## Title Page

# A PHASE 1, OPEN-LABEL, DOSE ESCALATION AND EXPANSION STUDY OF PF-07265028 AS A SINGLE AGENT AND IN COMBINATION WITH SASANLIMAB EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND ANTI-TUMOR ACTIVITY OF PF-07265028 IN PARTICIPANTS WITH ADVANCED OR METASTATIC SOLID TUMORS

| | |
|---|---|
| **Study Intervention Number:** | PF-07265028 |
| **Study Intervention Name:** | N/A |
| **US IND Number:** | 158275 |
| **EudraCT Number:** | N/A |
| **ClinicalTrials.gov ID:** | TBD |
| **Protocol Number:** | C4731001 |
| **Phase:** | 1 |

**Brief Title:** Phase 1 Study of PF-07265028 as Single Agent and in Combination with Sasanlimab in Participants with Selected Advanced Solid Tumors.

**Document History**

| Document | Version Date | Summary of Changes |
|---|---|---|
| Protocol Amendment #1 | 22 November 2021 | The purpose of this amendment is to incorporate required changes from FDA during the IND review.<br><br>1. Sections 1.1, 1.2, 4.1, 4.3.2, 6.1.1.1: Removed alternate dosing regimens.<br><br>2. Sections 1.1 and 5.1: Clarified the definition of primary resistance with checkpoint inhibitors in Part 1B combination therapy and Part 2 Dose expansion.<br><br>3. Sections 1.1 and 5.1: Revised inclusion criteria for adequate renal function including determining creatinine clearance per Cockcroft-Gault formula.<br><br>4. Sections 1.1 and 5.1: Revised inclusion criteria for adequate liver function to AST and ALT ≤1.5xULN.<br><br>5. Section 1.2, 4.1.1, 4.3.1: Added requirement that participants in Part 1B combination therapy will start combination with sansalimab at least one dose level lower of PF-07265028 than previously determined to be safe as monotherapy dose in Part 1A.<br><br>6. Section 1.3: Schedule of Activities revised to require ECGs be collected on day 1 of every cycle and additional PK samples will be collected at 12 hours on Days 1 and 15.<br><br>7. Section 1.3: a footnote added to Schedule of Activities to clarify that "X" means collection in every cycle unless otherwise noted. |

| Document | Version Date | Summary of Changes |
|---|---|---|
| | | 8. Section 4.1, 4.1.3, 4.2: added justifications for the assessment of food effect on PK and tolerability of PF-07265028.<br><br>9. Section 4.1: added criteria for determining when to evaluate continuous BID dosing.<br><br>10. Section 4.3.3: Added to the DLT definition that all treatment emergent adverse events that meet the DLT definition occurring during the first cycle will be considered DLTs unless they are attributed to underlying disease or intercurrent illness.<br><br>11. Section 4.3.5: Revised the definition of RP2D to reflect that it is based on an integrated assessment of target engagement/attainment, efficacy, safety and pharmacokinetic/pharmacodynamic (PK/PD) relationship.<br><br>12. Section 5.2 and 6.8.8: Added the restriction that the use of proton pump inhibitors are prohibited during study treatment. H2 blocking agent and antacids are permitted under specific conditions.<br><br>13. Section 5.2: Revised language in exclusion criterion #25 for participants with HBV, HCV, HIV or AIDS related illness.<br><br>14. Section 6.5: Added two tables for managing dose modifications for gastrointestinal toxicities and QTcF prolongation.<br><br>15. Sections 4.3.2 and 10.11.2: Revised dose escalation criteria requirement not to exceed 100% between dose level 1 |

| Document | Version Date | Summary of Changes |
|---|---|---|
| | | and 2, subsequent escalations would proceed in 60% maximum increments. |

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.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Brief Title:** Phase 1 Study of PF-07265028 as Single Agent and in Combination with Sasanlimab in Participants with Selected Advanced Solid Tumors.

**Rationale:**

The purpose of this FIH study is to (a) assess the safety, tolerability, PK, and PD of increasing doses of PF-07265028 as monotherapy and in combination with sasanlimab; (b) identify the MTD of PF-07265028; (c) evaluate the clinical activity of monotherapy and combination therapy; and (d) select the RDE of PF-07265028 monotherapy and the RDE of PF-07265028 in combination with sasanlimab for potential further studies and development. HPK1 inhibition is expected to have applicability across multiple tumor types, therefore this study will enroll participants with advanced solid tumors for whom standard therapies have failed or for whom no standard therapy is available.

**Objectives, Endpoints, and Estimands:**

**Dose Escalation (Part 1):**

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| • To assess safety and tolerability at increasing dose levels of PF-07265028 monotherapy and in combination with sasanlimab in successive cohorts of participants with advanced/metastatic solid tumors in order to estimate the MTD/MAD and select the Phase 1 Expansion Dose. | • First cycle DLTs.<br>• Adverse events (including irAEs) as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy.<br>• Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. | • DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period (Cycle 1). The attributes of this estimand are provided in Section 9.1.1.<br>• Incidence of AEs estimated during the AE-evaluation period, defined as the time from the first dose to earliest of (28 days post last dosing date and day of new anti-cancer therapy -1 day). |
| **Secondary:** | **Secondary:** | **Secondary:** |
| • To characterize the single and multiple dose PK of PF-07265028 when given as monotherapy and in combination with sasanlimab.<br>• To evaluate sasanlimab PK in participants receiving PF-07265028 and sasanlimab | • PK parameters of PF-07265028:<br>  • SD: $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC_{tau}$, and as data permit, $t_{1/2}$, $AUC_{inf}$, CL/F, and $V_z$/F.<br>  • MD: $C_{max,ss}$, $T_{max,ss}$, $AUC_{tau,ss}$, $AUC_{last,ss}$, $C_{min,ss}$, CL/F, and as data permit, $V_{ss}$/F, and $R_{ac}$ ($AUC_{tau,ss}$/$AUC_{tau,sd}$).<br>• PK of sasanlimab:<br>  • $C_{min}$ in selected cycles. | • Not applicable. |

| Objectives | Endpoints | Estimands |
|---|---|---|
| • To evaluate the effect of food on PF-07265028 PK in a subset of participants, if the food-effect assessment is performed in Part 1A. | • PK parameters of PF-07265028 (including $C_{max}$, $T_{max}$, $AUC_{tau}$, $AUC_{last}$) under fasted and fed conditions. | |
| • To evaluate the immunogenicity of sasanlimab when given in combination with PF-07265028 in Part 1B. | • Incidence and titers of ADA and NAb. | |
| • To evaluate preliminary anti-tumor activity. | • Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST and proportion of participants with PR and irPR, as appropriate. | |
| CCI [redacted] | | |

## Dose Expansion (Part 2)

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| • To evaluate preliminary anti-tumor activity of PF-07265028 in combination with sasanlimab. | • ORR, as assessed using the RECIST version 1.1 and irRECIST. | • The treatment effect of PF-07265028 in combination with sasanlimab assessed by ORR using the RECIST version 1.1 and irRECIST in the response evaluable analysis population. |
| • To assess safety and tolerability in combination with sasanlimab at the RDE.<br>• To determine the RP2D based on the RDE. | • Adverse Events (including irAE) as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy.<br>• Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. | • Incidence of AEs estimated during the AE-evaluation period, defined as the time from the first dose to earliest of (28 days post last dosing date and day of new anti-cancer therapy-1 day). |
| **Secondary:** | **Secondary:** | **Secondary:** |
| • To evaluate other anti-tumor activity. | • Time-to-event endpoints: eg, DoR, PFS, OS. | • Not applicable. |
| • To evaluate PK of PF-07265028 and sasanlimab when administered in combination (at combination RDE from Part 1). | • PK parameters of PF-07265028 (ie, $C_{ss,max}$ and $C_{ss,min}$) and sasanlimab (ie, $C_{min}$ in selected cycles). | |
| • To evaluate the effect of food on PF-07265028 PK in a subset of participants, if the food-effect assessment is performed in Part 2. | • PK parameters of PF-07265028 (including $C_{max}$, $T_{max}$, $AUC_{tau}$, $AUC_{last}$) under fasted and fed conditions. | |
| • To evaluate the immunogenicity of sasanlimab when given in combination with PF-07265028. | • Incidence and titers of ADA and NAb against sasanlimab. | |
| CCI [redacted] | | |

| Objectives | Endpoints | Estimands |
|---|---|---|
| CCI | [redacted] | |

**Overall Design:**

**Brief Summary**

This is a Phase 1, open-label, multicenter, multiple-dose, dose-escalation, dose-expansion, safety, PK, and PD study of PF-07265028 as a single agent and in combination with sasanlimab in cohorts of adult participants with advanced solid tumors that progressed after systemic anticancer therapy or for whom no standard therapy for curative intent is available or in the opinion of the participant and their treating physician, that standard therapy would not be appropriate, or who have refused standard therapy.

This study contains 2 parts:

- Part 1 of the study will consist of staggered dose escalation cohorts with PF-07265028 as monotherapy (Part 1A) and PF-07265028 administered in combination with sasanlimab (Part 1B).
- Part 2 of the study will consist of dose expansion cohorts of PF-07265028 administered in combination with sasanlimab in specific tumor types (Part 2A). The RDE and dosing regimen for the combination therapy as identified in Part 1B of the study will be used in the expansion cohorts during Part 2. Expansion of PF-07265028 as monotherapy (Part 2B) with the RDE as identified in Part 1A will be based on evidence of clinical data generated during monotherapy dose escalation.

**Number of Participants:**

A maximum sample size of 240 participants will be enrolled in the study including approximately 60 participants in Part 1 dose escalation and up to 180 participants in Part 2 dose expansion.

**Study Population and Specific Inclusion/Exclusion Criteria:**

Key inclusion and exclusion criteria are listed below:

**Selected Inclusion Criteria**

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

1. **Part 1A Monotherapy:** Histologically or cytologically confirmed advanced or metastatic solid tumors which have progressed following systemic anticancer therapies, or are resistant to standard therapy or for which no standard therapy is available, or for whom standard therapy is not tolerated.

2. **Part 1B Combination Therapy:** Histologically or cytologically confirmed advanced or metastatic solid tumor which have progressed following systemic anticancer therapies, including at least 1 checkpoint inhibitor and displayed primary resistance to checkpoint inhibitors. Primary resistance is defined as having received a checkpoint inhibitor for greater than or equal to 6 weeks with confirmed PD at least 4 weeks after initial PD or SD for less than 6 months. Immunotherapy naïve/secondary PDx -resistant tumors may be considered after discussion with the sponsor.

3. **Part 2 Dose Expansion:** Histologically or cytologically confirmed advanced or metastatic, gastric cancer, gastroesophageal junction cancer, HNSCC, or UC (NSCLC and other solid tumors may be explored based on emergent data from Part 1 and must have histologically or cytologically confirmed advanced or metastatic disease) who have progressed following systemic anticancer therapies, including at least 1 CPI and displayed primary resistance to therapy with CPIs. Primary resistance is defined as having received a checkpoint inhibitor for greater than or equal to 6 weeks with confirmed PD at least 4 weeks after initial PD or SD for less than 6 months. In addition PDx naïve solid tumors may be evaluated based on emergent data from Part 1.

    - Note: The requirement for prior CPI therapy will not be applicable if a cohort of immunotherapy naïve/secondary PDx-resistant tumors warrants further investigation based on Part 1.

4. ECOG PS ≤1.

5. Life expectancy ≥3 months.

6. Adequate hematologic function, including:
    - Absolute neutrophil count ≥1,500/µL;
    - Platelet count >100,000/µL;
    - Hemoglobin >9 g/dL.
7. Adequate renal function creatinine clearance ≥60 mL/min calculated using the Cockcroft-Gault formula.
8. Adequate liver function, including:
    - Total bilirubin ≤1.5 × ULN unless the participant has documented Gilbert's syndrome;
    - AST and ALT ≤1.5 × ULN; (≤5.0 × ULN if there are liver metastases);
    - Alkaline phosphatase ≤2.5 × ULN (≤5 × ULN if there are bone metastases).
9. Have measurable disease per RECIST 1.1.
10. Able to provide adequate pre-treatment and on-treatment tumor tissue.

    Pre-treatment tumor tissue:

    - All participants must provide archival FFPE tumor tissue that is of diagnostic quality and representative of their diagnosed malignancy.
        a. **Part 1:** If archival sample is older than 6 months, the participant must consent to undergo a fresh biopsy during the screening period. If a new biopsy represents a significant risk in the opinion of the investigator, the participant may be considered for enrollment, after discussion with the sponsor.
        b. **Part 2:** Fresh tumor biopsy during screening is required unless there is archival tissues less than 3 months old and was obtained subsequent to the last systemic anti-cancer therapy. If a new biopsy represents a significant risk, the participant may be considered for enrollment, after discussion with the sponsor.

    On-treatment biopsy:

        a. **Part 1:** Starting with DL3 or higher dose, participants may be asked to provide mandatory fresh pre-treatment and on-treatment biopsy. Consent for these procedures will occur during screening.

b. **Part 2:** Paired on-treatment biopsies will be mandatory for a subset of participants. Consent for these procedures will occur during screening. On-treatment biopsies are optional and encouraged for all other participants.

