYHA) Functional Classification III or IV), as well as unstable angina, serious uncontrolled cardiac arrhythmia, or myocardial infarction 6 months prior to study entry.

5. Clinically important (eg, uncontrolled) hypertension that cannot be controlled by medications (approximately above 150/90 mmHg) despite optimal medical therapy. Equivocal cases should be discussed with the sponsor prior to study entry.

6. Known or suspected hypersensitivity to, allergic history of, or prior treatment within the past 10 years on any vaccinia oncolytic, pox virus, or antiviral agents.

7. Known or suspected hypersensitivity to any anti-PDx antibody if planned to receive combination therapy with sasanlimab.

8. History of Grade ≥3 immune mediated AE (including AST/ALT elevations that were considered drug-related and cytokine release syndrome) that was considered related to prior immune modulatory therapy (eg, immune checkpoint inhibitors, costimulatory agents, etc.) and required immunosuppressive therapy.

9. Has a diagnosis of severe immunodeficiencies immunosuppression (eg, history of leukemia, lymphoma, solid organ transplantation, hematopoietic stem cell transplant recipients who are <24 months posttransplant, and hematopoietic stem cell transplant recipients who are >24 months posttransplant but who have graft-versus-host disease, and humoral or cellular immunity disorders such as T-cell and NK cell dysfunction (ex, Chediak-Higashi syndrome, Leukocyte Adhesion Deficiency, and myeloperoxidase deficiency).

10. Participants with known symptomatic brain metastases requiring steroids. Participants with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable for 3 months (requires MRI confirmation).

11. Participants with active ILD/pneumonitis or a history of ILD/pneumonitis requiring treatment with systemic steroids.

12. History of or ongoing severe immune response or inflammatory skin condition such as severe eczema (as determined by the investigator) requiring medical treatment.

13. Any prior or planned organ transplant.

14. Known history of immune-mediated colitis, inflammatory bowel disease, pneumonitis, or pulmonary fibrosis.

15. Ongoing bowel perforation or presence of bowel fistula or abscess or history of small or large bowel obstruction within 3 months of planned first dose, including participants with palliative gastric drainage catheters. Participants with palliative diverting ileostomy or colostomy are allowed if they have been symptom-free for more than 3 months.

16. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis or melena in the past 6 months.

17. Presence of any open, active wound requiring treatment for proper healing.

18. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

19. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s) (refer to Section 6.8).

20. Radiation therapy within 4 weeks prior to planned first dose. Exceptions include:

    - Limited, focal radiation therapy (including Gamma-Knife) require only a 3-day period before planned first dose and the absence of any radiation-induced complications.
    - Palliative radiation therapy within 2 weeks of planned first dose and the absence of any radiation-induced complications.

21. Vaccination with a live virus (eg, measles, mumps, rubella) within 4 weeks prior to planned first dose.

22. Participants requiring chronic systemic immunosuppressants.

23. Anticoagulation with vitamin K antagonists or factor Xa inhibitors is not allowed. Anticoagulation with subcutaneous heparin is allowed. Equivocal cases should be discussed with the sponsor prior to study entry.

24. Systemic anticancer therapy and chemotherapy within 4 weeks prior to planned first dose (6 weeks for mitomycin C or nitrosoureas). Prior targeted or endocrine therapy require an interval of 2 weeks or 5 half-lives (whichever is shorter) prior to planned first dose. If the last immediate anticancer treatment contained an antibody-based agent(s) (approved or investigational), then an interval of 4 weeks or 5 half-lives (whichever is shorter) of the agent(s) prior to receiving the study intervention treatment is required. With last prior anti-PDx therapy, the washout period may be extended based on emerging clinical data.

Blood Product Support:

25. Recent transfusion of RBCs or platelets within 4 weeks prior may be exclusionary. Discuss with the sponsor if participant had recent transfusion(s).

Prior/Concurrent Clinical Study Experience:

26. Participation in other studies involving investigational drug(s) within 4 weeks or 5 half-lives prior to planned first dose. A participant may be eligible if a long-term follow-up from prior investigational studies has been met. Cases must be discussed with sponsor's medical monitor to judge eligibility.

Diagnostic Assessments:

27. Serum pregnancy test (for females of childbearing potential) positive at screening.

28. Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) HBV, HCV, and known HIV or AIDS-related illness.

    a. COVID-19/SARS-CoV2 (Participants enrolled in Part 1A, Part 1B and Part 2): This protocol excludes participants with active infections, as noted above. While SARS-CoV2 testing is not mandated for entry into this protocol, testing should follow local clinical practice standards. If a participant has a positive test result indicating active SARS-CoV2 infection, is known to have active asymptomatic infection or is suspected of having active SARS-CoV2, he/she is excluded. Participants with a prior positive test who subsequently test negative may be eligible with prior sponsor approval.

b. HIV (Participants enrolled in Part 2 Only): In equivocal cases, participants whose viral load is negative may be eligible. HIV seropositive participants who are otherwise healthy and at low risk for AIDS-related outcomes may qualify for inclusion in the study after discussion with the sponsor, but AIDS is exclusionary. The following criteria for immune status and HIV ongoing therapy must be met for a HIV seropositive participant to be eligible for the study:

- Immune status criteria:
  - CD4+ T-cell counts ≥500 cells/μL at the study start;
  - No history of AIDS-defining opportunistic infections;
  - In general, patients should be eligible if they have not had an opportunistic infection within the past 12 months.
  - Ongoing HIV therapy criteria:
  - Must be receiving recommended concurrent ART treatment according to the guidelines (AIDSinfo, 2020);
  - Began ART treatment >4 weeks prior to study start (to ensure ART is tolerated and toxicities are not confused with study drug toxicities);
  - HIV viral load <400 copies/mL for >4 weeks prior to study start (to ensure ART is tolerated and HIV controlled).

c. HBV/HCV: Relevant laboratory tests should be performed at screening and added to the table in Appendix 2 Clinical Laboratory Tests. Refer to CDC website (https://www.cdc.gov/hepatitis/index.htm) for further details.

- Participants enrolled in Part 1A and Part 1B – History of chronic hepatitis as evidenced by the following: Any positive test results for hepatitis B virus or hepatitis C virus indicating presence of virus (eg, hepatitis B surface antigen positive), or hepatitis C antibody positive (except if hepatitis C ribonucleic acid [RNA] negative).
- HBV (Participants enrolled in Part 2 Only):
  - This criterion excludes participants with a positive HBsAg (ie, either acute or chronic active hepatitis).
  - However, participants with HBV antibody positivity indicating immunity, either due to vaccination or prior natural infection, are eligible.

- Participants with positive anti-HBcAb but negative HBsAg and anti-HBsAb profile may, depending on clinical circumstances, be eligible. Discussion with the sponsor is indicated.

- HCV (Participants enrolled in Part 2 only):

  - Positive HCV antibody is indicative of infection but may not necessarily render a potential candidate ineligible, depending on clinical circumstances.

29. Baseline 12 lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >470 msec, complete LBBB, signs of an acute or indeterminate age myocardial infarction, ST T interval changes suggestive of active myocardial ischemia, second or third degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >470 msec, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 470 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants. Cases must be discussed in detail with sponsor's medical monitor to judge eligibility.

30. Participants with an LVEF <50% by echocardiogram or MUGA.

31. Participants whose baseline pulse oximetry ≤ 92% "on Room air".

Other Exclusions:

32. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have

changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

Shedding From Sperm or Vaginal Secretion

Participants and/or sexual partners must practice sexual abstinence or use of condoms due to possible viral shedding from sperm or vaginal secretion. Please refer to Section 10.4.

5.3.2. Accidental Exposures and Viral Shedding Considerations

Guidelines for preventive/containment measures to limit spread of the shed product beyond the treated individual to minimize exposure of third parties are provided, as accidental exposure may lead to transmission of vaccinia virus and infection. In most cases, the potential for transmission to untreated individuals is extremely low when the oncolytic product is shed because of the derivation methods and modifications that are designed to attenuate the product when compared to the parent strain of virus (FDA Guidance for Industry – Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products (p.16) August 2015). As peak shedding occurs soon after treatment when the participant is monitored in a health-care setting, the possibility of transmission is mainly confined to HCPs within the clinical site such as the pharmacist or nursing staff handling the drug, and to a lesser extent, individuals that come into close contact with the participant. A second peak of shedding in the days following discharge of a participant from a health care setting in not expected, therefore there is limited possibility of transmission to contacts beyond the health care and home setting.

Treated participants should avoid touching or scratching infusion sites, spontaneous lesions, or their occlusive dressings, as doing so could lead to inadvertent transfer of PF-07263689 to other areas of the body.

HCPs, participant close contacts (household members, caregivers, sex partners, or perhaps sharing the same bed), pregnant women, newborns and neonates, elderly, and immunocompromised contacts should avoid direct contact with infusion site, dressings, or body fluids of treated patients. Caregivers should wear protective gloves when applying or changing occlusive dressings and observe safety precautions for disposal of used dressings, gloves, and cleaning materials.

In the event of an accidental exposure to PF-07263689 by needle stick, exposed individuals should clean the affected area thoroughly with soap and water and/or a disinfectant, following local institutional biosafety guidelines and procedures, such as cover the site of skin puncture with occlusive dressing along with dressing change at least twice a day, obtain blood test for measuring vaccinia virus titer level, and contact the Principal Investigator, the institution's Biosafety Specialists, and/or physician knowledgeable in the care of individuals experienced with vaccinia infection. If signs or symptoms of pox infection develop, apply topical anti-viral therapy (ie, ganciclovir), cover the lesion with occlusive dressing along with dressing change at least to match timing of topical anti-viral application, and contact

appropriate investigator for medical advice. Systemic toxicity from accidental needle stick is expected to be low due to the likely minimal exposure to the attenuated oncolytic vaccinia virus product in situations of a needle stick. Signs of systemic toxicity may include but are not limited to fever, regional lymphadenopathy, remote skin lesions. Accidental needle stick in HCPs and other accidental exposures during drug preparation and administration of PF-07263689 should be reported according to Section 8.3.5.3.

Shedding via Direct Contact or Respiratory Route

Appropriate infection control measures should be implemented to minimize the environmental risk, eg:

- Recommendations of good hygiene practices to participants/caregivers:
  - Cover mouth and nose while coughing or sneezing with a single-use tissue and dispose dirty tissues after use;
  - Frequent washing of hands with soap and water or use of alcohol-based products.
- Clothes, household linens, including cleaning cloths, should be washed at least at 60°C on a regular basis. The home should be cleaned regularly with standard household cleaners.
- Measures of social distancing should be considered, in particular with regard to immunocompromised persons or vulnerable populations (avoid touching, kissing or hugging, avoid sharing of eating utensils or drinking glasses).
- Participants with respiratory symptoms (e.g. running nose, coughing) should avoid crowded or poorly ventilated public places and, where applicable, avoid contact to susceptible animals or pets.

Shedding From Urine/Stools

Instructions on hygiene procedures should be provided to participants/caregivers (eg, hand washing, cleaning of surfaces that were in contact with bodily fluids, use of separate toilet (if possible), adding bleach or equivalent products to toilet after each use, no sharing of towels).