**Selected Exclusion Criteria**

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

1. Participants with any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix, Bowen's disease. Participants with other stable indolent malignancies and no evidence of progressive disease may be considered after discussion with sponsor.

2. Participants with primary immunodeficiency.

3. Participants who require immunosuppressive therapy including, but not limited to, treatment with corticosteroids in pharmacologic doses (equivalent to ≥10 mg prednisone daily).

4. Participants with active autoimmune conditions or history of autoimmune diseases that may relapse with the following exceptions:

   - Controlled Type 1 diabetes mellitus;
   - Hypothyroidism (managed with hormone replacement);
   - Controlled celiac disease;
   - Skin diseases not requiring systemic therapy (eg, vitiligo, psoriasis, alopecia).

5. History of interstitial lung disease, pneumonitis (non-infectious) or uncontrolled lung diseases.

6. History of allogeneic transplant.

7. History of prior irAEs Grade ≥3.

8. Participants with central nervous system metastases; however participants who have undergone surgery and/or radiation for brain metastases who are asymptomatic and radiologically stable and are no longer taking corticosteroids are eligible. Participants with leptomeningeal metastases are not eligible.

9. Impairment of GI function or GI disease that may significantly alter the absorption of PF-07265028.

10. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism; DVT; arterial occlusive disease; ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade that is uncontrolled, or QTcF interval >470 ms at screening.

11. Palliative radiation therapy within 14 days of study entry (2 weeks in the case of immunotherapy) and the absence of any radiation-induced complications.

12. Prior systemic anti-cancer therapy within 14 days (6 weeks for mitomycin C or nitrosoureas) prior to study treatment. Participant with prostate cancer are permitted to continue on LHRH agonists/antagonists.

13. Concomitant use or anticipated need for food (eg, grapefruit juice), supplements (eg, St John's Wort), or drugs (eg, ketoconazole) that are known strong and/or moderate CYP3A4 inhibitors, or strong CYP3A4 inducers, including their administration within 10 days or 5 half-lives of the CYP3A4 inhibitor/inducer (whichever is longer) prior to the first dose of study intervention.

14. Concomitant or anticipate use of sensitive substrates with NTI for CYP3A4, CYP2D6, UGT1A1, P-gp, and highly sensitive substrates for BCRP.

15. Blood product support: Transfusion of RBCs or platelets within 2 weeks.

**Intervention Groups and Duration:**

Study intervention will be administered in 28 -day cycles. Treatment with study intervention will continue until confirmed PD, participant refusal, unacceptable toxicity, investigator decision or study termination, or up to 24 months from first dosing, whichever occurs first. Participants who complete the maximum number of cycles/months on study intervention and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study intervention will be given the opportunity to continue treatment upon agreement between investigator and sponsor.

In monotherapy, starting dose for PF-07265028 is 25 mg orally QD on a continuous basis. BLRM is used for dose finding until reaching MTD. Continuous BID dosing may be evaluated, if indicated based on emerging clinical PK, PD and safety data. In combination therapy, sasanlimab 300 mg SC Q4W will be administered at the clinic together with oral administration of PF-07265028. On days when study intervention is administered in clinic, PF-07265028 is administered first and then followed by sasanlimab.

**Data Monitoring Committee or Other Independent Oversight Committee: No**

**Statistical Methods:**

There is no formal statistical hypothesis testing in this study.

For Part 1, determination of MTD will be performed using the Per Protocol analysis set (evaluable for MTD).

**Bayesian adaptive approach:** The dose escalation in the Part 1 of the study will be guided by a Bayesian analysis of Cycle 1 DLT data for PF-07265028. A traditional 2-parameter BLRM will be used to model the DLT relationship of PF-07265028 monotherapy, and a more complex BLRM model specifically designed for combinations will be used to model the dose toxicity relationship of PF-07265028 given in combination with sasanlimab. Using DLT data at all tested dose levels and pre specified prior distribution of model parameters, the posterior distribution for probability of having a DLT will be calculated for all dose levels.

**Assessment of participant risk:** After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07265028 monotherapy and combination therapy will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

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

**The EWOC principle:** Dosing decisions are guided by the escalation with overdose control principle.[1] In general, a dose may only be used for newly enrolled participants if the risk of excessive toxicity at that dose is less than 25%.

**Prior distributions:** Weakly informative prior distributions based on preclinical/expert opinion information will be chosen for the logistic parameters, see Appendix 11 Section 10.11.

A MAP approach may be used to derive the prior distribution for model parameters used in Part 1B based on the data collected in Part 1A and historical DLT data on sasanlimab as monotherapy. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data. MAP priors are derived from hierarchical models, which take into account possible differences between the studies. A full description of the application of the MAP approach to derive the prior distributions of the model parameters is given in Technical Supplement.

**Starting dose:** The starting dose is 25 mg. For this dose the prior risk of overdosing is 7.1%, which satisfies the EWOC criterion.

**Stopping criteria:** The number of participants in Part 1 dose escalation of the trial may be approximately 60. The trial for Part 1A and Part 1B will be stopped when the following criteria are met:

At least 6 participants have been treated at the MTD/RDE.

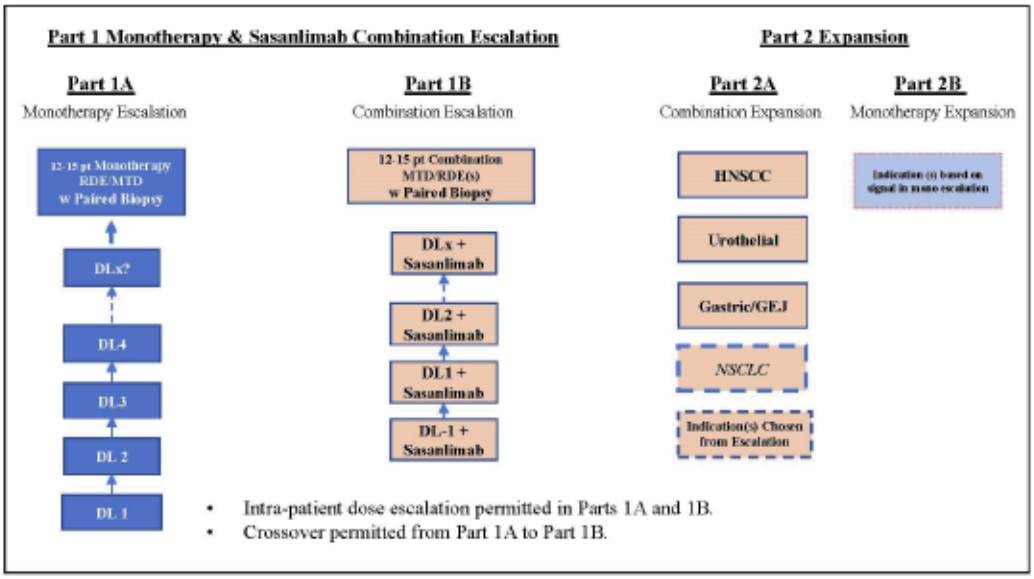
The dose $\tilde{d}$ satisfies 1 of the following conditions:

- The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$.
- A minimum of 12 participants have been treated for Part 1A, or a minimum of 9 participants have been treated for Part 1B.

**Sensitivity analysis:** To mitigate the risk of dichotomizing and misclassifying DLTs, a sensitivity analysis that uses weighted DLT/AE data (in equivocal cases) into the BLRM model estimation will also be performed. 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. See Appendix 11 Section 10.11 for more details.

The 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.

## 1.2. Schema




## 1.3. Schedule of Activities

The SoA tables provide 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, in order to conduct evaluations or assessments required to protect the well-being of the participant.

**Table 1. Schedule of Activities (Part 1 and Part 2)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | EOT | 30 day safety F/U | Long-term safety F/U | Notes: |
|---|---|---|---|---|---|---|---|---|---|---|
| Abbreviations used in this table may be found in Appendix 17. | ≤28 | Day 1 | Day 2 | Day 8 | Day 15 | Day 22 | See notes | See notes | | • EOT and 30-day F/U see Sections 8.2.8 and 8.2.9 for timing of visits. See Section 8.2.9 for 60- and 90-day F/U. • See Section 8.3.3 for follow-up AE and SAE assessments. |
| **Visit Window (Days)** | | ±2 | — | ±1 | ±1 | ±1 | | ±3 | ±7 | No Visit Window for C1D1. A 2-day Visit Window for Day 1 starts with Cycle 2. |
| 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 & medical history | X | | | | | | | | | Includes history of the cancer under study and any other relevant medical/surgical history. |
| Complete physical examination | X | | | | | | X | | | |
| Brief physical examination | | X | C1 | C1 & C2 | X | C1 | | X | | |
| Height | | C1 | | | | | | | | |
| Weight | | X | | | | | X | | | |
| Vital signs | X | X | C1 | C1 & C2 | X | C1 | X | X | | See Section 8.2.3 For additional information. |
| ECOG performance status | X | X | C1 | C1 & C2 | X | C1 | X | X | | See Section 8.2.2 and Section 10.14 for additional information. |
| Contraception check | | X | | | | | X | | | |

**Table 1. Schedule of Activities (Part 1 and Part 2)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | EOT | 30 day safety F/U | Long-term safety F/U | Notes: |
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| **Visit Window (Days)** | | ±2 | — | ±1 | ±1 | ±1 | | ±3 | ±7 | No Visit Window for C1D1. A 2-day Visit Window for Day 1 starts with Cycle 2. |
| **Laboratory Assessments** | | | | | | | | | | |
| ECG (standard 12lead) | X | See Table 2, Table 3 and Table 4. | | | | | X | | | See Section 8.2.4 for additional information. |
| Hematology | X | X | | C1 & C2 | X | C1 | X | X | | See Section 10.2. |
| Chemistry | X | X | | C1 & C2 | X | C1 | X | X | | See Section 10.2. |
| Coagulation | X | X | | C1 & C2 | X | C1 | X | X | | See Section 10.2. |
| Urinalysis | X | X | | | | | X | X | | See Section 10.2. |
| Endocrinology: Thyroid function studies: T3, T4, TSH | X | C1D1, C4D1, then Q12W thereafter (and if clinically indicated). | | | | | X | | | If TSH abnormal, analysis of reflex free T4 and free T3 should be obtained. Supplementation is acceptable to achieve a TSH WNL. In participants with abnormal TSH, if free T4 and T3 are normal and participant is clinically euthyroid, participant is eligible. |
| Pregnancy test | X | X | | | | | X | | | WOCBP only. |
| Viral disease screening | X | | | | | | | | | Subsequent HBV monitoring may be required per local practice for participants |

**Table 1. Schedule of Activities (Part 1 and Part 2)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | EOT | 30 day safety F/U | Long-term safety F/U | Notes: |
|---|---|---|---|---|---|---|---|---|---|---|
| Abbreviations used in this table may be found in Appendix 17. | ≤28 | Day 1 | Day 2 | Day 8 | Day 15 | Day 22 | See notes | See notes | | • EOT and 30-day F/U see Sections 8.2.8 and 8.2.9 for timing of visits. See Section 8.2.9 for 60- and 90-day F/U. • See Section 8.3.3 for follow-up AE and SAE assessments. |
| **Visit Window (Days)** | | ±2 | — | ±1 | ±1 | ±1 | | ±3 | ±7 | No Visit Window for C1D1. A 2-day Visit Window for Day 1 starts with Cycle 2. |
| | | | | | | | | | | who test positive for HBsAb and/or positive HBcAb. |
| **Safety Assessments** | | | | | | | | | | |
| Serious and nonserious AE monitoring | X | X | X | X | X | X | X | X | X | Includes injection site reaction on cycle for sasanlimab. See Sections 8.3 and 8.2.7. |
| Concomitant medication(s) monitoring | X | X | X | X | X | X | X | X | | See Section 6.8. |
| **Efficacy Assessments** | | | | | | | | | | |
| Serum tumor-associated marker(s) | X | X | | | | | | | | Participants with defined serum tumor markers should continue monitoring on day 1 of each cycle. |
| CT or MRI scans of chest, abdomen, pelvis, any clinically indicated sites of disease, and of bone | X | To be obtained every 8 weeks from C1D1 dose (±7 days) | | | | | | | | See Section 8.1.1. |
| **Study Intervention and Other Treatments** | | | | | | | | | | |
| PF-07265028 administration | | Continuous QD | | | | | | | | See Section 6.1. See SoA Table 2, and Table 3 Table 4. |

**Table 1. Schedule of Activities (Part 1 and Part 2)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | EOT | 30 day safety F/U | Long-term safety F/U | Notes: |
|---|---|---|---|---|---|---|---|---|---|---|
| Abbreviations used in this table may be found in Appendix 17. | ≤28 | Day 1 | Day 2 | Day 8 | Day 15 | Day 22 | See notes | See notes | | • EOT and 30-day F/U see Sections 8.2.8 and 8.2.9 for timing of visits. See Section 8.2.9 for 60- and 90-day F/U. • See Section 8.3.3 for follow-up AE and SAE assessments. |
| **Visit Window (Days)** | | ±2 | — | ±1 | ±1 | ±1 | | ±3 | ±7 | No Visit Window for C1D1. A 2-day Visit Window for Day 1 starts with Cycle 2. |
| **Only for Part 1B and Part 2A:** Sasanlimab administration | | X | | | | | | | | See Section 6. |
| **Pharmacokinetics Assessments** | | | | | | | | | | |
| PK plasma sampling for PF-07265028 | | See Table 2, Table 3 and Table 4. | | | | | | | | See Section 8.4.1. |
| **Only for Part 1B and Part 2A:** PK serum sampling for sasanlimab | | | | | | | | | | |
| **Immunogenicity Assessments** | | | | | | | | | | |
| **Only for Part 1B and Part 2A:** Immunogenicity for sasanlimab | | See Table 2, Table 3 and Table 4 | | | | | | | | |
| **Retained Research** | | | | | | | | | | |
| CCI [redacted] | | | | | | | | | | |

**Table 1. Schedule of Activities (Part 1 and Part 2)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | EOT | 30 day safety F/U | Long-term safety F/U | Notes: |
|---|---|---|---|---|---|---|---|---|---|---|
| Abbreviations used in this table may be found in Appendix 17. | ≤28 | Day 1 | Day 2 | Day 8 | Day 15 | Day 22 | See notes | See notes | | • EOT and 30-day F/U see Sections 8.2.8 and 8.2.9 for timing of visits. See Section 8.2.9 for 60- and 90-day F/U. • See Section 8.3.3 for follow-up AE and SAE assessments. |
| Visit Window (Days) | | ±2 | — | ±1 | ±1 | ±1 | | ±3 | ±7 | No Visit Window for C1D1. A 2-day Visit Window for Day 1 starts with Cycle 2. |
| **Biomarker Assessments** | | | | | | | | | | |
| CCI | | | | | | | | | | |

**Table 2. PART 1: PK, ECG, Immunogenicity, Biomarker, and Biospecimen Schedule of Assessments (Participants *NOT* in Food Effect Subset)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1[a] | | | | | | | | Day 2[a] | Day 8 | Day 15 | | | | | | | | Day 16 | Day 22 | | |
| Hours Before/After PF- 07265028 Dose | | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | 12 | Pre | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | 12 | Pre | Pre | | Window for predose samples (except for Day 1): within 30 minutes prior to the same-day morning dose and within 24hr (±3hr) from the prior morning dose. |
| Sampling Window (minutes) | | -30 | ±3 | ±6 | ± 10 | ± 15 | ± 30 | ±60 | ±180 | See note | See note | See note | ±3 | ±6 | ± 10 | ±15 | ±30 | ±60 | ±180 | See note | See note | | |
| Dose of PF-07265028 given in clinic | | X | | | | | | | | C1 | C1 | C1, C2 & C3 | | | | | | | | C1 | C1 | | PF-07265028 is administered at the site after the completion of predose sample collection and assessment. |
| PK blood sampling for plasma PF-07265028 | | X | C1 | C1 | C1 | C1 | C1 | C1 | C1 | C1* | C1 | C1 | C1 | C1 | C1 | C1 | C1 | C1 | C1 | C1* | C1 | | * If the emerging PK data suggest a BID regimen is appropriate, predose sample on D2 and D16 will not be collected. |
| PK blood sampling for serum sasanlimab | | See note | | | | | | | | | | C1 | | | | | | | | | | X | Only for Part 1B. Day 1 predose samples on Cycles 1, 2, 3, 6 and thereafter every 6 cycles. See Section 8.4. |
| Blood serum sample for sasanlimab immunogenicity (ADA and NAb) | | See note | | | | | | | | | | C1 | | | | | | | | | | X | Only for Part 1B. Day 1 predose samples on Cycles 1, 2, 3, 6 and thereafter every 6 cycles. See Section 8.7. |
| CCI | | | | | | | | | | | | | | | | | | | | | | | |

**Table 2. PART 1: PK, ECG, Immunogenicity, Biomarker, and Biospecimen Schedule of Assessments (Participants *NOT* in Food Effect Subset)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1[a] | | | | | | | | Day 2[a] | Day 8 | Day 15 | | | | | | | | Day 16 | Day 22 | | |
| Hours Before/After PF- 07265028 Dose | | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | 12 | Pre | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | 12 | Pre | Pre | | Window for predose samples (except for Day 1): within 30 minutes prior to the same-day morning dose and within 24hr (±3hr) from the prior morning dose. |
| Sampling Window (minutes) | | -30 | ±3 | ±6 | ± 10 | ± 15 | ± 30 | ±60 | ±180 | See note | See note | See note | ±3 | ±6 | ± 10 | ±15 | ±30 | ±60 | ±180 | See note | See note | | |
| Triplicate 12-lead ECG | | X | | | | C1 | | | | | C1 | C1 | | | | C1 | | | | | | | All scheduled ECGs should be performed after the participant has rested for at least 10 minutes in a recumbent or semi-recumbent position and before blood draws. See Section 8.2.4. |
| CCI | | | | | | | | | | | | | | | | | | | | | | | |

**Table 2. PART 1: PK, ECG, Immunogenicity, Biomarker, and Biospecimen Schedule of Assessments (Participants *NOT* in Food Effect Subset)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1[a] | | | | | | | | Day 2[a] | Day 8 | Day 15 | | | | | | | | Day 16 | Day 22 | | |
| Hours Before/After PF- 07265028 Dose | | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | 12 | Pre | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | 12 | Pre | Pre | | Window for predose samples (except for Day 1): within 30 minutes prior to the same-day morning dose and within 24hr (±3hr) from the prior morning dose. |
| Sampling Window (minutes) | | -30 | ±3 | ±6 | ± 10 | ± 15 | ± 30 | ±60 | ±180 | See note | See note | See note | ±3 | ±6 | ± 10 | ±15 | ±30 | ±60 | ±180 | See note | See note | | |
| CCI [redacted] | | | | | | | | | | | | | | | | | | | | | | | |
| Fresh pre-treatment and on-treatment biopsy | X | | | | | | | | | | | C2 (±7 days) | | | | | | | | | | X | - Paired fresh pre-treatment and on treatment biopsies are optional prior to dose level 3. See biomarker Section 8.6 for more information.<br>- On-treatment biopsy can be collected at the EOT visit if the participant discontinues the study before scheduled on treatment biopsy. Additional optional on treatment or EOT biopsies, after C4D1 (>6 weeks after initial on treatment biopsy) may also be collected. |

a. All Japanese participants in Part 1 should be hospitalized for PK sampling for at least 24 hours after first dosing of PF-07265028.

CCI [redacted]

"X" means collection in all cycles unless otherwise noted. "C1", "C2", or "C3" means collection in cycle 1, cycle 2, or cycle 3 only, respectively.

**Table 3. PART 2: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (For Participants *NOT* in Food Effect Subset)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | EOT | Notes: See Lab Manual for details. |
|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | Day 22 | | |
| Hours Before/After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 2 | Pre | | |
| PK Sampling Window (Minutes) | | -30 | ±15 | -30 | -30 | ±12 | -30 | | |
| Administration of PF-07265028 in clinic | | X | | C1 | X | | X | | PF-07265028 is administered at the site after the completion of predose assessment and sample collection. |
| Administration of sasanlimab | | X | | | | | | | Only for Part 2A. See Section 6. |
| PK blood sampling for plasma PF-07265028 | | X | | C1 | C1 | C1 | C1 | X | See Section 8.4.1. |
| Triplicate 12-lead ECG | | X | | | C1 | C1 | | | All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a recumbent or semi-recumbent position and before blood draws or vital signs. See Section 8.2.4. |
| PK blood sampling for serum sasanlimab | | See note | | | C1 | | | X | Only for Part 2A. Day 1 predose samples on Cycles 1, 2, 3, 6 and thereafter every 6 cycles. |
| Blood serum sample for sasanlimab immunogenicity | | See note | | | C1 | | | X | Only for Part 2A. Day 1 predose samples on Cycles 1, 2, 3, 6 and thereafter every 6 cycles. |
| CCI [redacted] | | | | | | | | | |

**Table 3. PART 2: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (For Participants *NOT* in Food Effect Subset)**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | EOT | Notes: See Lab Manual for details. |
|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | Day 22 | | |
| Hours Before/After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 2 | Pre | | |
| PK Sampling Window (Minutes) | | -30 | ±15 | -30 | -30 | ±12 | -30 | | |
| Blood for antigen responses analysis | X | C2 & C3 | | | | | | | |
| Blood for Tumor Antigen Prediction | X | | | | | | | | |
| CCI | | | | | | | | | |
| Fresh pre-treatment and on -treatment biopsy | X | | | | C2 (±7 days). | | | X (or second on-treatment) | - Fresh Pretreatment biopsies are mandatory for all participants in Part 2 with paired on-treatment biopsies mandatory for a subset of patients (~10), and encouraged for all others. See biomarker Section 8.6 for more information.<br>- On-treatment biopsy can be collected at the EOT visit if the participant discontinues the study before the collection of scheduled on treatment biopsy. Additional optional on treatment or EOT biopsies, after C4D1 (>6 weeks after initial on treatment biopsy) may also be collected. |
| CCI | | | | | | | | | |

"X" means collection in all cycles unless otherwise noted. "C1", "C2", or "C3" means collection in cycle 1, cycle 2, or cycle 3 only, respectively.

**Table 4. Food Effect: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (Participants in Food Effect Subset in Part 1A or Part 2 )**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | | | | | | Day 16 | | | | | | | Day 17 | Day 22 | | |
| Hours Before/ After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | Pre | | Sampling times are related to the morning dose on the same day |
| PK Sampling Window (Minutes) | | - 30 | ±15 | See note | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | See note | | Window for predose samples (except for Day 1): within 30 min prior to the morning dose and within 24 hr (±3 hr) from the prior morning dose. |
| Meal administration | | | | | | | | | | | | X | | | | | | | | | | On C1D16, drug administration under fed condition. See Section 6.1.1. |
| Dose of PF-07265028 given in clinic | | X | | X | X | | | | | | | X | | | | | | | X | X | | PF-07265028 is administered at the site after the completion of predose assessment and sample collection. |

**Table 4. Food Effect: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (Participants in Food Effect Subset in Part 1A or Part 2 )**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | | | | | | Day 16 | | | | | | | Day 17 | Day 22 | |
| Hours Before/ After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | Pre | | Sampling times are related to the morning dose on the same day |
| PK Sampling Window (Minutes) | | - 30 | ±15 | See note | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | See note | | Window for predose samples (except for Day 1): within 30 min prior to the morning dose and within 24 hr (±3 hr) from the prior morning dose. |
| PK blood sampling for plasma PF-07265028 | | X | | C1 | C1 | C1 | C1 | C1 | C1 | C1 | C* | C1 | C1 | C1 | C1 | C1 | C1 | C* | C1# | | X | * If the emerging PK data suggest a BID regimen is appropriate, an additional sample will be collected at 12 hr (±3 hr) postdose.<br># If the emerging PK data suggest a BID regimen is appropriate, Day 17 visit will not be needed. |
| CCI | | | | | | | | | | | | | | | | | | | | | | |

**Table 4. Food Effect: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (Participants in Food Effect Subset in Part 1A or Part 2 )**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | | | | | | Day 16 | | | | | | | Day 17 | Day 22 | |
| Hours Before/ After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | Pre | | Sampling times are related to the morning dose on the same day |
| PK Sampling Window (Minutes) | | - 30 | ±15 | See note | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | See note | | Window for predose samples (except for Day 1): within 30 min prior to the morning dose and within 24 hr (±3 hr) from the prior morning dose. |
| CCI [redacted] | | | | | | | | | | | | | | | | | | | | | |
| PK blood sampling for serum sasanlimab | | See note | | | | | | | | | | C1 | | | | | | | | | X | Only for Part 2A. Day 1 predose samples on Cycles 1, 2, 3, 6 and thereafter every 6 cycles. |

**Table 4. Food Effect: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (Participants in Food Effect Subset in Part 1A or Part 2 )**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | | | | | | Day 16 | | | | | | | Day 17 | Day 22 | | |
| Hours Before/ After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | Pre | | Sampling times are related to the morning dose on the same day |
| PK Sampling Window (Minutes) | | - 30 | ±15 | See note | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | See note | | Window for predose samples (except for Day 1): within 30 min prior to the morning dose and within 24 hr (±3 hr) from the prior morning dose. |
| Blood serum sample for sasanlimab immunogenicity | | See note | | | | | | | | | | C1 | | | | | | | | | X | Only for Part 2A. Day 1 predose samples on Cycles 1, 2, 3, 6 and thereafter every 6 cycles. |
| CCI | | | | | | | | | | | | | | | | | | | | | | |
| Triplicate Standard 12-lead ECG | | X | | | C1 | | | | C1 | | | C1 | | | | C1 | | | | | | See Section 8.2.4. |

**Table 4. Food Effect: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (Participants in Food Effect Subset in Part 1A or Part 2 )**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | | | | | | Day 16 | | | | | | | Day 17 | Day 22 | |
| Hours Before/ After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | Pre | | Sampling times are related to the morning dose on the same day |
| PK Sampling Window (Minutes) | | - 30 | ±15 | See note | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | See note | | Window for predose samples (except for Day 1): within 30 min prior to the morning dose and within 24 hr (±3 hr) from the prior morning dose. |
| Blood for immune phenotyping[a] | | X | | C1 | C1, C2& C3 | | | | | | | | | | | | | | | C1 | X | - Unscheduled samples should be collected if day of on-treatment biopsy is ±3 days from C2D15,<br>- Starting with C5, blood samples will be collected every third cycle pre-dose (ie, C5D1, C8D1, etc).<br>- If a participant is suspected to be experiencing an irAE, see footnote.[a] |
| CCI | | | | | | | | | | | | | | | | | | | | | | |