Shedding From Saliva

Participants should minimize exposure to others by refraining from kissing, sharing of eating utensils or drinking glasses.

5.3.2.1. Contacts Exhibiting Symptoms of Viral Infections

If a contact of a participant treated with PF-07263689 report symptoms of a possible PF-07263689 related toxicity:

1. Immediately notify the institution's Biosafety Specialist as applicable

2. The individual should be referred to and medically monitored by a physician knowledgeable in the care and treatment of patients with vaccinia infections

3. Report the event to Pfizer Safety within 24 hours of the investigator's awareness by completing and submitting a CT SAE Report Form (refer to Section 8.3) regardless of whether there is an associated SAE. Follow all instructions on the form regarding avoidance of excluded individuals, considerations (in conjunctions with consultation with infectious disease expert and the Sponsor) of antiviral treatment if warranted (refer to Section 6.8.1), obtaining clinical samples if applicable according to local guidelines, monitoring the individual for response to treatment (if any), and resolution of symptoms.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, up to a limit of 2 times. Rescreened participants should be assigned a new participant number as for the initial screening.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to PF-07263689 and sasanlimab.

6.1. Study Intervention(s) Administered

Study Interventions(s)		
Intervention Name	PF-07263689	Sasanlimab
ARM Name (group of patients receiving a specific treatment (or no treatment)	All	Part 1B and Part 2
Type	Biologic	Biologic
Dose Formulation	CCI [redacted]	[redacted]
Unit Dose Strength(s)	CCI [redacted]	[redacted]

Study Interventions(s)		
	(vial is labeled and dosed with the batch-specific measured release concentration)	
Dosage Level(s)	Q1W for 4 weeks	300 mg Q4W
Route of Administration	IV push	Subcutaneous
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor (manufactured by Pfizer). Refer to the IP Manual.	Provided centrally by the sponsor (manufactured by Pfizer). Refer to the IP Manual.
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in vials for 300 mg dose . Each prefilled syringe or vials will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	PF-07263689, OBIR-2, VV110	Sasanlimab, PF-06801591, RN888

6.1.1. Administration

No premedication will be administered with the first dose. Based on emerging data, premedication may be permitted for subsequent doses for all participants, consistent with institutional guidelines, and may include an antihistamine, anti-inflammatory agent, or pain reliever. Oral or parenteral steroids are not allowed during PF-07263689 treatment period, and for 1 week prior to and 2 weeks after PF-07263689 treatment. Please refer to Section 6.8 regarding concomitant therapy.

A cycle is defined as 28 days, regardless of missed doses or dose delays.

6.1.1.1. PF-07263689

PF-07263689 will be administered once weekly for 4 weeks as an IV push without adjustment for body size at every cycle. The infusion will occur over 10 minutes (for IV push) or up to 20 minutes (for syringe pump). Since PF-07263689 will be given every week for 4 weeks, no dose modifications are allowed in this study. If participants do not complete at least 3 of 4 scheduled doses of PF-07263689 due to toxicity related to study drug, then study treatment should be permanently discontinued. If an infusion cannot be completed within the time specified, the participant will be discontinued from study treatment and may be replaced.

Study staff should refer to the IP Manual for specific instructions on the handling and preparation of the study intervention.

Participants will be admitted for inpatient monitoring (per local standard of practice) during and for CCI [redacted] following the first dose of PF-07263689 and CCI [redacted] following the second dose of PF-07263689 for monitoring. Hospitalization period may be extended if the participant experiences abnormal laboratory findings or ongoing AEs that

require further hospitalization. For Day 15 and Day 22, participants will remain at the clinical site for up to 4 hours for observation and for labs. Additional monitoring may be required based on individual toxicities.

6.1.1.2. Sasanlimab

Sasanlimab will be administered at a fixed dose of 300 mg SC Q4W starting on Day 1. Sasanlimab must be administered after PF-07263689 on Cycle 1 Day 1.

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted. The maximum number of injections per participant [redacted]. Refer to Appendix 13 for details on administration of multiple injections to the abdomen.

Study staff should refer to the IP Manual for specific instructions on the handling and preparation of the study intervention.

A cycle is defined as the time from Day 1 dose to the next Day 1 dose. Participants will receive a single dose of sasanlimab on Day 1 of each cycle. A cycle will be 28 days (±2 days) for SC administration. Each participant may receive sasanlimab until completion of study treatment, progression of disease, unacceptable toxicity, withdrawal of consent, participant no longer willing to participate in study, end of study, or study termination.

6.1.2. Order of Administration (Part 1B and Part 2)

On the days of scheduled administration of both PF-07263689 and sasanlimab, PF-07263689 IV push should be administered first, followed by SC injection of sasanlimab. Please refer to the IP Manual for specific instructions.

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention once reconstituted and/or diluted.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare each study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Vials are for single-use only.

Preparation of PF-07263689 will be carried out in accordance with local regulatory requirements for Biosafety/Containment level (Level 1 or Level 2 depending on countries) in pharmacy or laboratory, according to site's SOPs and all applicable laws and regulations.

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

6.2.2. Additional Instructions for PF-07263689

6.2.2.1. Special Handling of PF-07263689

Depending on the country, CCI [redacted] All applicable infection control policies should be consulted and followed. Refer to the current PF-07263689 IB and PF-07263689 Safety Data Sheet for recommendations on handling PF-07263689.

For more information regarding biohazard risk group classification and biohazard safety levels see The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), April 2019: https://osp.od.nih.gov/biotechnology/nih-guidelines/ and CDC Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th Edition: https://www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf or https://www.cdc.gov/labs/BMBL.html.

6.2.2.2. Transport of PF-07263689

6.2.2.2.1. Interstate Transport

PF-07263689 will be shipped interstate as a "Biological Substance, Category B" in compliance with International Air Transportation Association and Department of Transportation regulations and other local regulations.

6.2.2.2.2. Transport within the Clinic

PF-07263689 should be transported within a sealed plastic transport bag or other sealed, leak-proof secondary container displaying a clearly marked biohazard symbol. Refer to the IP manual for further instructions.

6.2.2.3. Handling and Thawing

BSL-2 infection control policies should be utilized for preparation, transport, and disposal of PF-07263689. Appropriate gowns, gloves, safety glasses with side shields or face shields should be worn at all times during handling. Refer to the IP manual for detailed instructions about preparation and storage of the investigational product.

6.2.2.4. Cleaning/Disinfection and Disposal

Standard institutional policies should be followed for cleaning and decontamination while handling vaccinia virus-based products. Hospital-grade chemical disinfectants containing bleach (with at least 0.6% of active chlorine), alcohols (≥60%), aldehydes, hydrogen peroxide (3%), iodophor (75 ppm), phenols or quaternary ammonium compounds are adequate for routine cleaning and disinfection of work area after PF-07263689 handling. The

manufacturer's instructions should be followed to ensure adequate contact time and confirm the ability of the equipment to withstand the disinfectant used.

All contaminated material (eg, syringes, catheters, needles, tubing, gloves, used or unused vials, containers, bandages, etc.) should be disposed of in a clearly-marked biomedical waste container and discarded according to regular institution procedure for infections waste ie, autoclaving, incineration, or treatment with sodium hypochlorite solution. Biomedical waste will not be left unattended in a public area; autoclaved medical waste must not be disposed of as regular trash.

Textiles and fabrics can be laundered in hot water (71°F) with detergent and hot air drying.

6.2.2.5. Spills or Environmental Contamination

In the event of a spill, people in the immediate area will be alerted and other institutional personnel will be notified as required by institutional policies. Refer to PF-07263689 IB and Safety Data Sheet, for detailed instructions.

Spills and accidents that result in overt exposures to infectious material will be reported according to Section 8.3.4 and as required by local institutional policies.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study.

6.3.1. Allocation to Study Intervention

This is an open-label study that will not be randomized. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

Allocation of participants to treatment groups in Part 2 will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.5. Dose Modification

Every effort should be made to administer study intervention on the planned dose and schedule. Dose modification is limited to interruption or skipping a dose based on outlined criteria (see Section 6.5.1 and Section 6.5.2). No dose reductions are allowed. In the event of significant toxicity, dosing may be delayed as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed and attribution for the combination treatment (for combination therapy). Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom. In addition to dose interruption or skipping a dose, investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Selected toxicities that do not resolve or worsen following supportive care and dose modifications and with a clinical presentation consistent with a potential irAE without a clear alternative explanation, may require treatment with corticosteroids or other immunosuppressants and should be managed according to the management of irAEs as described in Appendix 3.

6.5.1. PF-07263689

No dose reductions or delays are permitted. PF-07263689 must be administered ± 1 day of the scheduled dose. There are no planned delays outside of this window. If for any reason PF-07263689 is not given within the allowed treatment window, it will be cancelled. If participants do not complete at least 3 of 4 scheduled doses of PF-07263689 due to toxicity related to study drug, then study treatment should be permanently discontinued.

6.5.2. Sasanlimab

No dose reductions are permitted, but the next dosing of sasanlimab may be delayed or skipped for the cycle based on persisting toxicity (see Table 7).

Dose modifications may occur in one of 2 ways:

- Within a cycle: dosing interruption until adequate recovery, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.

Events including, but not limited to, pneumonitis, colitis, creatinine and LFT elevation should be monitored carefully with this class of agents.

Table 7. Sasanlimab Recommended Treatment Modifications for Drug-Related Toxicity (Excluding irAEs)

Hematologic toxicities	
Grade 1 and Grade 2	• Continue as per schedule.
• **Anemia Grade ≥3** (hemoglobin <8 g/dL)	• Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. • Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. • Permanently discontinue sasanlimab if anemia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
• Neutropenia Grade ≥3 (ANC <1000/μL)	• Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. • Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. • Permanently discontinue sasanlimab if neutropenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
• **Thrombocytopenia Grade ≥3** (platelets <50,000/μL)	• Hold sasanlimab and monitor weekly until resolution to Grade ≤1 or baseline. • Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. • Permanently discontinue sasanlimab if thrombocytopenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Non-hematologic toxicities	
Grade 1 and Grade 2	• Continue as per schedule.

Table 7. Sasanlimab Recommended Treatment Modifications for Drug-Related Toxicity (Excluding irAEs)

Grade 3	• Hold sasanlimab. • Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline. • Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • **Exceptions are:** laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow guidance in Appendix 3.
Grade 4	• Permanently discontinue sasanlimab. • **Exceptions are**: laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow guidance in Appendix 3.

To facilitate the early recognition and prompt intervention in the event of clinically meaningful sasanlimab-related AEs, management algorithms have been developed for suspected pulmonary, GI, liver, endocrine, skin, neurological and renal toxicities (see Appendix 3).

6.6. Continued Access to Study Intervention After the End of the Study

As this is a FIH clinical study, no post-trial study intervention is currently planned to be provided to study participants at the end of the study. Depending on the overall development path, the sponsor will make an effort to provide post-trial study intervention to appropriate participants who are tolerating treatment and continuing to experience clinical benefit.

6.7. Treatment of Overdose

For this study, any dose of PF-07263689 or sasanlimab greater than the assigned dose level at any scheduled administration visit will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the sponsor's medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 6 months after the overdose of study intervention (whichever is longer).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Pfizer Safety only when associated with an SAE.