**Table 4. Food Effect: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (Participants in Food Effect Subset in Part 1A or Part 2 )**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | | | | | | Day 16 | | | | | | | Day 17 | Day 22 | | |
| Hours Before/ After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | Pre | | Sampling times are related to the morning dose on the same day |
| PK Sampling Window (Minutes) | | - 30 | ±15 | See note | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | See note | | Window for predose samples (except for Day 1): within 30 min prior to the morning dose and within 24 hr (±3 hr) from the prior morning dose. |
| Blood for tumor antigen prediction | X | | | | | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | | | | | | |
| Fresh pre-treatment and on-treatment biopsy | X | | | | C2 (±7 days) | | | | | | | | | | | | | | | | X | For participants in food effect study, fresh Pretreatment biopsies are mandatory with on-treatment |

**Table 4. Food Effect: PK, Immunogenicity, Pharmacodynamic/Biomarker, and Biospecimen Schedule of Assessments (Participants in Food Effect Subset in Part 1A or Part 2 )**

| Visit Identifier | Screening | 28 Day Treatment Cycle | | | | | | | | | | | | | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 8 | Day 15 | | | | | | | Day 16 | | | | | | | Day 17 | Day 22 | |
| Hours Before/ After PF-07265028 Dose | | Pre | 2 | Pre | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | 0.5 | 1 | 1.5 | 2 | 4 | 7 | Pre | Pre | | Sampling times are related to the morning dose on the same day |
| PK Sampling Window (Minutes) | | - 30 | ±15 | See note | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | ±3 | ±6 | ±10 | ±15 | ±30 | ±60 | See note | See note | | Window for predose samples (except for Day 1): within 30 min prior to the morning dose and within 24 hr (±3 hr) from the prior morning dose. |
| | | | | | | | | | | | | | | | | | | | | | | biopsies optional. See notes in Table 3 and biomarker Section 8.6 for more information. |
| CCI [redacted] | | | | | | | | | | | | | | | | | | | | | | |

"X" means collection in all cycles unless otherwise noted. "C1", "C2", or "C3" means collection in cycle 1, cycle 2, or cycle 3 only, respectively.

## 2. INTRODUCTION

PF-07265028 is an inhibitor of HPK1 that lowers the T cell receptor activation threshold, increases T-cell sensitivity to peptide antigens, as well as enable T cells to resist PGE2, an immunosuppressive metabolite found in tumor microenvironments (data on file: PF-07265028 Study Reports 025546, 030052, 030812, and 031127). In this first clinical study, PF-07265028 administered orally will be evaluated as a monotherapy for the treatment of adult participants with advanced solid tumors and in combination therapy with sasanlimab (PF-06801591) in participants with tumors demonstrating primary resistance to prior PD-1 or PD-L1 treatment for whom no standard therapy is available.

### 2.1. Study Rationale

ICB has emerged as an attractive target for cancer therapy. Multiple CPIs have been approved for use as a single agent or in combination therapy in more than 15 malignancies, but only 20-40% of patients respond initially and another 70% are non-responders or have progressive disease after a short-lived response.[2] As the majority of patients with various tumor types treated with CPIs do not respond to treatment, there is a large unmet need to improve upon these therapies to enhance clinical benefit.

Across most tumor types, responses to CPI correlate with the number of mutations within a tumor (ie, TMB).[3] Tumors with high TMB, particularly those with DNA repair defect which are deemed MSI-H, are more likely to be recognized by the immune system and benefit from CPIs, whereas tumors with low TMB, are less likely to be recognized and have sufficient immune responses that could be extended through ICB. Additional factors, such as the antigenic quality of mutations and immunosuppressive metabolites can also affect the strength of immune recognition of tumors.[4,5,6] The primary clinical hypothesis is that PF-07265028 will enable enhanced immune recognition and thus increase anti-tumor responses in participants with tumors demonstrating primary resistance to current CPI therapies (PD-1, PD-L1, or CTLA-4) because of low or poor quality mutation burden.

The purpose of this FIH study is to (a) assess the safety, tolerability, PK, and PD of increasing doses of PF-07265028 as monotherapy and in combination with sasanlimab; (b) identify the MTD of PF-07265028; (c) evaluate the clinical activity of monotherapy and combination therapy; and (d) select the RDE of PF-07265028 monotherapy and the RDE of PF-07265028 in combination with sasanlimab for potential further studies and development. HPK1 inhibition is expected to have applicability across multiple tumor types, therefore this study will enroll participants with advanced solid tumors for whom standard therapies have failed or for whom no standard therapy is available.

The combination dose escalation of PF-07265028 with sasanlimab will be evaluated in participants with tumors demonstrating primary resistance to PDx (ie, PD-1 or PD-L1) therapies, as well as those who benefit from monotherapy with PF-07265028 regardless of PD-1/PD-L1 treatment status.

The dose expansion phase (Part 2) will evaluate specific tumors, including UC, HNSCC, gastric/GEJ carcinomas, and NSCLC, which have demonstrated primary resistance to approved PDx-containing therapies. Additional indications may be chosen from the dose-escalation phase (Part 1) based on evolving data.

## 2.2. Background

### 2.2.1. Overview of Checkpoint Immunotherapy Use

The American Cancer Society estimates that 83,730 new cases of UC will be diagnosed in the US in 2021 and that 17,200 people will die of the disease.[7] There are significant numbers of patients and new treatment therapies required in the first-line and higher settings.

First-line, platinum-based combinations are active in locally advanced and metastatic UC. However, long-term outcomes, including disease-specific and overall survival, remain suboptimal, and unfortunately, about 40-50% of patients with advanced UC have coexisting medical issues that preclude the use of cisplatin-based therapy. MVAC or GC are standard combination regimens for treatment of metastatic bladder cancer with ORRs of 57%-70% (CR of 15-20%). Median OS is 13-15 months, and the 2-year survival rate is 15-20%.[8,9,10] Multiple CPIs have been approved for UC in the second-line setting following PD on a platinum-based therapy. Multiple CPIs have been approved for UC in the second-line setting following PD on a platinum-based therapy. CPIs are also beginning to establish a role as first-line agents in UC patients who are not candidates for cisplatin chemotherapy. Agents in this category include the PDx inhibitors atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab. These agents have shown response rates of 15-20% with median OS of 8-10 months.[11-17]

Gastric and GEJ adenocarcinoma is the fifth most common cancer worldwide and the third leading cause of cancer-related mortality worldwide.[18] In metastatic disease, the prognosis is dismal and standard-of-care therapies have limited impact on patient outcomes with median OS ranging from 4 months with BSC only and 12 months with chemotherapy.[19-21] Clinical trials that examine the use of CPIs (pembrolizumab and nivolumab) either as monotherapy or in combination with cytotoxic chemotherapy in gastric and GEJ cancers have only led to limited approval in the first-line, second-line, and third-line settings with relatively low response rates ranging from 5-30% and median PFS of 3.3-6.6 months. Patients whose tumors demonstrate MSI-H, dMMR, and PDx-positivity (CPS $\geq$1 and $\geq$10) have a better prognosis.

HNSCC is a malignancy of high morbidity and mortality, with 400,000-600,000 new cases globally. Until the addition of CPIs, patients with recurrent or metastatic HNSCC for whom a platinum-based treatment regimen failed had a dismal prognosis with OS <6 months. The approval of pembrolizumab and nivolumab for HNSCC has improved OS to more than 1 year in patients with a CPS $\geq$20 but not in those with lower CPSs. Response rates however still remain less than 25%.

Lung cancer is the leading cause of cancer-related deaths in the world.[22] Several large-scale Phase 3 trials of first-line treatments for advanced NSCLC have documented prolonged patient survival, including PFS and OS for ICIs used alone or in combination with platinum-based chemotherapy with or without anti-angiogenesis agent or in combination with another immunotherapy leading these treatment regimens to become the standard of care in the treatment of NSCLC. Such agents include pembrolizumab, atezolizumab, nivolumab or cemiplimab. Tumors with high PD-L1 expression and TMB have better prognoses. Response rates in first-line treatment-naïve patients ranged from 26-63% depending on whether CPI was administered as monotherapy, or when used in combination with chemotherapy or another immunotherapy. Unfortunately, the PFS is only modest ranging from 4.2-10.3 months with 30-40% progressing within 3 months and 40-60% in 6 months. The response rate is only around 10-20% in second-line-treatment and the PFS is also similar to or poorer than that for the conventional second-line chemotherapy.[23-32]

Enhancing responses to IO therapies is clearly a high unmet medical need.

### 2.2.2. Mechanism of Primary Resistance to CPI

Primary resistance to CPIs is the inability of the immune system to mount an anti-tumor response after initial CPI drug exposure. Patients who have confirmed PD after having received at least 6 weeks of CPI therapy but no more than 6 months are considered to have primary resistance to CPI therapy (Table 5).[33] Primary resistance is different from relapsed disease where patients have previously demonstrated a response to CPI therapy. There are many potential mechanisms for primary resistance, including lack of immune tumor recognition, defective antigen presentation, inability of T cells to traffic to or penetrate effectively into viable areas of the tumor or suppression T cells to due to other checkpoints and soluble inhibitory factors in addition to PD-1/PD-L1 axis. Checkpoints such as TIGIT and LAG-3, inhibitory cells such as M2 macrophages, and TGF-β have been implicated; however, recognition of the tumor by the immune system remains a major barrier to responses.

**Table 5. Definitions of Primary and Secondary Resistance in Advanced Disease Setting**

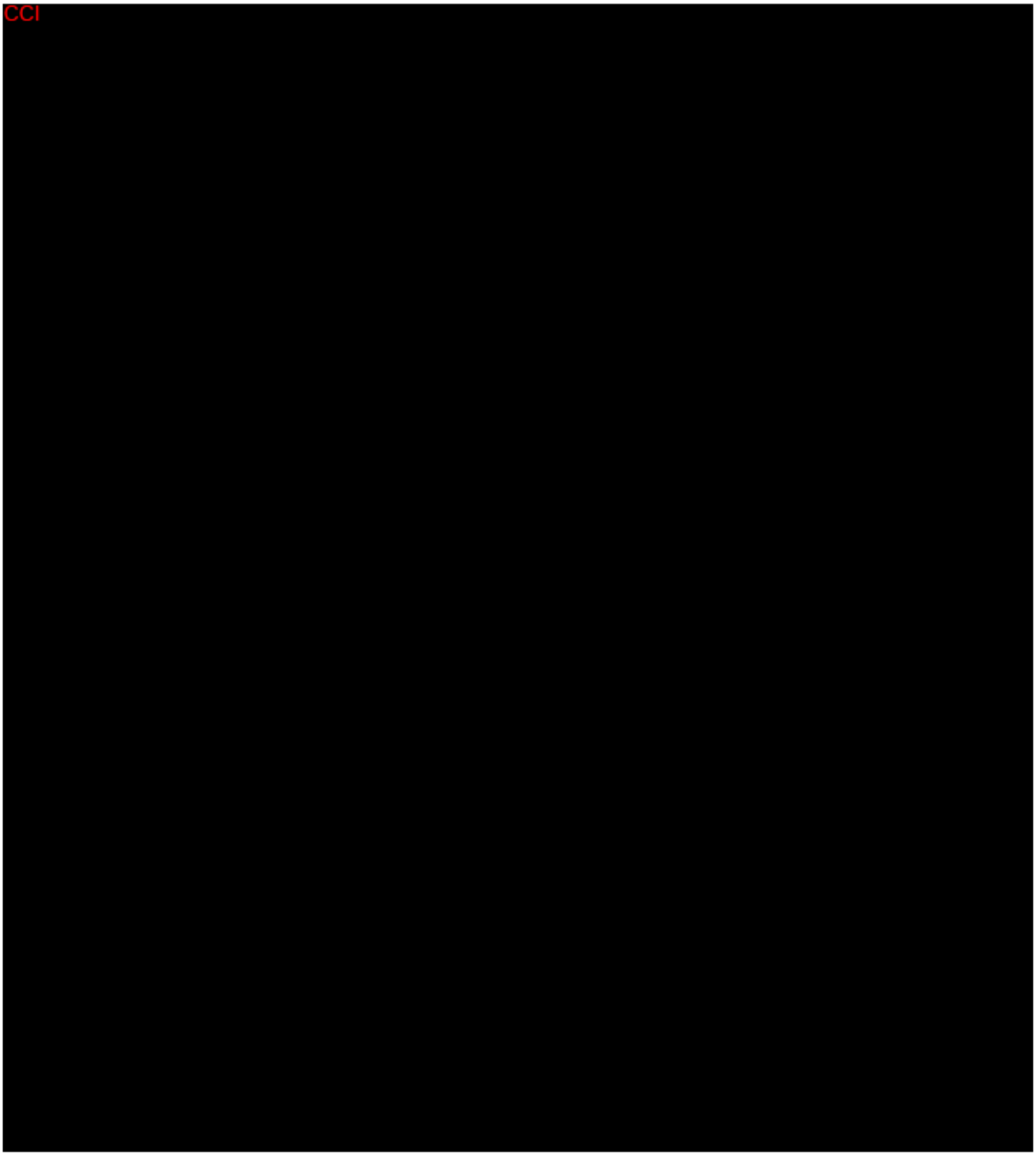
| Resistance Phenotype Confirmatory Scan Timeframe | Drug Exposure Requirement | Best Response | Confirmatory Scan for PD Requirement |
|---|---|---|---|
| Primary Resistance | ≥6 weeks | PD; SD for <6 months | Yes; at least 4 weeks after initial PD |
| Secondary Resistance | ≥6 months | CR, PR, SD for >6 months | Yes; at least 4 weeks after PD |

The close association of TMB and tumor immune recognition with response to PD-1 is highlighted in the KEYNOTE 158 study.[34] Of the 790 patients evaluated for TMB, patients in the high TMB group had approximately twice the response rate of those in the low TMB group (29% versus 10%). This study led to the pan-tumor approval of pembrolizumab monotherapy treatment in patients with tumors ≥10 mutations per megabase of DNA.

However, in the example of KEYNOTE 158, only 13% of patients evaluated demonstrated high TMB.

Thus, a significant portion of patients treated with current available CPI have suboptimal levels of TMB to generate tumor immune recognition, and there even remains room for improved responses even in those with ≥10 mutations per megabase of DNA.

CCI



### 2.2.4. Sasanlimab Mechanism of Action

Sasanlimab (PF-06801591) 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. Sasanlimab blocks the engagement of PD-1 with its ligands, PD-L1 and PD-L2, which 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.[45-47]

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-$\gamma$ 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 anti-tumor immunity and form the basis for an immunotherapeutic approach to treat cancer.

### 2.2.5. Nonclinical Pharmacology

- **Biochemical Affinity:** PF-07265028 inhibits the kinase activity of activated (phosphorylated) full-length recombinant enzyme with a inhibition constant ($K_i$) below the limit of quantitation of chelation-enhanced fluorescence biochemical assay a <0.05 nM (N=10; AssayQuant Technologies, Inc). The potent inhibition of HPK1 by PF-07265028 in biochemical assay was confirmed by surface plasmon resonance measuring an affinity ($K_D$) of 266 pM (N=2) and a dissociative half-life ($t_{1/2}$) of 97 minutes.

- **Selectivity:** The kinome selectivity of PF-07265028 was assessed using in-house and commercial biochemical kinase panels. PF-07265028 was >100x selective over >98% of kinases tested in a biochemical panel of 395 kinases at Thermo Fisher Scientific, Inc. (Waltham, MA), including the immune-relevant kinases LCK, PKC theta, JAK3, TYK2, Src family kinases, MAP4K2 and MAP4K4. Within 30x selectivity were only MAP4K5, STK4 (MST1) and TAOK1, and within 100x selectivity were LRRK2 and MAP4K3 and LRRK2. In an orthogonal in-cell engagement panel of 205 kinase assays at Promega Corp., only HPK1, CLK1, CLK2 and CLK4 demonstrated >50% occupancy at 200 nM, above the projected therapeutic doses. Overall, PF-07265028 has demonstrated a highly selective profile based on the broad biochemical and cell engagement kinase panels profiling.

- CCI [redacted]

CCI [redacted]

**Sensitized T Cell Activation:** PF-07265028 enhanced T cell proliferation and cytokine release with TCR stimulation. Examining activation of pan-T cells by CD3-binding antibodies across 9 donors, PF-07265028 increased T cell proliferation response to 280% with an $EC_{50}$ of 9.02 nM. Measuring cytokine release from 6 donors, increases in the CD4 cytokine IL-2, and that pan-T cell cytokines TNFα and IFN-γ were observed with $EC_{50}$s of 25.75, 15.46, and 14.65 nM. Similarly, examining a CD8 recall response in PBMCs treated with viral peptide antigens, a 361% IFN-γ response with an $EC_{50}$ of 26.91 nM was observed with PF-07265028 treatment across 10 donors. Together, these results support sensitizing CD4 and CD8 T cell responses and concentrations comparable to inhibition of SLP76 phosphorylation.

Moreover, sensitized T cell activation was retained in the presence of PGE2. T cell proliferation decreased ~50% with 250 nM PGE2, and PF-07265028 reversed this effect across 6 donors with an $EC_{50}$ of 28.6 nM.

**Combination Benefit with PD-1 Blockade:** As HPK1 inhibition sensitizes T-cell activation, it is expected that HPK1 inhibitor treatment will upregulate the T-cell activation marker PD-1, and lead to engagement of the PD-1/PD-L1 immune checkpoint. Consistent with this, preclinical mouse tumor models have found that genetic ablation of HPK1 synergizes with PD-1/PD-L1 blockade.[43] To model the effect of PF-07265028 on human anti-tumor immunity, we examined co-cultures of a human tumor cell line with tumor-reactive T cells. Addition of 111 nM PF-07265028 increased the T-cell-mediated clearance of tumor cells from 9.4% to 23.4%. In the presence of the PD-1-blocking antibody sasanlimab, PF-07265028 increased A375 cell clearance from 29.5% to 52.6% while also further increasing the frequency of apoptotic tumor cells and the IFN-γ released beyond either single agent. Across the dose response of PF-07265028 either alone or in combination, increasing anti-tumor benefit was observed from 8 nM through 300 nM drug concentrations. Specific information regarding the data and experimental designs can be found in the PF-07265028 IB.

**Predicted Efficacious Concentration:** Comparing across the previously described assays, PF-07265028 inhibits SLP76 phosphorylation at $IC_{50}$s ranging from 14.8 to 31.5 nM while sensitizing T-cell activation and effector functions with $EC_{50}$s ranging from 9 to 28.6 nM. The high similarity in PF-07265028 concentration dependencies across experiments supports that modulation of the CCI [redacted] correlates with the expected benefit towards T-cell activation. Moreover, at 50% inhibition of SLP76 phosphorylation, measurable anti-tumor benefit was observed in co-cultures of T cells with tumor cells. This supports the notion that anti-tumor efficacy is expected once drug exposures result in an average of approximately 50% inhibition of SLP76 phosphorylation, corresponding to a projected human efficacious dose of 140 mg QD with an average unbound plasma concentration of ~23 nM. However, by virtue of the high-specificity and safety profile of PF-07265028, we anticipate the feasibility of dosing to exposures that would reach an

average of 90% inhibition of SLP76 phosphorylation, and that this level of modulation may provide an even greater benefit towards anti-tumor immunity.

### 2.2.6. Nonclinical Pharmacokinetics and Metabolism

Details of the nonclinical ADME properties of PF-07265028 are provided in the PF-07265028 IB.

The predicted human plasma clearance and volume of distribution of PF-07265028 are 5 mL/min/kg and 5 L/kg respectively, with an effective half-life of 12 hours. High to complete absorption following oral administration is expected, with an estimated oral bioavailability of 56% at the predicted efficacious dose of 140 mg QD.

The major route of clearance for PF-07265028 is predicted to be CYP3A4-mediated oxidative metabolism, with minor contributions from CYP3A5, 2D6, 2J2, and 1A1 ($f_{m,\ CYP3A} = 0.80$). No human-specific metabolite was observed in hepatocytes or liver microsomes.

Human plasma protein-binding was measured, with a fraction unbound of 0.0674. Human blood-to-plasma ratio was measured, with a ratio of 1.1.

PF-07265028 is a potential perpetrator of DDIs by time-dependent inhibition of CYP2D6, reversible inhibition of CYP3A, UGT1A1, and transporter-mediated inhibition of P-gp, BCRP, and OCT1 at the clinically relevant dose of 140 mg QD. Potentially, UGT1A9 and MATE2K could also be inhibited at higher doses of PF-07265028. In isolated human hepatocytes treated with PF-07265028, no significant induction of CYP1A2 was observed; however, a concentration-dependent downregulation of CYP3A4 and CYP2B6 mRNA and enzyme activity was observed, and the potential for induction of these enzymes in cells could not be determined.

PF-07265028 was highly permeable in RRCK cells, with an apparent permeability of ~$9 \times 10^{-6}$ cm/s. PF-07265028 is a substrate of MDR1 (P-gp) and BCRP efflux transporters with low apical-to-basolateral permeability ($P_{app,AB}$) and high ERs in MDCK-MDR1 (NIH) cells ($P_{app,AB}$ of $0.29\times 10^{-6}$ cm/s and ER of 110) and MDCK-hBCRP cells ($P_{app,A-B}$ of $1.1 \times 10^{-6}$ cm/s and ER of 31.9). PF-07265028 is not a substrate of OCT1 in vitro.

Since the absorption in human is predicted to be high, and the predominant clearance mechanism is expected to be via metabolism, the potential risk of DDIs due to transporter inhibition for PF-07265028 as a victim is low.

Based on GastroPlus simulations, the oral absorption of PF-07265028 is not anticipated to be sensitive to stomach pH changes.

### 2.2.7. Nonclinical Safety

The toxicity profile of PF-07265028 in mice and cynomolgus monkeys was determined after oral gavage administration in GLP toxicity studies of up to 1 month in duration. PF-07265028 was tolerated at doses up to 30 mg/kg/day in mice (NOAEL and STD10) and 15 mg/kg/day in cynomolgus monkeys (NOAEL and HNSTD). The combined sex total plasma concentrations achieved at the NOAEL/STD10 in mice are $C_{max}$ of 877 ng/mL and $AUC_{ss}$ of 7680 ng•h/mL. The combined sex total plasma concentrations achieved at the NOAEL/HNSTD in cynomolgus monkeys are $C_{max}$ of 187 ng/mL and $AUC_{ss}$ of 2580 ng•h/mL.

At a higher dose of 30 mg/kg/day in cynomolgus monkeys, PF-07265028 was not tolerated resulting in early termination due to clinical signs indicative of moribundity including decreased activity, hunched posture, fecal changes (liquid/soft/mucoid), emesis, thin appearance, decreased skin turgor, and decreased body weight and/or food consumption. Microscopic findings in the gastrointestinal tract including mucosal degeneration were considered to be a contributing factor in the observed moribundity.

The key toxicities of potential clinical importance involve the gastrointestinal system and lymphocyte populations. GI findings of minimal to moderate mucosal erosion, epithelial degeneration/regeneration and dilatation were noted in cynomolgus monkey at non-tolerated doses; fecal changes (decreased/liquid/soft/mucoid) and emesis (cynomolgus only) were also noted at these doses. Additionally, decreases in circulating lymphocyte populations were noted and correlated with decreased cellularity in the spleen and thymus.

PF-07265028 was evaluated for potential cardiovascular effects using conscious, telemetered cynomolgus monkeys. The overall cardiovascular profile included modest changes in hemodynamic parameters (heart rate/blood pressure), left ventricular pressure and contractility. No changes were noted in ECG parameters including the QT-interval.

PF-07265028 is not mutagenic or clastogenic, but was aneugenic in vitro and in vivo. Micronuclei formation was noted in reticulocytes of mice administered 100 mg/kg/day, but not 30 mg/kg/day.

PF-07265028 may have potential risk for phototoxicity based on light absorption within the 290-400 nm range with a calculated MEC >1000 L/mol/cm. PF-07265028 will be evaluated for phototoxicity prior to any large-enrollment clinical trials.

Developmental and reproductive toxicity studies have not been conducted with PF-07265028. Reproductive organ toxicities were not identified in the 1-month toxicity studies in mice and monkeys.

In summary, oral administration of PF-07265028 was tolerated in nonclinical species. The toxicities of potential clinical importance involve the gastrointestinal system and lymphocyte cell populations. These findings are anticipated to be reversible in nonclinical species. Monitoring for these toxicities is recommended, although they are considered clinically manageable in the intended advanced cancer patient population.

Further details of the nonclinical safety program are provided in the current PF-07265028 IB.

### 2.2.8. Clinical Overview

This is a FIH study for PF-07265028; therefore, no clinical data are available.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07265028 may be found in the PF-07265028 IB, which is the SRSD for PF-07265028.

#### 2.2.8.1. Sasanlimab Clinical Experience in Study B8011001

B8011001 is a completed Phase 1, open-label, multicenter, multiple dose, dose escalation and expansion, safety, PK, and PD study of sasanlimab. The primary purpose of this study was to evaluate safety and early signs of efficacy.

Study enrollment was completed and a total of 146 participants were enrolled. The available clinical data indicate sasanlimab has an acceptable safety profile and evidence of efficacy, both of which are highly consistent with other approved anti-PD-1 agents. Refer to the IB for a clinical summary of B8011001.[48]

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sasanlimab may be found in the sasanlimab IB, which is the SRSD for sasanlimab for this study.[48]

### 2.3. Benefit/Risk Assessment

Since this is the FIH study, no human studies have been conducted to date evaluating PF-07265028. For selected disease indications where effective treatment options are not available, the benefit/risk relationship has been carefully considered in the planning of this trial based on pre-clinical, toxicology studies and nonclinical safety profiles of PF-07265028.