5. Obtain a blood sample for PK analysis with clear documentation of the time it is collected relative to the date of the last dose of study intervention if requested by the sponsor's medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

All prior and concomitant treatments, received by participants from screening and up to 30 days after the last dose of study treatment, or up to the start of new anti-cancer therapy, including supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions) will be recorded on the CRF. Concomitant medications for AEs and SAEs should follow respective guidance for the AE and SAE reporting period. Only subsequent anti-cancer therapy initiated after end of study treatment(s) will be reported at the follow-up visits.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions received by participants from screening until the EOT visit will be recorded on the CRF.

Prohibited therapies and concomitant therapy instructions during the study are listed in this section and in the sub-study appendices. If there is a clinical indication for 1 of the medications specifically prohibited during the study, discontinuation from the study treatment may be required. Participants may receive other medications that the investigator deems to be medically necessary. The final decision on any supportive therapy rests with the Investigator and/or the participant's primary physician. The decision to continue the participant in the study requires mutual agreement of the investigator, the sponsor and the participant.

Any questions regarding administration of concomitant medications should be directed to the sponsor.

6.8.1. Other Prohibited and/or Limited use of Anti-tumor/Anti-Cancer or Experimental Drugs, or Procedures

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements for an anticancer treatment is not permitted.

In view of the current lack of data about the interaction of PF-07263689 with radiotherapy, palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. Palliative radiotherapy should be delayed until completion of PF-07263689 treatment.

6.8.2. Agents with Potential Inhibitory Activity Against Vaccinia Viruses

In the extremely unlikely case of generalized vaccinia virus infection, encephalitis or another clinically-significant, progressive toxicity that, in the opinion of the Investigator could be related to PF-0726389 replication. Investigators may consider the use of agents with vaccinia inhibitory activity, if available in their country for such clinical use. Such agents may include anti-vaccinia immune globulin (VIG), cidofovir, and/or Arestvyr. In addition, based on limited preclinical data, interferon, ribavirin, ganciclovir, and sorafenib may have anti-vaccinia activity.

None of these agents have been used or approved for this purpose to date. Since these agents have not been used in PF-07263689 treated participant, clinical judgement should be used when determining optimal regiment and duration of treatment.

The availability of these or similar antiviral products is country-dependent; options will be investigated and a plan for response to infection-related toxicities will be documented and communicated to study staff prior to initiation of the clinical trial.

6.8.3. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current ASCO guidelines (Schiffer et al, 2018).

6.8.3.1. Supportive Care for Superficial Skin Lesion(s)

A small (< 1 cm) superficial skin or oral mucous membrane lesion containing PF-07263689 may develop after PF-07263689 treatment. If lesions develop, they do so typically within 1 week after the first administration. These lesions generally resolve within approximately the following 2-3 weeks, a time course that is consistent with the usual course following intentional vaccination with non-attenuated vaccinia vaccine. Lesions may resolve without complications or the need for specific anti-viral treatment.

Participants will be recommended to treat any skin pox lesion(s) possibly related to virus with topical acyclovir/ganciclovir 5% six times per day for at least 7 days until lesion(s) have disappeared, and cover the lesion(s) with occlusive dressing or bandage.

6.8.3.2. Supportive Care for Infusion Related Reactions

In the event of infusion-related reactions, Investigators should institute treatment measures according to best medical and nursing practice.

If chills and fever (>100.4°F/38.0°C) or hypotension occur, the infusion should be interrupted. Participants should be treated symptomatically according to best medical and nursing practice and the infusion should be restarted at 50% of the original rate.

If infusion reactions, characterized by fever and chills, and less commonly hypotension, are experienced either by an individual participant or in other participants, pretreatment medication may be administered prior to subsequent doses to reduce the incidence and severity. The following pretreatment regimen is suggested, although a different regimen based on local standard of care is permitted:

- Participants should be pretreated with acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each study drug administration. Pretreatment medications will not be supplied by Pfizer. Suggested starting doses are 650 to 1000 mg acetaminophen and 50 mg diphenhydramine (or equivalent of other antihistamine) IV or oral. Two (2) additional doses of acetaminophen may be administered approximately every 4 to 6 hours after the initial pretreatment or as needed.

6.8.3.3. Supportive Care for CRS

Symptoms associated with CRS vary greatly and may be difficult to distinguish from other conditions. The more common symptoms include fever, nausea, headache, tachycardia, hypotension, rash, and shortness of breath. The severity of symptoms can be mild to life-threatening and thus there should be a high suspicion for CRS if these symptoms occur. The severity of CRS will be assessed according to the ASTCT modified grading (Lee et al, 2019). A suggested treatment algorithm for the management of CRS is provided in Appendix 11; however, if local standard of care is a different regimen, this should be utilized.

Depending upon study findings, a decision might be made to incorporate pre medication (ie, corticosteroids and other anti-inflammatory agents) for CRS prophylaxis in study participants. This decision would only occur following discussions between the sponsor and the investigators. Any pretreatment medication will not be supplied by Pfizer.

Potential medications to use in the supportive care of CRS, including active therapy and possibly prophylactic use, include these agents combined in a single regimen:

- Acetaminophen 650 mg PO
- Diphenhydramine 25 mg PO or IV
- Dexamethasone 20 mg PO or IV
- Corticosteroids (refer to Section 6.8.6)

In cases of suspected CRS, additional unscheduled blood samples will be collected for cytokine release assay analysis at the time of the event and every 2 to 3 days after at the discretion of the investigator (if there are no collections normally scheduled).

6.8.3.4. Supportive Care for Hypersensitivity Reactions Types 1 and 3

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of infusion and may include symptoms such as rash, urticaria, polyarthritis, myalgia, polysynovitis, fever, and, if severe, glomerulonephritis.

All participants should be closely observed while receiving study intervention infusions and monitoring for clinical signs of a systemic reaction will continue thereafter for clinical signs of allergic reactions/hypersensitivity.

In the case of a hypersensitivity reaction, the participant will be treated symptomatically with supportive care, further monitoring, and treatment with anti-histamines and/or corticosteroids. Study infusions may be stopped and the participant will be followed until the end of the study.

Detailed guidance on treatment, dose interruptions and potential retreatment is provided in Section 6.5.

6.8.3.5. Supportive Care for Immune-Related Adverse Events

While theoretically any immune checkpoint–blockade toxicity can occur at any time, certain toxicities have been reported earlier in the treatment course, while others develop as later complications. Commonly encountered irAEs include rash/dermatitis, diarrhea/colitis, hepatitis, and endocrinopathies. Algorithms for the clinical management of these events are provided in Section 10.3.5.

Prior to administration of the next dose of sasanlimab, the investigator should perform a comprehensive review of systems with specific focus on common and serious toxicities, such as skin changes, diarrhea and abdominal pain, headache, fever, shortness of breath, cough,

and neurologic changes. Routine laboratory testing, including hematologic profile, comprehensive metabolic panel, and TSH level, should be reviewed. Any new symptoms or abnormalities in examination or laboratory test results should be evaluated prior to administration of the next dose of sasanlimab.

6.8.4. Hematopoietic Growth Factors

Primary prophylactic use of colony stimulating factors is not permitted during the first 14 days of Cycle 1 Part 1, but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines (Schiffer et al, 2018). During the screening window, granulocyte colony stimulating factors are not permitted to qualify a participant with low WBC counts.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia. Erythropoietin is not approved in some countries for anemia caused by cancer treatment.

6.8.5. Antidiarrheal, Antiemetic Therapy

Primary prophylaxis beyond the first cycle is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Therapy section (Section 6.8).

6.8.6. Corticosteroids

Oral or parenteral steroids are not permitted during PF-07263689 treatment period, and for 1 week prior to and 2 weeks after PF-07263689 treatment. Chronic systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

If immune-related AEs occur, immune suppressive treatment should be administered according to local standards or practice.

The use of steroids during this study is restricted as follows:

a) Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in the respective sub-study appendices.

b) Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.

c) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection) are permitted.

Any other use of corticosteroids should be discussed with the sponsor before implementation.

6.8.7. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Therapy section (Section 6.8).

6.8.8. Vaccines Administration

No vaccines (licensed or investigational) other than study vaccine, influenza, and pneumococcal vaccines should be given during the study. Other vaccines may be administered only if medically necessary (eg, tetanus post exposure prophylaxis). COVID-19 vaccine should not be administered during the first 28 days of treatment (Cycle 1).

For participants who receive sasanlimab, live attenuated vaccines should not be administered within 30 days prior to or after dosing with sasanlimab. The administration of inactivated vaccines are allowed.

6.8.9. Surgery

Caution is advised for any surgical procedures during the study. The appropriate interval of time between surgery and PF-07263689 and sasanlimab required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping study intervention is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate study intervention treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery

6.8.10. Radiation Therapy

Palliative radiotherapy to a limited field but not to a target lesion(s) is allowed after consultation with the sponsor's medical monitor during study participation, unless clearly indicative of disease progression. Due to lack of data regarding the interaction of PF-07263689 with radiotherapy, PF-07263689 should be interrupted 7 days prior to the start of radiotherapy and resumed after the participant has returned to baseline. If the effects of palliative radiotherapy cannot be distinguished from the effects of PF-07263689 on antitumor efficacy, response assessments should be considered as non-evaluable.

6.8.11. Rescue Medicine

Standard medical supportive care must be provided to manage the AEs.

Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 5 days following the administration of study intervention. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Refer to Section 6.8.1 for agents with potential inhibitory activity against vaccinia viruses.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention may include the following:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

NOTE: In Part 1B and Part 2 where participants are treated with PF-07263689 in combination with sasanlimab, participants will be allowed to continue study treatment beyond progression, if the treating physician feels that it is in the participant's best interest in the case of radiological progression, and the absence of clear clinical progression.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for at least 90 days after discontinuation of study intervention. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

Follow-Up:

Participants will attend a follow-up visit 28 to 90 days after discontinuation of study intervention and survival follow-up visits Q12W (±7 days) until study discontinuation; the procedures for these visits are listed in the SoA.

7.1.1. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 μmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 μmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 μmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 participants in a given period are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 μmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.2. ECG Changes

A participant who meets either of the following criteria based on the average of triplicate ECG readings will be withdrawn from the study intervention:

- QTcF >500 msec.
- Change from baseline: QTcF >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Cardiac Adverse Events

Any participant who has an occurrence of Grade ≥3 myocarditis will be permanently discontinued from the study.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study may include:

- Refused further study procedures;
- Lost to followup;
- Treatment interruption;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for/attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to followup, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 500 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1. Efficacy Assessments

8.1.1. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging will include contrast enhanced chest, abdomen and pelvis computed tomography or MRI scans; brain computed tomography or MRI scan for participants with known or suspected brain metastases; bone scan and/or bone x-rays for participants with known or suspected bone metastases. For participants with known computed tomography contrast allergy, a non-contrast computed tomography of the chest with contrast enhanced abdominal and pelvic MRI can be used. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the , whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks). Tumor response assessment will be performed locally. Assessment of response will be made using RECIST version 1.1 (see Appendix 10).

All participants' files and radiologic images must be available for source verification and for potential peer review.

For Part 1A, participants will be assessed for radiological response on Day 43 (±5 day window). Additional scans may be performed Q6W (±7 days) following Day 43. For Part 1B and Part 2, all participants will be assessed for radiographic response Q6W (±7 day window) through Week 24 followed by Q12W (±7 days) until starting new anticancer therapy or at time of radiographic progression, whichever is earlier.

For Part 2 Dose Expansion, radiographic imaging scans may be submitted to a central imaging core laboratory for the purpose of holding for possible future central review if deemed necessary. In the event that central review is conducted, it would not be a complete medical review of participant and non-incidental findings will be shared with the PI, site staff, or participant. All safety reviews will be the sole responsibility of the site staff.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Safety assessments will include collection of AEs, SAEs, vital signs and physical examinations, ECG (12-lead), dermatologic examinations, laboratory assessments, including pregnancy tests and verification of concomitant treatments.

8.2.1. Participant Demographics and Other Baseline Characteristics

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include relevant medical and surgical history within the last 10 years and current illnesses.

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's malignancy under study, including date and stage at initial diagnosis, date and extent of metastatic disease at study entry, tumor histology and known gene alterations, relevant disease characteristics and prior anti-cancer treatments, including systemic, radiation and surgical procedures, will be recorded.

8.2.2. Physical Examinations

Participants will have a physical examination to include weight, vital signs, assessment of ECOG performance status, and height; height will be measured at screening only.

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses. As superficial skin lesions or oral mucous membrane lesion may develop after PF-07263689 treatment, investigators should report any clinical findings.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat

surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.3. Skin Monitoring

Participants should be monitored not only for infusion site reactions but also any skin lesions in whole body following PF-7263689 administration (Parts 1A, 1B, and 2), as well as injection site reactions following administration of sasanlimab (in Parts 1B and 2). Record the location of the infusion and skin lesions found other than infusion site, and, for combination treatment with sasanlimab, record the injection site location, time of each injection and any injection site reactions in the participant's source records and study CRF.

8.2.4. Vital Signs

BP and pulse rate measurements will be assessed either in the sitting position with feet supported (ie, not dangling) or the supine position. It is recommended that the same position be used consistently throughout the study duration unless circumstances, eg, hospitalization, dictate otherwise. BP should be obtained using the auscultatory method or via an automated BP device, ensuring use of an appropriately sized cuff on the bare arm and consistent technique of measurement (eg, using the same arm each time). Care should be taken to use the appropriate size BP cuff for the participant's arm circumference as incorrect cuff sizes can lead to falsely elevated BP measurements.

Abnormal readings should be repeated and confirmed.

Pulse rate preferably should be obtained using a pulse oximeter, automated BP device, or other pulse measurement device. Temperature may be determined using oral, tympanic, axillary, or temporal (ie, forehead scan) methods of measurement, as long as the chosen method is used consistently (oral preferred).

During inpatient monitoring, temperature, pulse rate, and BP will be collected every 6 hours (±10 min) and as needed.

Pulse oximetry (SpO2) will also be measured as described on SoA.

8.2.5. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead

placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

Triple 12-lead ECGs should be performed approximately 1 to 4 minutes apart to determine mean QTcF interval.

If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QT value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.6. Echocardiogram or MUGA

Participants must be in supine position in a rested and calm state for at least 5 minutes before LVEF assessment is conducted. If the participant is unable to be in the supine position, the participant should be in the most recumbent position possible.

The investigator or designated site physician will review all echocardiograms. Once signed, the original echocardiogram will be retained with the participant's source documents. At the request of the sponsor, a copy of the original echocardiogram will be made available to Pfizer. Standard echocardiogram machines should be used for all study-related echocardiogram requirements.

Echocardiogram or MUGA will be measured at time point(s) specified in the SoA or if clinically warranted. Imaging method must be consistent throughout the study for individual participants.

8.2.7. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 (±7) days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

No need to repeat a clinical laboratory assessments on Cycle 1 Day 1 if the baseline assessment was performed within 14 days prior to that date.

8.2.8. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the 30-day follow-up visit. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.2.9. Vector Shedding Kinetics and Infectivity Assessments:

Whole blood will be collected for viral load kinetics of PF-07263689 according to the SoA table.

In addition, saliva, urine, injection site swabs, and swabs from any spontaneous skin lesions will be collected for vector shedding according to the SoA table.

Samples, except blood, that are positive for viral DNA in qPCR shedding assay at levels above the LLOQ of the infectivity will be analyzed for infectious virus. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor.

The actual date and time (24-hour clock time) of each sample will be recorded. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the sampling time window specified in Table 4 and Table 5 (collection of samples within 10% of the nominal time relative to dosing [eg, within 6 minutes of a 60-minute sample]) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, patient, and sponsor.

Samples collected for analyses of PF-07263689 in whole blood, saliva, urine, injections site swabs, and swabs from any spontaneous skin lesions, may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for evaluation of the bioanalytical method, or for other internal exploratory purposes.

Samples collected for measurement of viral load kinetics in whole blood, vector shedding in saliva, urine, injection site swabs, and swabs from spontaneous skin lesions will be analyzed using a validated analytical method in compliance with applicable SOPs.

Viral load kinetics and vector and shedding samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK and shedding sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.2.10. Mouth Swab and Urine Specimens

Mouth swabs should be collected as described in the Laboratory Manual.

Participant will collect a mid-stream urine sample of approximately 50 mL. Urine samples will be processed according to the Laboratory Manual.

Specimens will be collected as specified in the SOA. If the specimen is positive on Day 22 then follow-up specimen collection will be performed on Day 29 (C2D1) and also potentially on Day 43 if the Day 29 (C2D1) sample is positive.

8.2.11. Photographs of Skin Lesions

Documentation by color photography, including a ruler (or caliper) to estimate the size of the lesion, is recommended. Photographs of visible skin lesions may be taken at any time during the study period, or copies of pre-existing photographs may be collected if available. Whole limb photographs may be taken at baseline, as appropriate, to document overall disease status and to document responses. If any clinically notable visible phenomenon appears at any time, this should be photographed and followed up by photography at each subsequent visit until it resolves. The sponsor may use, copy and/or distribute the photographs for educational purposes, in scientific lectures, journal articles, and textbooks. The sponsor may also use the photographs for general commercial purposes and may have the photographs published, circulated, or presented in any way either alone or with other written, printed, graphic, or audio matter to members of the medical, nursing, pharmaceutical and related progressions, as well as to the public at large. The participants' identity will not be disclosed in any photographs. Written authorization must be obtained from the participants and IRB/IEC/REB prior to the release of such information.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant/parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing

any study related procedure and/or receiving study intervention), through and including a minimum of 90 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form. The SAEs identified during long-term follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study intervention.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

If an accidental human exposure to PF-07263689 occurs, the following is recommended:

- Implementation of local, institutional needle stick, or other exposure guidelines.
- Wash area thoroughly with soap and water.
- Cover area with non-occlusive dressing and provide local wound care (as needed) until complete resolution.

Refer to Section 5.3 for additional details and management guidance.

The investigator must report any instance of environmental exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the environmental exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file. If applicable, the institution's Biosafety Specialist should be informed.

8.3.5.1. Exposure During Pregnancy

An exposure during pregnancy (EDP) occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by semen, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by semen, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedural test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by semen, inhalation, or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with

authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file. If applicable, the institution's Biosafety Specialist should also be informed. Refer to Section 5.3.2 for additional details.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Based on the GLP nonclinical studies, the key toxicities of potential clinical importance that should be classified as AESIs CCI [redacted], which may manifest at any time during treatment. Such events include but are not limited pneumonitis, myocarditis, hepatitis, colitis, endocrinopathies, and rash. As a routine precaution, participants will be admitted for inpatient monitoring for CCI [redacted] following the first dose of PF-07263689 and a CCI [redacted] following the second dose of PF-07263689. For subsequent doses (Day 15 and Day 22), all participants must be observed for 4 hour post infusion.

Adverse events of special interest (AESIs) are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

This study is primarily designed to investigate the safety of PF-07263689; thus, this does not apply.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include, but are not limited to:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Pharmacokinetics

PK samples will be collected for sasanlimab only. Traditional PK analysis is not considered relevant for oncolytic viruses/cancer vaccines (FDA, 2013; WHO, 2005).

Blood samples (approximately 3 mL) to provide serum for the analysis of sasanlimab concentrations will be collected, in Parts 1B and Part 2 of the study as outlined in the SoA.

The actual date and time (24-hour clock time) of each sample will be recorded. In addition to samples collected at the scheduled times, an additional blood sample should be collected from participants experiencing unexpected and/or serious AE's and the date and time of blood sample collection and of last dosing prior to PK collection documented in the CRF.

Samples collected for analyses of sasanlimab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these serum samples (unless consent for this was included in the informed consent). Participant confidentiality will be maintained.

Samples collected for measurement of serum concentrations of sasanlimab will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.5. Genetics

8.5.1. Specified Genetics

Not applicable.

8.5.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s) and the cancer under study. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

8.6. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Optional samples for biomarker research that should be collected from participants in the study as appropriate are the following:

- CCI [redacted]

Biospecimens collected for target engagement, pharmacodynamic and other biomarker assessments will include peripheral blood and tumor tissues which will be used to (1) detect virus/transgene, and (2) analyze DNA, RNA, and proteins, for achieving planned biomarker objectives. Refer to the SoA for sample collection time points and Study/Laboratory Manual for sample processing and shipping. The following biospecimen types are planned to be collected in support of study objectives. Additional biospecimens collected over the course of participant disease management may be submitted for biomarker analyses.

8.6.1. Tumor Biopsies

Tumor biospecimens from archival, de novo pretreatment, and on-treatment biopsies will be used to analyze candidate nucleic acid and protein biomarkers for their ability to (1) demonstrate the presence of virus and transgene expression in tumor post-treatment, and (2) identify those participants who are most likely to benefit from treatment with the study drugs. Biomarkers may include, but are not limited to, nucleic acid and protein analyses, as well as cell types and constituents of the TME. De novo tumor biopsies obtained upon disease progression may be used to investigate target engagement, pharmacodynamic activities,

mode of action and acquired mechanisms of resistance ie, presence of virus/transgene, evaluating immune cells by quantifying intra-tumoral CD8+ T cells, regulatory T cells, NK cells or dendritic cells in on-treatment versus baseline TME. Additional information on tissue collection procedures can be found in the Laboratory/Study Manual.

Pre-treatment archival FFPE material containing tumor that is of diagnostic quality and representative of the diagnosed malignancy collected ≤1 year prior to study start is required of all participants, and if not available, a pre-treatment de novo (fresh) tumor biopsy will be required. If the archived sample is older than 1 year and a biopsy during screening cannot be performed, the investigator must contact the sponsor to discuss eligibility prior to enrollment.

CCI [redacted]

Participants should not be subjected to a significant risk procedure to obtain the biopsies (ie, the absolute risk of mortality or major morbidity in the participant's clinical setting and at the institution completing the procedure should be <2%). Additional information on tissue collection procedures can be found in the Laboratory Manual.