Safety findings with PF-07265028 that were observed in the nonclinical studies include: gastrointestinal toxicity, reductions in lymphocytes in blood and secondary lymphoid tissues and increases in blood pressure/heart rate. During this Phase 1 study, clinical assessments will include frequent safety monitoring. The participants will be monitored during and for at least 7 hours following their first dose. This will be implemented throughout dose escalation. In Japan, the participants will be monitored during and following their first dose with at least 24-hour inpatient hospitalization period. When a participant is discharged from the hospital during the DLT evaluation period, the conditions (tests, medical examinations, etc) described should be performed on the day of the scheduled discharge by the investigators, and the propriety of discharge should be determined. This will be implemented throughout dose

escalation and length of inpatient hospitalization will be re-assessed based on safety data prior to starting dose expansion cohorts).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07265028 may be found in the PF-07265028 IB, which is the PF-07265028 SRSD for this study.

### 2.3.1. Risk Assessment

Potential risks of clinical significance for sasanlimab are provided in the sasanlimab IB.

**Study Intervention: PF-07265028**

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Immune-related toxicity | The potential overlapping risks are based on the sasanlimab IB and nonclinical studies for PF-07265028. | • Guidelines for treatment interruption/dose reductions and discontinuation in case toxicities, and guidelines for steroid treatment implementation are incorporated in Section 6.5.1. |
| ISRs | The potential risks of sasanlimab administered with PF-07265028 are based on the sasanlimab IB and nonclinical studies for PF-07265028. | • Participants should be monitored for serious and nonserious AEs, including ISRs, following administration of sasanlimab (in Parts 1B and 2A).<br>• When appropriate, at the discretion of the investigator, a participant with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR. If injection site reaction is noted, site tolerability assessments should continue until the symptoms resolve. Refer to Section 8.2.7. |
| Gastrointestinal (mucosal erosion, epithelial degeneration/regeneration) with accompanying clinical signs of emesis and diarrhea. | The potential risks are based on nonclinical toxicology data for PF-07265028 in mice and monkeys. | • Participants will be monitored for gastrointestinal toxicity.<br>• At the discretion of the investigator therapeutic and prophylactic supportive care may be considered.<br>• Dose reductions/ interruptions and discontinuations are permissible.<br>• Potential of dosing with food. |
| Marrow (increased myeloid to erythroid ratio) | The potential risks are based on nonclinical toxicology data for PF-07265028 in mice and monkeys. | • Participants will be monitored for hematologic toxicity.<br>• At the discretion of the investigator therapeutic and prophylactic supportive care may be considered.<br>• Dose reductions/ interruptions and discontinuations are permissible. |
| Increased hemodynamics (increased heart rate and/or blood pressure) | Identified in a single dose cynomolgus monkey telemetry study of PF-07265028. | • Participants will have serial vital signs performed. |
| Potential for phototoxicity | The molar extinction coefficient of PF-07265028 exceeds 1000 L/mol/cm which increases the risk of phototoxicity. | • Participants will be instructed to use UVA and UVB sunblock and to limit exposure to direct sunlight. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Procedures** | | |
| De novo (fresh) tumor biopsy (pre-and on-treatment biopsies<br>• stinging pain from injection of local anesthetic;<br>• pain or discomfort from the biopsy procedure;<br>• discomfort from lying still for an extended time;<br>• bleeding, swelling, scarring, soreness, or bruising at the biopsy site;<br>• infection of wound<br>• contamination of cancer cells to unaffected tissue when removing biopsy needle.<br>• Biopsies of certain sites may increase chances of life-threatening complications, eg pneumothorax during biopsy of lung. | There is a risk associated with any tumor biopsy. | • Local anesthetic will be administered.<br>• Sterile techniques will be used.<br>• Procedures will be performed by qualified medical practitioners.<br>• 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%). |
| Blood sample collections for local safety assessment and PD/PK data analysis will be completed. | A blood draw may cause inflammation of the vein, pain, bruising, discomfort, redness, burning, or bleeding at the site where the needle is placed to draw the blood. Blood draw may cause a participant to feel dizzy or faint. There is a slight chance of infection. | • All blood draws will be completed by qualified and trained medical personnel.<br>• Sterile technique will be used.<br>• Blood sample collections will be conducted at facilities prepared for adverse reactions related to the collection. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Participants will have contrast-enhanced CT scans during study participation. | CT scans expose participants to a small dose of radiation. Contrast dye used for CT scans may cause pain or burning upon injection, may worsen kidney function in participants with kidney disease and may cause allergic reactions that could be severe and life-threatening. | • The radiation exposure is similar to what participant would have under SOC and should not create a significant risk to health.<br>• Participants must meet renal inclusion criteria. CT scans will be conducted at facilities prepared for adverse reactions to the contrast dye. |
| Participants will have MRI scans with ferromagnetic contrast enhancement during study participation. | MRI scans expose participants to harmless, brief episodes of changes in the local magnetic field.<br>The contrast used for MRI (gadolinium or similar agents) may cause headache, nausea, or dizziness that is mild to moderate in intensity and transient with rapid spontaneous resolution. Contrast should not be used in participants with compromised renal function, or known hypersensitivity reactions. | • Participants must meet renal inclusion criteria. MRI scans will be conducted at facilities prepared for adverse reactions to the contrast dye. No dye will be given to those with known hypersensitivity reactions. |

### 2.3.2. Benefit Assessment

There continues to be a significant unmet medical need for effective therapies for advanced or metastatic carcinomas that have relapsed on or are refractory to current immunotherapies. Mechanistically, preclinical data with ex vivo human T cells have shown that a small-molecule inhibitor of HPK1 approach results in enhanced T-cell activation, reversal of PGE2 immunosuppression, and in vitro anti-tumor activity in co-cultures of tumor cells with T cells. Inhibition of HPK1 combined with PD-1 blockade in T cell and tumor cell co-cultures further increases IFN-γ production and elimination of tumor cells, compared with either single-agent treatment. Although the breadth of mechanisms by which an HPK1 inhibitor enhances T-cell activation from T-cell priming to effector functions remain to be fully elucidated, it is believed that when used in combination with PD-1 blockade (eg, sasanlimab), PF-07265028 will improve clinical outcomes in participants whose anti-tumor immune response is limited by poor T cell activation due to low-quality tumor antigens or PGE2 immunosuppression.

Although there is no prior clinical experience with PF-07265028, tumor reduction was observed in in vitro preclinical studies, as noted above. As such, there is a potential benefit of the participant's tumors shrinking due to the study treatment, which could translate into decreased cancer-related symptoms, increased PFS, and longer OS. The participant would also be contributing to the development of a novel therapy in an area of unmet need. 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.

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 PF-07265028 without significant overlapping toxicity, resulting in a similar or better benefit/risk profile compared with PF-07263689 as a monotherapy.

### 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-07265028 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:** | **Primary:** | **Primary:** |
| • To assess safety and tolerability at increasing dose levels of PF-07265028 monotherapy and in combination with sasanlimab in successive cohorts of participants with advanced/metastatic solid tumors in order to estimate the MTD/MAD and select the Phase 1 Expansion Dose. | • First cycle DLTs.<br>• Adverse events (including irAEs) as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy.<br>• Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. | • DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period (Cycle 1). The attributes of this estimand are provided in Section 9.1.1.<br>• Incidence of AEs estimated during the AE-evaluation period, defined as the time from the first dose to earliest of (28 days post last dosing date and day of new anti-cancer therapy -1 day). |
| **Secondary:** | **Secondary:** | **Secondary:** |
| • To characterize the single and multiple dose PK of PF-07265028 when given as monotherapy and in combination with sasanlimab.<br>• To evaluate sasanlimab PK in participants receiving PF-07265028 and sasanlimab<br>• To evaluate the effect of food on PF-07265028 PK in a subset of participants, if the food-effect assessment is performed in Part 1A. | • PK parameters of PF-07265028:<br>  • SD: $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC_{tau}$, and as data permit, $t_{1/2}$, $AUC_{inf}$, CL/F, and $V_z$/F.<br>  • MD: $C_{max,ss}$, $T_{max,ss}$, $AUC_{tau,ss}$, $AUC_{last,ss}$, $C_{min,ss}$, CLss/F, and as data permit, $V_{ss}$/F, and $R_{ac}$ ($AUC_{tau,ss}/AUC_{tau,sd}$).<br>• PK of sasanlimab:<br>  • $C_{min}$ in selected cycles.<br>  • PK parameters of PF-07265028 (including $C_{max}$, $T_{max}$, $AUC_{tau}$, $AUC_{last}$) under fasted and fed conditions. | • Not applicable. |
| • To evaluate the immunogenicity of sasanlimab when given in combination with PF-07265028 in Part 1B. | • Incidence and titers of ADA and NAb. | |
| • To evaluate preliminary anti-tumor activity. | • OR, as assessed using the RECIST version 1.1 and irRECIST and proportion of participants with PR and irPR, as appropriate. | |
| CCI [redacted] | | |

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| CCI [redacted] | | |

### 3.2. Dose Expansion (Part 2)

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| • To evaluate preliminary anti-tumor activity of PF-07265028 in combination with sasanlimab. | • OR, as assessed using the RECIST version 1.1 and irRECIST. | • The treatment effect of PF-07265028 in combination with sasanlimab assessed by ORR using the RECIST version 1.1 and irRECIST in the response evaluable analysis population. |
| • To assess safety and tolerability in combination with sasanlimab at the RDE.<br>• To determine the RP2D based on the RDE. | • Adverse Events (including irAE) as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy.<br>• Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. | • Incidence of AEs estimated during the AE-evaluation period, defined as the time from the first dose to earliest of (28 days post last dosing date and day of new anti-cancer therapy-1 day). |

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Secondary:** | **Secondary:** | **Secondary:** |
| • To evaluate other anti-tumor activity. | • Time-to-event endpoints: eg, DoR, PFS, OS. | • Not applicable. |
| • To evaluate PK of PF-07265028 and sasanlimab when administered in combination (at combination RDE from Part 1). | • PK parameters of PF-07265028 (ie, $C_{ss,max}$ and $C_{ss,min}$) and sasanlimab (ie, $C_{min}$ in selected cycles). | |
| • To evaluate the effect of food on PF-07265028 PK in a subset of participants, if the food-effect assessment is performed in Part 2. | • PK parameters of PF-07265028 (including $C_{max}$, $T_{max}$, $AUC_{tau}$, $AUC_{last}$) under fasted and fed conditions. | |
| • To evaluate the immunogenicity of sasanlimab when given in combination with PF-07265028. | • Incidence and titers of ADA and NAb against sasanlimab. | |
| CCI [redacted] | | |

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a Phase 1, open-label, multicenter, multiple-dose, dose-escalation, dose-expansion, safety, PK, and PD study of PF-07265028 as a single agent and in combination with sasanlimab in cohorts of adult participants with advanced solid tumors that progressed after systemic anticancer therapy or for whom no standard therapy for curative intent is available or in the opinion of the participant and their treating physician, that standard therapy would not be appropriate, or who have refused standard therapy.

This study contains 2 parts (see Section 1.2):

- Part 1 of the study will consist of staggered dose escalation cohorts with PF-07265028 as monotherapy (Part 1A) and PF-07265028 administered in combination with sasanlimab (Part 1B). In addition Part 1 may also evaluate continu-ous BID dosing based on emerging clinical and PK data.

- Part 2 of the study will consist of dose expansion cohorts of PF-07265028 administered in combination with sasanlimab in specific tumor types (Part 2A). The RDE and dosing regimen for the combination therapy as identified in Part 1B of the study will be used in the expansion cohorts during Part 2. Expansion of PF-07265028 as monotherapy (Part 2B) with the RDE as identified in Part 1A will be based on evidence of clinical data generated during monotherapy dose escalation.

A maximum sample size of 240 participants will be enrolled in the study including approximately 60 participants in Part 1 dose escalation and up to 180 participants in Part 2 dose expansion. The actual number of participants enrolled in Part 1 will depend on the tolerability of PF-07265028 as monotherapy and in combination with sasanlimab and the number of dose levels required to identify the MTD/MAD and RDE. In Part 2A for combination therapy (4 cohorts in total), up to 40 participants will be enrolled for each expansion cohort. If the expansion cohort as monotherapy is explored based on emerging clinical, safety, PK, or PD data, then up to 20 additional participants will be enrolled for Part 2B. The actual number of participants enrolled in Part 2 will depend on both safety and the anti-tumor activity of PF-07265028 as monotherapy and in combination with sasanlimab.

In monotherapy, starting dose for PF-07265028 is 25 mg administered orally QD on a continuous basis. BLRM is used for dose finding until reaching MTD. Continuous BID dosing may be explored The potential switch from continuous QD dosing to BID dosing would be based on emerging PK, PD and safety data. This switch may be needed if data demonstrate that PF-07265028 has a shorter than expected half-life with inadequate PK/PD coverage through QD dosing, or there are AEs related to $C_{max}$ which might be mitigated by a lower dose given BID.