CCI [redacted]

CCI [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

8.6.2. Whole Blood, Plasma, Serum

CCI [redacted]

4 ml of blood samples for exploratory molecular analysis and biobanking will be collected at the time specified in the SoA. Instructions for sample collection, processing, storage shipment and detailed panels of cytokine/chemokine and immunophenotyping markers will be provided in the laboratory manual.

8.6.3. Retained Research Samples for Biomarkers

Retained Research Samples for Biomarkers will not be collected in this study.

8.7. Immunogenicity Assessments

8.7.1. PF-07263689 Immunogenicity Assessments

Blood samples of approximately 4 mL will be collected to provide serum for analyses of anti-IL-2 antibodies and detection of anti-VV NAb into appropriately labeled tubes, in Part 1A, Part 1B, Part 2 of the study, at times as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes.

Genetic analyses will not be performed on these plasma/serum/whole blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

8.7.2. Sasanlimab Immunogenicity Assessments

Blood samples of approximately 4 mL, to provide serum for detection of ADA and NAb against sasanlimab will be collected into appropriately labeled tubes, in combinations portions of Part 1B and Part 2 of the study, at times as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.8. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

There is no formal hypothesis testing in this study.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined.

Participant Analysis Set	Description
Full Analysis Set (FAS)	All enrolled participants. Enrolled denotes a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety Analysis Set (SAS)	All enrolled participants who receive at least 1 dose of study intervention. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses.
DLT Evaluable Set	This is defined for the DLT observation period only. A participant is classified as DLT evaluable if they either 1.) receives at least 3 of 4 doses of PF 07263689, did not miss the first and the last dose, and has completed the safety assessments during the DLT observation period or 2) has experienced a DLT. If a participant withdraws from the study during the DLT observation period, they may be replaced by a participant at the same dose. The sole exception to criterion 1.) is if the participant has missed a minority of safety assessments due to emergency situations (eg, site accessibility issues, inability to go to an external lab, etc.). In such cases, the DLRM may judge the participant evaluable, depending on the abundance of the available data.
Blood viral load Kinetics Parameter Set	All enrolled participants treated who do not have protocol deviations influencing viral load kinetics assessment, and have sufficient information to estimate at least 1 of the parameters of interest.
Vector Shedding Analysis Set	All enrolled participants who are treated and have at least 1 analyte concentration above the lower limit of quantitation.
Response Evaluable Set	All enrolled participants who received at least one dose of study treatment and had adequate baseline disease assessment and at least one post baseline disease assessment. Patients who discontinued early or died will be included.
Pharmacodynamic/ Biomarker Analysis Set(s)	The Pharmacodynamic/Biomarker analysis population is defined as all enrolled participants with at least 1 of the Pharmacodynamic/Biomarkers evaluated at pre and/or post dose.
Immunogenicity Analysis Set	The immunogenicity analysis set includes all enrolled participants who received at least one dose of study treatment and have at least one sample tested for ADA.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

9.3.2. Primary Endpoint(s)/Estimand(s)/Analysis

For Part 1, determination of MTD is achieved prior to the MFD will be performed using the DLT Evaluable set.

The dose escalation in the Part 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07263689 using a 2-parameter BLRM (Part 1A) or for the combination of PF-07263689 and sasanlimab using a 5-parameter BLRM (Part 1B). Weakly informative prior distributions based on preclinical/expert opinion information will be chosen for the logistic parameters in Part 1A; the observed DLT data in Part 1A and DLT data of sasanlimab will be used to form prior distribution for the BLRM in Part 1B (see Appendix 9).

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07263689 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0, 0.16]
Targeted dosing:	[0.16, 0.33]
Overdosing:	[0.33, 1]

Dosing decisions are guided by the EWOC principle (Rogatko 2007). A dose may only be used for newly enrolled participants if the risk of excessive toxicity at that dose is less than 25%. Initially, dose escalation increases will be limited to no more than a half log increase from the previous dose level, which is a common approach for biologic compounds (Saber et al. 2017; Saber et al. 2016). Following the observation of a DLT in the current cohort, subsequent dose escalation increases will be limited to no more than 100%. A return to half log dose increases may be permitted at the discretion of the sponsor if no DLT are seen at the following dose level.

Stopping criteria

The dose escalation will be stopped when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD or at the MFD.
- The dose satisfies 1 of the following conditions:
    - The probability of target toxicity at dose exceeds 50%, ie, Pr(0.16 ≤0.33)≥50%.
    - A minimum of 15 participants have been treated in the study.

In case all doses explored appear to be overly toxic and the MTD cannot be determined, the overall study will stop.

Dose escalation will stop when stopping criteria are met (see DLT Definition).

Additionally, when any of the following safety criteria are met, enrollment and study intervention administration will be paused, all available clinical safety data will be reviewed by the Sponsor together with the Investigators prior to determining next steps:

- Any death that is not related to disease progression occurring within 30 days of receiving IP or does not have a determined alternative etiology.
- Occurrence of 2 Grade ≥4 DLTs in 2 study participants at the starting dose.
    - For subsequent dose levels after the starting dose, a criterion guiding pause on enrollment at the current cohort is defined based on Bayesian posterior probabilities using a non-informative Beta (0.5, 0.5) prior distribution. The probabilities will be calculated for total number of participants in the current cohort. The safety criterion is met if the number of evaluable participants observed to have a DLT due to Grade 4 or higher AE results in a posterior probability that the true rate of such event exceeding 30% is ≥0.80.
- Any Grade 4 hypersensitivity reaction/anaphylaxis observed.

CCI [redacted] which satisfies the EWOC criterion. A full assessment of the prior risk to participants is given in Appendix 9.

To mitigate the risk of misclassifying DLTs, a sensitivity that uses weighted DLT/AE data (in equivocal cases) within the BLRM may be performed. If all investigators and the sponsor agree on the equivocal DLT/AE data, the DLT weighting approach could be the primary dose escalation method.

For Part 2, ORR will be a primary endpoint, along with safety and tolerability assessment. ORR evaluation, as well as other secondary efficacy endpoints, are described in Section 9.3.3.

9.3.3. Secondary Endpoint(s)/Estimands Analysis

9.3.3.1. Efficacy Endpoint(s)

Response evaluable set will be used for all response related analysis including ORR and DOR. Tumor response will be presented in the form of participant data listings that include, but are not limited to, tumor type, dose on Day 1, tumor response at each visit, and best overall response. In addition, progression date, death date, date of first response and last assessment date, and date of last contact will be listed. A summary of tumor response and best overall response based on RECIST 1.1 will also be presented.

The Kaplan-Meier method will be used for time-to-event type of efficacy endpoint.

The efficacy endpoints that will be analyzed in this study are defined as follows:

- ORR is defined as the percentage of participants with a best overall response of CR or PR relative to the appropriate analysis set.
- DOR is defined as the time from first documentation of CR or PR to date of first documentation of PD or death due to any cause.
- PFS is defined as time from start date of treatment to the date of first documentation of PD or death due to any cause.
- TTP is defined as the time from start date of treatment to the date of the first documentation of PD.
- OS is the time from start date of treatment to the date of death due to any cause.

The detailed analyses will be described in the SAP.

9.3.3.2. Sasanlimab Pharmacokinetic Analysis

The concentration-time data of sasanlimab will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) according to dosing cohort and time for each part of the study.

9.3.3.3. Viral Load Kinetics and Vector Shedding Analysis

Viral load kinetics in whole blood: Individual participant whole blood viral titer-time data after first dose and after second dose will be analyzed using noncompartmental methods to determine relevant parameters. The parameters will include whole blood C_{max}, whole blood T_{max}, and AUC from time 0 to the last quantifiable time point (AUC_{last}).

Vector shedding in saliva, urine and skin swabs: Viral titers in each matrix will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose, day and nominal time.

Peak viral titer levels from shedding qPCR assay in saliva, and urine will also be summarized descriptively by dose cohort and study visit separately if sufficient data is available. Further, duration of shedding may be reported if sufficient data is available. For samples that are tested for infectious virus, descriptive statistics will be provided for each matrix by dose, day, and nominal time.

9.3.3.4. Analysis of Immunogenicity Data

For the PF-07263689 immunogenicity data, the percentage of participants with anti-vaccinia virus neutralizing antibodies and positive anti-IL2 antibodies will be summarized.

For sasanlimab immunogenicity data, the percentage of participants with positive ADA and neutralizing antibodies will be summarized. For participants with positive ADA or neutralizing antibodies, the magnitude (titre), time of onset, and duration of ADA or neutralizing antibodies response will also be described, if data permit.

9.3.4. Tertiary/Exploratory Endpoints

For the tertiary and exploratory endpoints as described in Section 3, summary statistics will be presented. For each pair of specimens, the percent change from baseline will be calculated.

Results from tertiary/exploratory analyses will be reported in the CSR where possible. However, given the exploratory nature of exploratory objectives and endpoints, the analyses may not be complete at the time of the CSR. Results from exploratory analyses that are not included in the CSR will be shared with the scientific community through publication at a scientific conference and/or in a peer-reviewed scientific journal. Detailed analysis for the tertiary and exploratory endpoints will be specified in a separate technical document outside of the SAP.

9.3.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, cardiac monitoring results, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories (see Table 9) will be tabulated by treatment:

Table 9. Safety QTcF Assessment

Degree of Prolongation	Mild (ms)	Moderate (ms)	Severe (ms)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as the most recent ECG measurements prior to the cycle 1 day 1 dosing.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for HR (QTcF) using standard correction factors (ie, Fridericia's (default correction), Bazett's, and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT interval, HR, RR interval, PR interval, QRS complex, QTcF *(*and other correction factors, eg, QTcB as appropriate), and by dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute value of the corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point. Details of additional analysis (if any) will be specified in SAP.

9.3.5.2. AEs

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using MedDRA. AE data will be reported in tables and listings. Summaries of AE by appropriate MedDRA terms, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death and premature withdrawal from study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Listings of DLTs and deaths will be provided.

9.3.5.3. Laboratory Test Abnormalities

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

CCI [redacted]

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

CCI [redacted]

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant’s personal data.

The participant or his or her legally authorized representative must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or his or her legally authorized representative.

The participant or his or her legally authorized representative must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or his or her legally authorized representative must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 60 days from the previous ICD signature date.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local

laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data available from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including the definition of study critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the contract.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Study Management Plan which is maintained by the sponsor.

Description of the use of the computerized system is documented in CRF Guidelines, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.
- Sites in a specific country may be closed early if enrollment is complete in that country but is ongoing in other countries to meet a required number of participants.
- Sites may be closed early if they are unable to continue to enroll participants if a treatment arm is discontinued, as described in Section 9.4.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed

confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Assessments

The following laboratory tests will be performed at times defined in the SoA section of this protocol (see Table 10). Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 10. Laboratory Tests

Phase 1	Notes
Hematology	Database should be constructed to allow capture of differential counts as percent and absolute values but only one or the other should be used by the site to collect data. Results will be reported as absolute values after conversion and graded according to the CTCAE criteria
Hemoglobin	
Platelets	
WBC	
Absolute Neutrophils	
Absolute Lymphocytes	
Absolute Monocytes	
Absolute Eosinophils	
Absolute Basophils	
Chemistry	
ALT	
AST	
AP	
Sodium	
Potassium	**Ad hoc Central Lab Cytokine Analyses**[a]
Magnesium	IL-6
Chloride	IL-10
Total Calcium	IL-1β
Total Bilirubin***	IL-2
BUN or Urea	sIL2R
Creatinine	IL-15
Uric Acid	IL-17
Glucose (non-fasted)	IL-1b
Albumin	IL-8
Phosphorus or Phosphate	IFNγ
	MCP-1
Coagulation	IP10
PT or INR	TNF-α
PTT/aPTT	Other cytokines
Urinalysis	
Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)	
Urine dipstick for urine blood: if positive collect microscopic (Reflex Testing)	
Pregnancy Test	
For female participants of childbearing potential, on serum or urine (to be specified in the protocol)	
Hepatitis Serology	**Cardiac Biomarkers**
HBsAg	CPK (CK-MP)

Table 10. Laboratory Tests

anti-HCV antibody or HCV RNA	Troponin I and/or Troponin T
Endocrinology	
ACTH	
TSH	
Free T4	
Tumor Biomarkers	
CA125 for OvCA	
CEA for CRC	
CA15-3 for BRCA	
PSA for prostate cancer	

***For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and alkaline phosphatase.

a. Cytokines for central lab evaluation will be collected if CRS is suspected. Local lab evaluation of cytokine is only required if the site requires this information for participant management.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:
a. Results in death.
b. Is life-threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity.

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has

a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Severity section).

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with exposure during pregnancy or breastfeeding **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE). **

Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

***Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

The investigator will then record all relevant AE or SAE information in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Severity

- The investigator will make an assessment of severity for each AE reported during the study and assign it to 1 of the categories listed below (as defined by the NCI CTCAE system). An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

GRADE	Clinical Description of Severity
1	MILD AE
2	MODERATE AE
3	SEVERE AE
4	LIFE-THREATENING; urgent intervention indicated
5	DEATH RELATED TO AE

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- New or updated information will be recorded in the originally submitted documents.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.

- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.3.5. Guidance for Immune-Related Adverse Events

Table 11. Management of Immune-Related Adverse Events

	Grade	Management	Follow-Up
Gastrointestinal irAEs	**Grade 1** Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	Symptomatic treatment	Continue study intervention therapy
	Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold study intervention therapy Symptomatic treatment	If improves to Grade 1: Resume study intervention therapy. If persists >5-7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent. When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study intervention therapy per protocol. If worsens or persists >3 to 5 days with oral steroids: Treat as Grade 3 to 4.
	Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs	Discontinue study intervention therapy. 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent. Add prophylactic antibiotics for opportunistic infections Consider endoscopy.	If improves: Continue steroids until Grade 1, then taper over at least 1 month. If persists >3 to 5 days, or recur after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis.
Dermatitis irAE	**Grade 1 to 2** Covering ≤30% body surface area	Symptomatic therapy (eg, antihistamines, topical steroids) Continue study intervention therapy.	If persists >1 to 2 weeks or recurs: Consider skin biopsy Withhold study intervention therapy. Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study intervention therapy If worsens: Treat as Grade 3 to 4.
	Grade 3 to 4 Covering >30% body surface area; life threatening consequences	Withhold or discontinue study intervention therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent.	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. Resume study intervention therapy.

Table 11. Management of Immune-Related Adverse Events

	Grade	Management	Follow-Up
Pneumonitis irAEs	**Grade 1** Radiographic changes only	Consider delay of study intervention therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults.	Re-image at least every 3 weeks If worsens, treat as Grade 2 or Grade 3 to 4.
	Grade 2 Mild to moderate new symptoms	Withhold study intervention therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy.	Re-image every 1 to 3 days If improves: When symptoms return to near baseline, taper steroids over at least 1 month and then resume study intervention therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
	Grade 3 to 4 Severe new symptoms; New/worsening hypoxia; life-threatening	Discontinue study intervention therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to baseline: Taper steroids over at least 6 weeks. If not improving after 48 hours or worsening: Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil).
Hepatitis irAEs	**Grade 1** Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue study intervention therapy.	Continue liver function monitoring If worsens, treat as Grade 2 or 3 to 4.
	Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Withhold study intervention therapy Increase frequency of monitoring to every 3 days.	If returns to baseline: Resume routine monitoring, resume study intervention therapy. If elevations persist >5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study intervention therapy.
	Grade 3 to 4 AST or ALT >5 x ULN and /or total bilirubin >3 x ULN	Discontinue study intervention therapy. Increase frequency of monitoring to every 1 to 2 days.	If returns to Grade 2: Taper steroids over at least 1 month. If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily.

Table 11. Management of Immune-Related Adverse Events

	Grade	Management	Follow-Up
		1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist. Consider obtaining MRI/ computed tomography scan of liver and liver biopsy if clinically warranted.	If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Endocrine irAEs	Asymptomatic TSH abnormality	Continue study intervention therapy.	If TSH <0.5 x LLN, or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult.
	Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary MRI scan. If symptomatic with abnormal lab/pituitary scan: Withhold study intervention therapy: 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent. Initiate appropriate hormone replacement therapy. If normal lab/pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks/MRI in 1 month.	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections. Resume study intervention therapy. Participants with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
	Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Withhold or discontinue study intervention therapy. Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids. Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy.	
	Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue study treatment Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Table 11. Management of Immune-Related Adverse Events

	Grade	Management	Follow-Up
		Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	
	Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold study treatment Consider hospitalization ----- Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	Resume study treatment once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
	Hypopituitarism/ Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : -Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) -Hormone replacement/suppressive therapy as appropriate -Perform pituitary MRI and visual field examination as indicated **If hypophysitis is confirmed:** -Continue study treatment if mild symptoms with normal MRI. Repeat the MRI in 1 month -Withhold study treatment if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month.	Resume study treatment once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume study treatment only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

Table 11. Management of Immune-Related Adverse Events

	Grade	Management	Follow-Up
		Add prophylactic antibiotics for opportunistic infections.	
Renal irAEs	**Grade 1** Creatinine increased > ULN to 1.5 x ULN	Continue study treatment	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
	Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold study treatment Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume study treatment following steroids taper. If worsens: Treat as Grade 4.
	Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue study treatment Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs Myocarditis	New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin I, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold study treatment. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Consult cardiologist to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start study treatment. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
	Immune-mediated myocarditis	Permanently discontinue study treatment. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A, abatacept).
Other irAEs (not described above)**	**Grade 2 or Grade 3** clinical signs or symptoms suggestive of a potential irAE	Withhold study treatment pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting study treatment

Table 11. Management of Immune-Related Adverse Events

	Grade	Management	Follow-Up
			If irAE is confirmed, treat as Grade 2 or 3 irAE.
	Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold study treatment 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume study treatment following steroids taper.
	Recurrence of same Grade 3 irAEs	Permanently discontinue study treatment 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
	Grade 4	Permanently discontinue study treatment 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue study treatment Specialty consult	

*Local guidelines, or eg. ESC or AHA guidelines
ESC guidelines website https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website: https://www.heart.org/en/professional/quality-improvement
**For other irAEs not specifically covered in this table (such as uveitis), refer to the NCCN Management of Immunotherapy-Related Toxicities for detailed guidance:
https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1486

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 90 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 90 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 90 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing and Non-Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition,

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

        - A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion. [eg, bilateral tubal ligation]

5. Vasectomized partner.

    - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole 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. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

- Transdermal;

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

8. 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 intervention. 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.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
- [redacted]
- [redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are “adaptors” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AE
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcB or QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious AE
• QTcF prolongation >500 ms. • New ST-T changes suggestive of myocardial ischemia. • New-onset left bundle branch block (QRS >120 ms). • New-onset right bundle branch block (QRS >120 ms). • Symptomatic bradycardia. • Asystole: • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node. • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer. • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm. • Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAE

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.8.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Participants with active infections are excluded from study participation as per Exclusion Criterion #28. When the infection resolves, the participant may be considered for rescreening.

10.8.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.8.3.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.8.3. Alternative Facilities for Safety Assessments

10.8.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- All safety laboratory tests (Table 10)

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.8.3.2. Imaging

If the participant is unable to visit the study site for safety imaging assessment(s), the participant may visit an alternative facility to have the safety imaging assessment(s) performed. Qualified study site personnel must order, receive, and review results.

10.8.3.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.8.3.4. Echocardiogram or MUGA

If the participant is unable to visit the study site for Echocardiogram or MUGA, the participant may visit an alternative facility to have the Echocardiogram or MUGA performed. Qualified study site personnel must order, receive, and review results.

10.8.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

The following is recommended for the administration of study intervention for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to consider potential drug-drug interactions as described in Section 6.8 for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.8.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the SoA. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Review and record study intervention(s), including compliance and missed doses.

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.5.

- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.8.3.1 of this appendix regarding pregnancy tests.

10.8.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.8.7. Efficacy Assessments

If the participant is unable to visit the study site for CT or MRI scan, the participant may visit an alternative facility to have the CT or MRI scan performed. Qualified study site personnel must order, receive, and review results.

10.8.8. Independent Oversight Committees

No IOCs will be used in this study.

10.9. Appendix 9: Detailed Dose Escalation/De-Escalation Scheme for BLRM Design

This appendix provides the details of the statistical model, the general description of the prior distribution of the model parameters, and the sensitivity analysis. The BLRM will be set up separately for the dose-toxicity relationship when PF-07263689 when administered as monotherapy (Part 1A) and in combination with sasanlimab (Part 1B). The derivation of prior distributions for the model parameters is detailed in a separate Technical Supplement to this appendix. The results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model are also presented in the separate Technical Supplement.

10.9.1. Statistical Model for Monotherapy

Let $rr(d)$ be the risk of DLT for PF-07263689 given as a single agent at dose d. The dose-DLT model is logistic:

$$\text{Logit}(rr(d)) = \log(a) + [3\log(d / d*)$$

$d*$ is the reference dose in the model and will be used to scale the doses of PF-07263689. Hence, α (>0) are the PF-07263689 odds of a DLT at $d*$; and β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the parameters $\log(\alpha)$ and $\log(\beta)$. A weakly informative prior will be used as there are no relevant human historical DLT data available for PF-07263689. It is assumed that model parameters will follow a bivariate normal (BVN) distribution.

$$(\log(a), \log([3)) \sim N\_2(m, S)$$

with prior means $m = (m\_1, m\_2)$, and prior covariance matrix *S* composed of standard deviations and the correlation. The specifications of these parameters, and the operating characteristics of the BLRM are detailed in the separate Technical Supplement document.

10.9.2. Statistical Model for Combination with Sasanlimab

In dose finding Part 1B, the dose/DLT relationship will be described by a 5-parameter BLRM for the combination of PF-07263689 with sasanlimab, formulated as follows:

- PF-07263689 single agent toxicity, represented by parameters α_1, and β_1.

$$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log\left(\frac{d_1}{d_1^*}\right)$$

- The single agent toxicity of sasanlimab, represented by parameters α_2, and β_2.

$$\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log\left(\frac{d_2}{d_2^*}\right)$$

where $\pi_1(d_1)$ and $\pi_2(d_2)$ are the probability that a participant experiences a DLT during the first cycle of combination treatment with PF-07263689 and sasanlimab at dose d_1 and d_2 respectively and where d_1^* and d_2^* are the PF-07263689 and sasanlimab reference doses.