PF-07265028 will initially be administered under the empty stomach condition. The effect of food on PF-07265028 PK will be evaluated in at least 6 participants (food effect subset) at a dose level not exceeding the PF-07265028 MTD and RDE, either as a cohort in Part 1A or in 1 of the Part 2 cohorts. If emerging PK data from the food effect assessment suggest the effect of food on PF-07265028 PK is not clinically meaningful, participants may be instructed to take PF-07265028 without regards to food. In addition, the study has included a plan to assess the effect of food intake on tolerability and safety, if treatment-related Grade ≥2 GI toxicity is observed in ≥30% participants with a minimum of 6 participants enrolled in total across all dose levels. The dose of PF-07265028 for the evaluation of food effect on tolerability is expected to yield a steady-state AUC and $C_{max}$ not exceeding the AUC and $C_{max}$ of PF-07265028 at the MTD administered under the empty stomach condition. If food intake could allow participants to tolerate the same or higher systemic exposure of PF-07265028 compared to the empty stomach condition, subsequent parts of the study will continue with the dosing regimen of PF-07265028 administered with food.

In combination therapy, sasanlimab 300 mg SC Q4W will be administered at the clinic together with oral administration of PF-07265028.

Study intervention will be administered in 28-day cycles. Treatment with study intervention will continue until confirmed PD, participant refusal, unacceptable toxicity, investigator decision or study termination, or up to 24 months from first dosing, whichever occurs first. Participants who complete the maximum number of cycles/months on study intervention and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study intervention will be given the opportunity to continue treatment upon agreement between investigator and sponsor.

Every effort should be made to administer study intervention per the planned dose level and schedule. In the event of significant toxicity, dosing of PF-07265028 may be delayed and/or reduced and/or the dosing of sasanlimab may be delayed or skipped. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

For progressive disease, irRECIST will be used (see Section 10.13). Participants with radiological progression per RECIST will be permitted to continue on study treatment while PD is confirmed, 4 or more weeks later as per irRECIST if the investigator believes that it is in the best interest of the participant. Participants who have confirmed progression per irRECIST may continue on therapy if, after discussion with the sponsor, the investigator considers that the participant is deriving clinical benefit from treatment; participants with rapid progression or sites of disease adjacent to or invading major blood vessels are not eligible for treatment beyond progression. Participants experiencing toxicities, including a DLT, may be managed with dose reductions/interruptions of PF-07265028 and/or interruption of sasanlimab or discontinuation from 1 or both treatments. After the discontinuation of study intervention, all participants will complete an EOT and safety follow-up visits for assessment of AEs (see Sections 8.2.8 and 8.2.9).

### 4.1.1. Part 1A Monotherapy and Part 1B Combination Therapy Dose Escalation

In Part 1A of this study, PF-07265028 as monotherapy and Part 1B, PF-07265028 in combination with sasanlimab, will be evaluated for safety in adult participants with advanced solid tumors that progressed after standard systemic anti-cancer therapy or for whom no standard therapy for curative intent is available or in the opinion of the participant and their treating physician, that standard therapy would not be appropriate, or who have refused standard therapy. Participants in the combination arm must have received at least 1 prior CPI and demonstrated primary resistance to treatment with PDx therapies. Participants, who are naïve to immunotherapy or who have secondary resistance to PDx therapy, may be considered after discussion with the sponsor.

In Part 1A monotherapy, the first dose level will be 25 mg administered orally QD on Days 1 through 28 in a 28-day cycle. There will be a minimum of 48 hours between the first dose administered to the first participant and administration of PF-07265028 to the subsequent participants enrolled at the same dose level, to allow for sponsor analysis of initial safety data.

The dose escalation decision including the recommended dose increment for the next cohort of patients will be guided by BLRM with EWOC principle. Maximum allowable PF-07265028 dose increment is 60%, with the exception for the increment from DL1 to DL2, which may be up to 100%. Please see more details in Section 4.3.2, Criteria for Dose Escalation.

In Part 1B, combination therapy escalation will begin, after at least the first 2 dose levels of PF-07265028 have been determined to be safe in Part 1A, in combination with sasanlimab 300 mg SC Q4W. The first PF-07265028 dose level evaluated in Part 1B in combination with sasanlimab will be based on emerging PK/PD data from Part 1A (eg, exposure of PF-07265028, target engagement and/or evidence of biomarker modulation/biologic activity) and will be at least one dose level lower (N-1) than the previously tolerated monotherapy dose in Part 1A. The enrollment of participants into the combination cohort will be conducted within the range of the dose levels at which the monotherapy is tolerated in Part 1A. Dose levels explored in Part 1B combination will not initiate until they have been deemed safe in Part 1A and are at least one does level lower and will not be escalated above the MTD determined in the monotherapy arm.

Dose levels that have cleared the DLT period in Part 1 may be expanded up to 10 participants PF-07265028 administered as monotherapy or in combination sasanlimab at or below the MTD. Expansion of dose levels will be based on evolving clinical data (including safety, PK, and PD) to explore activity and help identify the RDE of the monotherapy and/or combination in Part 2.

Please see below for intra-participant dose escalation rules and rules for crossover from Part 1A to Part 1B.

- To minimize the risk that an individual participant may be exposed to a sub-therapeutic dose, intra-participant dose escalation of PF-07265028 in Part 1 to the maximal dose level that has previously been determined to be safe (based on BLRM) may be allowed if the protocol required safety assessments for the previous treatment cycle have been performed and as follows:

  1. Participant has completed 2 cycles of treatment at the current dose level; or if disease progression occurs.

  2. No Grade ≥3 treatment-emergent toxicities were experienced at the participant's current dose level.

  3. If a clinical rationale is provided by the investigator and approved by the sponsor.

- In Part 1A (monotherapy dose escalation) participants with SD after 2 cycles of treatment, and additionally participants with a RECIST response of PR or CR, who then experience PD, may rollover to the combination cohort regardless of prior PDx status.

Participants in Part 1 must have recently obtained archival tumor tissue available (collected within 6 months prior to screening). If the archival sample is older than 6 months, the participant must consent to undergo a fresh pre-treatment biopsy during the screening period. If a new biopsy represents a significant safety risk in the opinion of the investigator, the participant may be considered for enrollment with archival samples only after discussion with the sponsor.

After starting DL3 in monotherapy (Part 1A) and the corresponding dose level in combination (Part 1B) participants may be asked to provide mandatory paired fresh pre-treatment and on treatment biopsy samples to enable evaluation of tissue biomarker PD activity. Initiation of the paired tumor sample collections will be based on evaluation of emerging clinical data including available safety, tolerability, PK, and PD findings by the sponsor and may occur at a dose level higher than DL3. If a participant has a recently obtained biopsy (within the past 3 months), collected after their most recent therapy, it may be submitted instead of collecting a fresh pre-treatment biopsy.

The BLRM guided by the EWOC principle will be used for the MTD determination throughout Part 1.

#### 4.1.2. Part 2 Dose Expansion

After determination of the combination recommended dose and schedule for expansion (combination RDE) from Part 1B, PF-07265028 administered in combination with sasanlimab will be evaluated in Part 2, for further safety evaluation and preliminary efficacy. The combination of PF-07265028 with sasanlimab will enroll cohorts of gastric and GEJ cancers, HNSCC and UC which have demonstrated primary resistance to CPIs. Also, the sponsor may enroll participants in combination cohorts with NSCLC or other solid tumor

types and PDx status based on emerging clinical data in Part 1 warranting further evaluation. Each expansion cohort will enroll up to 40 participants. In addition, a monotherapy cohort may be included if emerging clinical data from Part 1 warrants further investigation; this expansion cohort would enroll up to 20 participants.

Fresh pre-treatment biopsies in Part 2 will be required from all participants unless they have a recently obtained biopsy sample that was collected in the past 3 months and after their most recent therapy. Additionally, archival tumor samples are requested to help establish the effects of prior therapy on immune activation state of the tumor and efficacy observations. If a new biopsy represents a significant safety risk in the opinion of the investigator, the participant may be considered for enrollment with archival samples only after discussion with the sponsor.

For a subset of participants in all cohorts (minimum of 10 participants in each cohort), mandatory on-treatment biopsy samples (in addition to the fresh pre-treatment biopsies discussed above) will be collected to confirm the mechanism of action and evaluate potential resistance mechanisms during treatment. For all other participants, on-treatment biopsies are optional but encouraged. If 15 participants have been enrolled in a cohort and <5 paired pre- and on-treatment biopsies have been collected, collections may be made mandatory for the remaining participants.

### 4.1.3. Food Effect Assessment

In Part 1A or Part 2, the effect of food on PF-07265028 PK will be evaluated in at least 6 evaluable participants at a dose level that was tolerated when PF07265028 was administered with empty stomach. The food effect assessment will be performed in Part 1A if treatment-related Grade ≥2 GI toxicity is observed in ≥30% participants with a minimum of 6 participants enrolled in total across all dose levels. Otherwise, the food effect assessment will be performed in a subset of participants from Part 2. Each participant will serve as their own control in which PK profile during a dose interval will be assessed when drug is administered with under fasted and fed conditions on Cycle 1 Day 15 and Day 16, respectively.

On Cycle 1 Day 15, participants will receive an oral dose of PF-07265028 under the fasted condition (overnight fasting of at least 6 hours; water permitted except for 1 hour before and 1 hour after drug administration). On Cycle 1 Day 16, participants will receive another oral dose of PF-07265028 with a high-fat, high-calorie meal (breakfast) following 6-hour overnight fasting (water permitted except for 1 hour before and 1 hour after drug administration). Serial PK samples will be collected after each dose on Day 15 and Day 16 per the SoA Table 4. Subsequently, participants will receive the remaining study intervention under an empty stomach condition. Participants who have dietary or other restrictions that preclude a 6-hour overnight fast (water permitted) or consumption of the high-fat, high-calorie meal will not be required to participate in this assessment. Details regarding PF-07265028 administration and food requirements for participants in the food-effect assessment are provided in Section 6.1.1.1.

### 4.2. Scientific Rationale for Study Design

CCI

[redacted]

The study plans to evaluate the effect of food on PK, as the data could inform whether the empty stomach condition for drug administration can be relaxed. If the results show that there is no effect of food on PK, PF-07265028 may be administered without regards to food. On the other hand, if the results show that food may meaningfully alter PF-07265028 PK, whether or not PF-07265028 will continue to be administered under the empty stomach condition or with food will be decided with further assessment of the effect of food on tolerability and safety. There is a potential that food intake could help improve the GI tolerability, as observed with other oncology drugs (eg, imatinib mesylate, ceritinib).

#### 4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants with the distribution of characteristics shown below to ensure the study population is representative of the participant population that will use PF-07265028 in clinical practice.

- Utilize study sites in different geographical locations in the US with diverse participant populations.
- Utilize sites in Japan which may enroll participants from the Asia Pacific region.
- Review site processes for outreach to diverse populations for enrollment into clinical trials.
- Provide translational services as needed.

#### 4.2.2. Adjudication Committee

This is an open-label non-randomized Phase 1 study. This study will not use a DMC. For the purpose of this protocol, Pfizer procedures for periodic safety review by a safety review team, comprised of the investigators and the sponsor, will be applied in order to review individual and summary data collected in the safety and clinical databases for participants who have received at least 1 dose of study intervention, including those participants who are determined to be not evaluable for DLT assessment.

Discussions between the investigators and the sponsor regarding safety will occur in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and determine if further participant enrollment is appropriate.

#### 4.2.3. Choice of Contraception/Barrier Requirements

Nonclinical studies suggest risk for severe manifestations of developmental toxicity at relevant clinical exposures for sasanlimab. There are no nonclinical studies to date with PF-07265028, but because its mechanism of action is to cause immune activation, fetal toxicity cannot be ruled out. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

#### 4.2.4. 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 for Dose

#### 4.3.1. Starting Dose in Monotherapy and Combination

**Part 1A:** The proposed clinical starting dose for the monotherapy is 25 mg QD based on the totality of toxicity data, pharmacology assessments, and benefit/risk analysis related to PF-07265028.

In the 1-month GLP toxicity study, the HNSTD in cynomolgus monkey is 15 mg/kg, and the one-sixth of the HED is 50 mg QD. No test article-related mortality was observed in mice, and therefore the STD10 (severely toxic dose) is greater than the highest administered dose of 30 mg/kg/day, for which the 1/10$^{th}$ of the HED is 15 mg QD. The key target organ toxicities identified in the 1-month GLP toxicity studies are considered to be monitorable and reversible.

- Nonclinical data supported that the cynomolgus monkey is a pharmacologically relevant species for HPK1 inhibition and may be more relevant to the prediction of the pharmacological effects of PF-07265028 in humans.
- CCI [redacted]
- Furthermore, oral administration of PF-07265028 to cynomolgus monkeys was demonstrated to result in both the activation and proliferation of T cell.
- In contrast, in vitro experiments on mouse T cells did not result in enhanced proliferation as was observed on human T cells.

In vitro human cytokine release assays and in vivo cytokine evaluation in the cynomolgus monkey suggest that there is low risk of acute CRS following the administration of PF-07265028.

A starting dose of 25 mg QD was considered to present favorable benefit/risk. The projected $C_{ave,ss}$ or $AUC_{ss}$ in human at 25 mg QD results in 11x and 4x safety margin relative to the $C_{ave,ss}$ or $AUC_{ss}$ at NOAEL in mouse and HNSTD in cynomolgus monkey respectively (Table 6). The respective exposure margins are considered adequate for a starting dose treating participants with advanced cancer.