Then, the dose-DLT relationship of the combination is defined as:

$$\text{Odds}(rr_{12}(d_1, d_2)) = \frac{rr_{12}(d_1, d_2)}{1 - rr_{12}(d_1, d_2)}$$
$$= \exp(\eta_{12}) \left[\frac{rr_1(d_1) + rr_2(d_2) - rr_1(d_1)rr_2(d_2)}{(1 - rr_1(d_1))(1 - rr_2(d_2))}\right]$$

where η_{12} is the interaction parameter between PF-07263689 and sasanlimab. The interaction parameter is set up depending on the assumption that the drug combination may produce a toxic effect whose magnitude is less than (protective, $\eta_{12} < 0$), equal to (no interaction, $\eta_{12} = 0$), or greater than (synergistic, $\eta_{12} > 0$) that obtained by the treatments acting independently.

The Bayesian approach requires the specification of prior distributions for the model parameters $\log(a_1)$, $\log([3_1)$, $\log(a_2)$, $\log([3_2)$ and the interaction parameter η_{12}. The prior for $\log(a_1)$, $\log([3_1)$ will be based on emerging DLT data from PF-07263689 in Part 1A. The prior for $\log(a_2)$, $\log([3_2)$ will be based on safety data available in the literature for Palbociclib. A weakly informative prior for the interaction parameter η_{12} will be used reflecting the current uncertainty about the interaction.

Meta-Analytic-Predictive Priors Approach

A MAP prior may be used to define the prior for any or all of the treatment in the dose escalation in order to account for heterogeneity between the available safety data and the actual study protocol population and treatment regimen/schedule. A MAP prior may be used instead of, or in addition to a weakly informative prior to form a weighted mixture prior and account for uncertainty. A mixture prior can take the form

$$p \times BVN_{MAP} + (1 - p) \times BVN_{Weak}$$

The weights of the mixture prior are driven by clinical judgement. The aim of the MAP prior approach for treatment is to derive a prior distribution for the logistic parameters $(\log(a_i^*), \log([3_i^*))$ using prior DLT data, available from previously conducted trial, or from the same study but with another regimen.

Let r_i and n_i be the number of participants with a DLT, and the total number of participants at dose d_i in the DLT data available from the historical trial. The corresponding probability of a DLT is rr_{di}. The model specifications are as follows:

$$r_i \mid rr_{di} \sim Bin(rr_{di}, n_i)$$

$$logit(rr_{di}) = \log(a_i) + [3_i \log(d_i/d^*)$$

$$(\log(a_i), \log([3_1)) \; I \; \mu, 1/ \sim BVN(\mu_i, 1/_i)$$

$$(\log(a_i^*), \log([3_i^*)) \; I \; \mu, 1/ \sim BVN(\mu_i, 1/_i)$$

The parameter $\mu_i = (\mu_{i1}, \mu_{i2})$ is the mean for the logistic parameters, and $1/_i$ is the between-regimen/study covariance matrix. Covariance matrix $1/_i$ is defined by the standard deviations (t_{i1}, t_{i2}), and correlation r_i.

The following priors will be used for these parameters:

- Normal priors for μ_{i1} and μ_{i2};
- Log-normal priors for t_{i1} and t_{i2}; and
- A uniform prior for r_i.

To further specify the details of these distributions the principles described in Neuenschwander et.al., 2014 will be followed. The MAP prior for model parameters of PF-07263689, $(\log(a_i^*), \log([3_i^*))$, is the predictive distribution.

$$(\log(a_i^*), \log([3_i^*)) \; I \; (r_i, n_i)$$

Since the predictive distribution is not available analytically, the MCMC method is used to simulate values from this distribution. This is implemented using JAGS version 4.10.

10.9.3. Sensitivity Analysis

Despite being prespecified in the protocol, some AEs that fall into the category of DLTs may need to be considered differently. Conversely, some AEs that are not defined as a DLT per protocol should be considered by the dose escalation algorithm. Accordingly, the new

concept of an "equivocal" DLT or AE is introduced: most AE/DLTs are considered "unequivocal," but certain types of AEs/DLTs are considered to be "equivocal."

To mitigate the risk of dichotomizing and misclassifying DLTs, the sensitivity analysis that uses those weighted equivocal DLT/AE data into the BLRM model estimation will also be performed. The BLRM model uses all the equivocal and unequivocal AE/DLT data, but the variability associated with equivocal AEs/DLTs (less interpretable) is increased. So, the model recommendations are more heavily weighted towards unequivocal data. See below for the posterior distribution of the BLRM model parameters based on the theory of power prior.

Suppose n participants treated at dose with m unequivocal DLTs and r equivocal DLTs/AEs, and the weight w for the equivocal data, then based on the power prior,

$$\text{Posterior}(a, \beta \mid d, m, r, w) \propto L(m \mid a, \beta, d, w) \times L(r \mid a, \beta, d, w)^{w} \times \text{prior}(a, \beta)$$

$$\propto p(a, \beta, d)^{m} \times [1 - p(a, \beta, d)]^{n-r-m} \times p(a, \beta, d)^{rw} \times \text{prior}(a, \beta),$$

where L is the likelihood of the observed DLT data, and p (a, β, d) is the probability of DLT at dose d that is modeled by logistic regression in BLRM. To achieve the equality sign, appropriate normalizing constant is required.

The contribution of equivocal AEs/DLTs to the data (likelihood) and the Bayesian posterior estimation of the MTD are weighted; the weight parameter controls the influence and can be interpreted as a precision parameter for the equivocal AE/DLT data, similar to the scale parameter in the power prior for the Bayesian historical borrowing.

The weight for an equivocal DLT is decreased (eg, 1 decreased to 0.5) and the weight for an equivocal AE (non-DLT by protocol) is increased (eg, 0 increased to 0.5). To maintain the integrity of a trial, the weight is pre-specified as 0.5 in the analysis. If all the investigators and the sponsor agree on the equivocal DLT/AE data, the DLT weighting approach could be the primary dose escalation method. This DLT weighting approach provides a flexible and powerful tool that may incorporate the clinician's valuable experience with some specific DLTs/AEs and improve MTD estimation in dose escalation trials.

10.10. Appendix 10: RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from Eisenhauer EA, et al (2009).

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the CRF (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete response: Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial response: Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR, or progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective progression: 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate: Progression has not been documented, and:

  - one or more target measurable lesions have not been assessed.

  - or assessment methods used were inconsistent with those used at baseline.

  - or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure).

  - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

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

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the EOT CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 12. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following Table 13 will be used:

Table 13. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

10.11. Appendix 11: CRS Mitigation and Management

CRS is a non-antigen-specific cytokine-associated toxicity that occurs as a result of high-level immune activation. CRS is a potentially life-threatening toxicity that has been observed following administration of immune-base therapies for cancer (antibodies and adoptive T cell therapies). CRS is likely to be a common toxicity that can be managed through supportive care and anti-cytokine interventions.

In cases of suspected CRS, a serum sample should be provided for cytokine release assay analysis by the local laboratory (see Section 6.8.3.3) provided the sampling does not interfere with the medical treatment of the participant.

Early intervention should be undertaken at the first sign of CRS; signs may include pyrexia, tachycardia, tachypnea and/or hypotension and are temporally related to PF-07263689 in the absence of alternative etiologies.

The ASTCT CRS criteria proposed by Lee et al. as presented in Table 14 will be used for the assessment of the CRS severity grade which will be captured on the AE CRF and on the CRS CRF (Lee et al, 2019).

Table 14. ASTCT CRS Revised Grading System

CRS parameter:	Fever*	With Hypotension	And/or† Hypoxia
Grade 1	Temp. ≥38°C	None	None
Grade 2	Temp. ≥38°C	Not requiring vasopressors	Requiring low-flow‡ nasal cannula, low-flow‡ facemask or blow-by
Grade 3	Temp. ≥38°C	Requiring a vasopressor with or without vasopressin	Requiring high-flow‡ nasal cannula, high-flow‡ facemask, nonrebreather mask, or Venturi mask
Grade 4	Temp. ≥38°C	Requiring multiple vasopressors (excluding vasopressin)	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS should still be graded according to CTCAE v 5.0 and do not influence CRS grading.

* Fever is defined as temperature ≥38°C and not attributable to any other cause. In participants who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

‡ Low-flow nasal cannula or facemask is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula or facemask is defined as oxygen delivered at >6 L/min. This is modified from original ASTCT criteria to differentiate between low-flow and high-flow facemask.

The definitions for high-dose vasopressors are shown in Table 15.

Table 15. Definition of High Dose Vasopressor

Pressor	**High Dose** (doses less than these would be considered low)
Norepinephrine monotherapy	20 g/min
Dopamine monotherapy	10 g/kg/min
Phenylephrine monotherapy	200 g/min
Epinephrine monotherapy	10 g/min
If on vasopressin	Vasopressin + norepinephrine equivalent of 10 g/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of 20 g/min*

* VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (g/min)] + [dopamine (g/kg/min) ÷ 2] + [epinephrine (g/min)] + [phenylephrine (g/min) ÷10

CRS Management Guidelines (Lee et al, 2019).

These may be modified as needed by the responsible Investigator according to the best practices at their institute.

ASTCT Grade 1 CRS:

- Monitor vital signs for worsening of condition.

Fever

- Acetaminophen/paracetamol and hypothermia blanket for the treatment of fever.
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen can be used as second treatment option for fever if not contraindicated.
- Assess for infection using blood and urine cultures, and chest radiography.
- Empiric broad-spectrum antibiotics and filgrastim if neutropenic.

- Maintenance IV fluids for hydration.
- Symptomatic management of constitutional symptoms or organ toxicity.
- Consider tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever.

ASTCT Grade 2 CRS:

- Monitor vital signs every 4 hours for worsening of condition.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV fluid bolus of 500-1000 ml of normal saline. Can give second IV fluid bolus if systolic blood pressure remains <90 mmHg.
- Consider tocilizumab 8 mg/kg (maximum dose 800 mg) IV or siltuximab 11 mg/kg IV for treatment of hypotension refractory to fluid boluses; tocilizumab can be repeated after 6 h if needed.
- If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, obtain ECHO, and initiate other methods of hemodynamic monitoring.
- In participants at high-risk (bulky disease, older age or comorbidities) or if hypotension persists after 1-2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 hrs.

Hypoxia

- Supplemental oxygen.
- Tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension.

ASTCT Grade 3 CRS:

- Monitor patient (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, as needed, as recommended for Grade 2 CRS.
- Tocilizumab and siltuximab as recommended for Grade 2 CRS if not administered previously.
- Vasopressors as needed.
- Dexamethasone 10 mg IV every 6 hrs; if refractory, increase to 20 mg IV every 6 hrs.

Hypoxia

- Supplemental oxygen including high-flow oxygen delivery.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above.

ASTCT Grade 4 CRS:

- Monitor patient (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as recommended for grade 3 CRS.
- Methylprednisolone 1 g/day IV.

Hypoxia

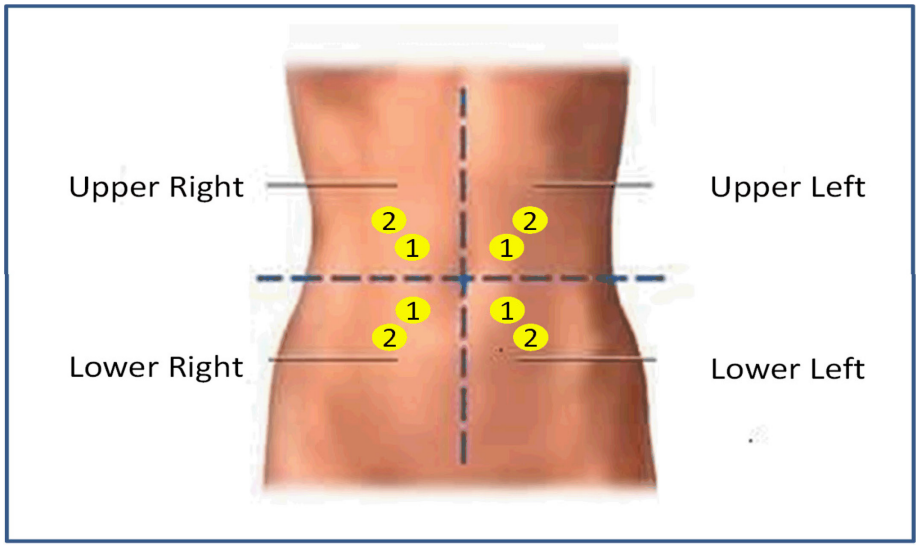
- Supplemental oxygen via positive pressure/mechanical ventilation.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above.

10.12. Appendix 12: ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken M et al. 1982.

10.13. Appendix 13: Sasanlimab Subcutaneous Injection Site Location Diagram



Injection site locations include a maximum of 8 unique administration sites distributed across 4 abdominal quadrants with a possibility of up to 2 injection locations per quadrant. Location 1 is proximal to the umbilicus and Location 2 is distal to the umbilicus.

Administer the required number of injections in the following order:

- Lower Left Quadrant Location 1.
- Lower Right Quadrant Location 1.
- Lower Left Quadrant Location 2.
- Lower Right Quadrant Location 2.
- Upper Right Quadrant Location 1.
- Upper Left Quadrant Location 1.
- Upper Right Quadrant Location 2.
- Upper Left Quadrant Location 2.

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs.
SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

Track the participant's injection site(s) sequentially on this diagram with a red pen and mark the injection sites on the participant's abdomen according to your clinic's standard practice.

Record the location, time of each injection and any injection site reactions in the participant's source records and study CRF. Complete 1 CRF per injection.

10.14. Appendix 14: Preliminary Clinical Summary for Study B8011001 Phase 1 FIH (PF-06801591)

Data Cutoff Date: 03 August 2020.

10.14.1. Study Design

B8011001 is an ongoing Phase 1, open-label, multicenter, multiple dose, dose escalation and expansion study of PF-06801591 in patients with locally advanced or metastatic melanoma, HNSCC, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma or other solid tumors. The primary purpose of this study is to evaluate safety and early signs of efficacy of PF-06801591. This clinical study is divided into a dose escalation (Part 1) phase, and a dose expansion (Part 2) phase.

Part 1 Dose Escalation

Part 1 dose escalation evaluated 4 pre-specified IV dose levels (0.5, 1, 3, and 10 mg/kg administered every 3 weeks [q3w]), and 1 subcutaneous (SC) dose level (300 mg administered every 4 weeks [q4w]) in adult patients with locally advanced or metastatic melanoma, HNSCC, ovarian cancer, sarcoma, small cell lung cancer (SCLC), adenocarcinoma of salivary gland, endometrial adenocarcinoma, malignant peritoneal neoplasm, esophageal adenocarcinoma or renal cell carcinoma. Participants had progressive disease on ≥1 prior line of therapy for locally advanced or metastatic disease or refused standard of care therapy; were not previously treated with an anti-PDx agent; and had adequate renal, bone marrow, liver, and cardiac function, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Forty participants were enrolled into Part 1 with 25 participants total enrolled into the IV dose cohorts and 15 participants enrolled into the SC dose cohort.

Part 2 Dose Expansion

The 300 mg SC dose was evaluated in an expanded population of 106 participants. This included 68 participants with locally advanced or metastatic NSCLC and 38 participants with locally advanced or metastatic UC who were anti-PDx treatment-naïve and who had progressive disease on or were intolerant to systemic therapy or for whom standard of care systemic therapy was refused or unavailable. Participants with NSCLC could have received up to 1 line of prior systemic therapy for locally advanced or metastatic disease and if they had known EGFR-activating mutation or an ALK rearrangement were required to have, in addition, at least 1 targeted therapy for their disease. Participants with UC could have received up to 2 lines of prior systemic therapies for locally advanced or metastatic disease. The selected participants had adequate renal, bone marrow, liver, and cardiac function, with ECOG performance status 0 or 1. All participants received 300 mg of PF-06801591 SC every 4 weeks.

10.14.2. Exposure

As of 03 August 2020, 146 participants have been dosed on the study as shown in Table 16.

Table 16. Part 1 and Part 2 Cohort Enrollment Details

Cohort	Route of Administration	N Treated
0.5 mg/kg	IV	2
1 mg/kg	IV	8
3 mg/kg	IV	8
10 mg/kg	IV	7
300 mg Part 1	SC	15
300 mg Part 2 NSCLC	SC	68
300 mg Part 2 UC	SC	38
Total	IV and SC	146

10.14.3. Summary of Safety

10.14.3.1. Dose Limiting Toxicities (DLTs)

No dose limiting toxicities were observed and thus, there was no maximum tolerated dose identified.

10.14.3.2. Adverse Events

Part 1, IV administration (n = 25)

Information about AEs in the IV dose levels can be found in the PF-06801591 IB.

Part 1, SC administration (n = 15)

CCI

[redacted]

Part 2, SC administration (n = 106) in participants with NSCLC and UC

CCI

[redacted]

10.14.3.3. Serious Adverse Events (SAEs)

CCI

[redacted]

CCI [redacted]

10.14.4. Summary of Efficacy

Part 1 Dose Escalation

As of 27 July 2020, efficacy of Study B8011001 was evaluated CCI [redacted]

Part 2 Dose Expansion

Safety and clinical activity of SC administered anti-PD-1 antibody PF-06801591 in Phase 1 dose expansion cohorts of locally advanced or metastatic NSCLC and UC were reported in ESMO of 2019 (Cho et al, 2019).

The efficacy analyses were performed with 68 participants with NSCLC and 38 participants with UC that were evaluable for efficacy. As of 27 July 2020, the observed ORR in the NSCLC cohort was 20.6% (95% CI: 11.7, 32.1%) with 14 confirmed PR, and 24 (35.3%) participants with NSCLC achieved a BOR of SD. In the UC cohort the ORR was 21.1% (95% CI 9.6, 37.3%) with 8 confirmed PR and 12 (31.6%) participants had SD. In the NSCLC cohort, median duration of response was 230 (57–445) days. In the UC cohort, median duration of response was 183 (23–371) days (Cho et al, 2020).

Updated results of SC (PD-1) receptor antibody PF-06801591 for locally advanced or metastatic NSCLC or UC were reported in September of 2020. These details are provided in the full citation from ESMO 2020.

10.14.5. Summary of Clinical Pharmacology

PF-06801591 demonstrated pharmacokinetic (PK) characteristics typical of IgG4 monoclonal CCI [redacted]

10.14.6. Conclusions

Based on the available safety and efficacy data for PF-06801591, the benefit risk profile of PF-06801591 is expected to be favorable.

10.15. Appendix 15: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Ab	antibody
ACTH	adrenocorticotropic hormone
ACV	acyclovir
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	alkaline phosphatase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of last measurable concentration
AV	atrioventricular
BLRM	Bayesian logistic regression model
BP	blood pressure
Bpm	beats per minute
BNP	B-type natriuretic peptide
BOR	best overall response
BRCA	breast cancer
BUN	blood urea nitrogen
CA	cancer antigen
CD	cluster of differentiation
CEA	carcinoembryonic antigen
cfDNA	circulating free DNA
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CK-MB	creatine kinase MB
C_{max}	maximum observed concentration
CPAP	Continuous positive airway pressure
CNS	central nervous system

Abbreviation	Term
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	clinical trial/computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CxDx	cycle x day x
DC	dendritic cell
DCR	disease control rate
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	escalation with overdose control
FAP	fibroblast activation protein
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
GCL	Global Clinical Lead

Abbreviation	Term
GCP	Good Clinical Practice
GCV	ganciclovir
GGT	gamma-glutamyl transferase
GH	growth hormone
GI	gastrointestinal
GLP	Good laboratory practice
GM-CSF	granulocyte-macrophage colony stimulating factor
gv	glycovariant
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCP	health care provider
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severe toxic dose
HR	heart rate
HRT	hormone replacement therapy
HSV	herpes simplex virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
IFN-γ	interferon-gamma
IgG	Immunoglobulin gamma
IHC	immunohistochemistry
C CI	[redacted]
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
irAE	immune-related adverse events
IRB	institutional review board
IRC	internal review committee
IRR	infusion related reaction
IRT	interactive response technology
IT	intratumoral

Abbreviation	Term
IV	Intravenous(ly)
IWR	interactive Web-based response
LBBB	left bundle branch block
LFT	liver function test
LH	luteinizing hormone
LLOQ	lower limit of quantitation
LLN	lower limit of normal
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MAP	meta-analytic-predictive
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MFD	maximum feasible dose
mIL-2v	Mouse interleukin 2 variant
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MSS	microsatellite stable
MUGA	multiple-gated acquisition
NA	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NIMP	non-investigational medicinal product
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small-cell lung carcinoma
NZW	New Zealand white
ORR	objective response rate
OS	overall survival
OV	oncolytic virus
OvCA	ovarian cancer
PD	pharmacodynamics(s); progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PDx	programmed cell death protein 1/programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFU	plaque-forming unit
PI	principal investigator
PK	pharmacokinetic(s)

Abbreviation	Term
PR	partial response; pulse rate
PRL	prolactin
PS	performance status
PSA	prostate-specific antigen
CCI	[redacted]
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
QxW	every x week
QTc	corrected QT
QTcB	corrected QT (Bazett method)
QTcF	corrected QT (Fridericia method)
QTL	quality tolerance limit
RBC	red blood cell
RCC	renal cell carcinoma
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SCLC	small cell lung cancer
SCr	serum Creatinine
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
SpO2	oxygen saturation
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
T4	thyroxine
TBili	total bilirubin
TCR	T-cell receptor
TGI	tumor growth inhibition
TEAE	treatment emergent adverse event(s)
TETRAE	treatment-related adverse events
TK	thymidine kinase
TK^-	thymidine kinase deletion
T_{max}	time to maximum concentration
TME	tumor microenvironment
TNF	tumor necrosis factor

Abbreviation	Term
TSH	thyroid-stimulating hormone
TTP	time to progression
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VIG	Vaccinia immune globin
VEGF	vascular endothelial growth factor
VV	Vaccinia virus
VV-Cop	Vaccinia virus Copenhagen strain
VV-WR	Vaccinia virus Western Reserve strain
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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