CCI [redacted]

Collectively, the nonclinical data and supportive PK/PD evaluations support the use of 25 mg QD as the starting dose of PF-07265028.

**Table 6. Predicted Exposure Margins and Pharmacological Effect for Different Human Starting Dose**

| | Predicted Exposure Margin | | | | CCI [redacted] |
|---|---|---|---|---|---|
| Starting Dose (mg QD) | Mouse | | Monkey | | |
| | $C_{ave,ss}$ | $C_{max,ss}$ | $C_{ave,ss}$ | $C_{max,ss}$ | |
| 15 | 18x | 25x | 6x | 5x | |
| 25 | 11x | 15x | 4x | 3x | |
| 50 | 5x | 7x | 2x | 2x | |

N=6 mice per group/timepoint (3 male, 3 female); N= 6 monkeys per group (3 male, 3 female)
Mouse and monkey exposure data were from 1-month GLP toxicity study.

**Part 1B:** Sasanlimab has been shown to be safe and tolerable in humans when administered at 300 mg Q4W. The first dose level for PF-07265028 to be evaluated in Part 1B in combination with sasanlimab 300 mg Q4W SC, will be based on emerging PK/PD and safety data from Part 1A (eg, exposure of PF-07265028, target engagement and/or evidence of biomarker modulation/biologic activity) and will start at a monotherapy dose that is at least one dose level lower than the previously tolerated monotherapy dose (N-1). The initiation of Part 1B at a dose that at least is one dose level lower than tested safe in Part 1A is intended to accelerate evaluation of potentially efficacious combination doses based on predicted minimum biological activity and safety based on predicted potential for overlapping irAE profiles.

### 4.3.2. Criteria for Dose Escalation

BLRM guided by the EWOC principle will be used in dose escalation. See Section 9.3.1 and Appendix 11 for more details on the model. Using DLT data at all tested dose levels and pre-specified prior distribution of model parameters, posterior probabilities of having a DLT falling into 3 dosing intervals (underdosing, target dosing, overdosing) will be calculated for all dose levels. In general, 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 dose levels to be evaluated are listed in Table 7.

**Table 7. Provisional Dose Levels for PF-07265028 in Monotherapy Escalation**

| DL | Dose [mg QD][a] |
|---|---|
| DL1 (Starting Dose) | 25 |
| DL2 | 50 |
| DL3[b] | 80 |
| DL4[b] | 125 |

a. The proposed doses may be modified during the study based on the emerging safety and PK data and the dosing frequency may be modified to continuous BID. Intermediate or lower doses may be considered when deemed necessary based on ongoing evaluation of safety and toxicity data. For BID dosing, the total daily dose/ dose increase for the next dose level will be similar (as tablet size allows) regardless of dosing schedule, if it satisfies the EWOC criterion.

b. Dose increment from DL2 to DL3 and above may be up to 60% based on BLRM, until MTD/RDE is determined.

Dose escalation will stop when stopping criteria are met (see Section 9.3.2). In an unlikely situation of observing DLT(s) at the starting dose level, lower dose levels might be considered. The dose level will be recommended by BLRM in such a way that EWOC criteria are fulfilled. The decision of the recommended dose for a new cohort will be jointly made by the investigators and the sponsor. A dose based on a slightly higher EWOC threshold (eg, 30%) or a dose lower than the one recommended by BLRM may be considered if it is deemed safe and appropriate by an overall safety data review.

### 4.3.3. DLT Definition

A participant is classified as DLT-evaluable if the participant either 1) received at least 75% of the planned doses of the study intervention and have received all scheduled safety assessments during the DLT-observation period (Cycle 1 [28 days]) or 2) have experienced a DLT regardless of the percentage of planned doses received. The percentage of drug received is calculated as the percentage of the actual total amount of drug(s) administered during the DLT-observation period in relation to the planned total amount of drug(s) to be administered for the DLT-observation period. If a participant fails to meet these criteria, the participant is deemed non-evaluable for a DLT, and may be replaced. The sole exception to criterion 1 above 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.

For the purpose of dose escalation, all treatment-emergent AEs meeting the definition of DLT occurring in the first cycle of treatment (within 28 days of the first dose or until the participant receives the first dose of the second treatment cycle in the event of treatment delays) will be considered DLTs unless they are clearly attributable to underlying disease or intercurrent illness.

Severity of AEs will be graded according to CTCAE version 5.0. For those AEs involving a worsening of a baseline abnormality, a DLT must represent a clinically significant (in the opinion of the Investigator after discussion with the sponsor) shift from baseline.

#### 4.3.3.1. Hematological DLTs

- Grade >3 neutropenia lasting >7 days;
- Febrile neutropenia, defined as an 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 associated with a Grade ≥2 bleeding event; (for bleeding events with no grading available, clinically significant bleeding is defined as requiring hospitalization or urgent medical intervention).
- Grade 3 thrombocytopenia requiring transfusion (Japan only).
- Grade 4 thrombocytopenia;
- Grade 4 anemia (Japan only: Grade 3 anemia requiring transfusion).

#### 4.3.3.2. Non-Hematological DLTs

- Any treatment-emergent Grade >3 non-hematologic toxicity
- Hepatic toxicity events consistent with Hy's Law, ie,
  - >3-fold elevations above the ULN of ALT or AST AND
  - >2 × ULN elevation of serum total bilirubin without alternative explanation (eg, cholestasis or Gilbert's syndrome) AND
  - Absence of initial findings of cholestasis (eg, elevated serum ALP) AND
  - Absence of other reason(s) to explain the combination of increased ALT or ALT and TBili, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.
- For participants with Grade 2 hepatic transaminase or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis, a hepatic transaminase or alkaline phosphatase level >10 × ULN.
- Grade 3 fatigue lasting ≥5 days.
- Grade ≥3 nausea/vomiting or diarrhea lasting ≥3 days despite adequate anti-emetic and other supportive care.
- Grade ≥3 CRS of any duration.

- Grade 3 QTcF prolongation:
    - In an asymptomatic participant, the following assessment and confirmation procedure is required: repeat testing, reevaluate by a qualified person, and correct reversible causes (such as electrolyte abnormalities or hypoxia). If, after correction of any reversible causes, the Grade 3 QTcF prolongation persists, then the event should be considered a DLT.
- Any Grade 4 QTcF prolongation.
- Treatment-emergent AEs resulting in failure to deliver 75% of doses of the first cycle doses of PF-07265028 and sasanlimab.
- Grade 5 event unless attributed to a cause clearly not related to study treatment.

#### 4.3.3.3. Other DLTs

- Clinically important, persistent treatment-emergent toxicities that occur the DLT period (Cycle 1) that are not included in the above criteria may also be considered a DLT following review by the investigators and the sponsor.

**The following AEs will not be adjudicated as DLTs:**

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Grade ≥2 endocrinopathy controlled by hormonal replacement.
- Grade ≤3 injection reaction or allergic reaction is not a DLT (unlikely to be dose-related, but all available information on these events will be collected).
- Grade 3 AE of tumor flare (defined as local pain, irritation or rash localized at sites of known or suspected tumor).

### 4.3.4. MTD Definition

The MTD is defined as the highest dose not expected to cause DLT in more than 33% of the treated participants in the first cycle. The target interval for the DLT rate is defined as (0.16, 0.33).

For any given participant that is on-treatment at dose levels that are subsequently considered to be above the MTD, the option to dose reduce will be discussed. If a participant tolerated the above MTD dose level well and is benefiting from therapy, continuation of treatment at the above MTD dose level will require re-consenting.

#### 4.3.5. RP2D Definition

The RP2D is the dose chosen for further investigation based on the Phase 1 study results. The recommended RP2D is based on an integrated assessment of target engagement/attainment, efficacy, safety and pharmacokinetic/ pharmacodynamic (PK/PD) relationship. This integrated approach may result in a RP2D lower than the MTD if supported by the careful consideration of the data generated during dose escalation and demonstrated favorable risk-benefit profile. This may result in a different RP2D dose and schedule being identified for monotherapy and for combination with sasanlimab , as well as for specific tumor indications.

### 4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study, including the long-term safety follow-up visits, or death whichever comes first.

The end of the study is defined as the date of the last visit of the last participant in the study or 24 months 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.

## 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. At least 18 years of age (20 years for Japan).

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

3. **Part 1A Monotherapy:** Histologically or cytologically confirmed advanced or metastatic solid tumors which have progressed following systemic anticancer therapies, or are resistant to standard therapy or for which no standard therapy is available, or for whom standard therapy is not tolerated.

4. **Part 1B Combination Therapy:** Histologically or cytologically confirmed advanced or metastatic solid tumor which have progressed following systemic anticancer therapies, including at least 1 checkpoint inhibitor and displayed primary resistance to checkpoint inhibitors. Primary resistance is defined as having received a checkpoint inhibitor for greater than or equal to 6 weeks with confirmed PD at least 4 weeks after initial PD or SD for less than 6 months. Immunotherapy naïve/secondary PDx-resistant tumors may be considered after discussion with the sponsor.

5. **Part 2 Dose Expansion:** Histologically or cytologically confirmed advanced or metastatic malignancies, including gastric/GEJ cancer, HNSCC, or UC (NSCLC and other solid tumors may be explored based on emergent data from Part 1 and must have histologically or cytologically confirmed advanced or metastatic disease) who have progressed following systemic anticancer therapies, including at least 1 CPI and displayed primary resistance to therapy with checkpoint inhibitors. Primary resistance is defined as having received a checkpoint inhibitor for greater than or equal to 6 weeks with confirmed PD at least 4 weeks after initial PD or SD for less than 6 months. In addition PDx naïve solid tumors may be evaluated based on emergent data from Part 1.

    - Note: The requirement for prior CPI therapy will not be applicable if a cohort of immunotherapy naïve/secondary PDx-resistant tumors warrants further investigation based on Part 1.

**Informed Consent:**

6. 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:**

7. ECOG PS ≤1.

8. Life expectancy ≥3 months.

9. Adequate hematologic function, including:

    - Absolute neutrophil count ≥1,500/μL;

    - Platelet count >100,000/μL;

- Hemoglobin >9 g/dL.

  Note: Transfusions and growth factor support to achieve inclusion are not permitted within 14 days prior to enrollment.

10. Adequate renal function, including:

    - Creatinine clearance ≥60 mL/min calculated using the Cockcroft-Gault formula.

11. Adequate liver function, including:

    - Total bilirubin ≤1.5 × ULN unless the participant has documented Gilbert's syndrome;
    - AST and ALT ≤1.5 × ULN; (≤5.0 × ULN if there are liver metastases);
    - Alkaline phosphatase ≤2.5 × ULN (≤5 × ULN if there are bone metastases).

12. Have measurable disease per RECIST version 1.1. Lesions previously irradiated are considered measurable if progression has been demonstrated in such lesions.

13. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment.

14. Pre-treatment tumor tissue:

    - All participants must provide archival FFPE tumor tissue that is of diagnostic quality and representative of their diagnosed malignancy.

i. **Part 1:** If archival sample is older than 6 months, the participant must consent to undergo a fresh biopsy during the screening period if it can be performed safely. If a new biopsy represents a significant risk in the opinion of the investigator, the participant may be considered for enrollment, after discussion with the sponsor.

ii. **Part 2 and mandatory biopsy dose levels of Part 1:** Fresh tumor biopsy during screening is required unless there is archival tissues less than 3 months old and was obtained subsequent to the last systemic anti-cancer therapy and can be performed safely. If a new biopsy represents a significant risk, the participant may be considered for enrollment, after discussion with the sponsor.

15. On-treatment biopsy:

    a. Part 1: Starting with DL3 or higher dose, participants may be asked to provide mandatory fresh pre-treatment and on-treatment biopsy. Consent for these procedures will occur during screening.

    b. Part 2: Paired on-treatment biopsies will be mandatory for a subset of participants. Consent for these procedures will occur during screening. On-treatment biopsies are optional and encouraged for all other participants.

16. Participants undergoing biopsies must have at least 1 lesion not identified as a target lesion that can be safely biopsied.

17. Females of childbearing potential must have a negative pregnancy test within 72 hours of first dose of study treatment.

### 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 enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix, Bowen's disease. Participants with other stable indolent malignancies and no evidence of progressive disease may be considered after discussion with sponsor.

2. Participants sustaining major surgery defined as a complex procedure performed under regional or general anesthesia or conscious sedation with a recovery period of at least 4 weeks prior to study intervention.

3. Participants with primary immunodeficiency.

4. Participants who require immunosuppressive therapy including, but not limited to, treatment with corticosteroids in pharmacologic doses (equivalent to ≥10 mg prednisone daily).

    - Topical, ocular, intra-articular, intranasal or inhalational corticosteroids with minimal systemic absorption are permitted.

    - Short course (≤7 days) of corticosteroids prescribed prophylactically (eg, contrast drug allergy) or for the treatment of nonautoimmune conditions (eg, hypersensitivity reaction) are permitted.

5. Participants with active autoimmune conditions or history of autoimmune diseases that may relapse with the following exceptions:

    - Controlled Type 1 diabetes mellitus;

    - Hypothyroidism (managed with hormone replacement);

    - Controlled celiac disease;

    - Skin diseases not requiring systemic therapy (eg, vitiligo, psoriasis, alopecia).

6. History of interstitial lung disease, pneumonitis (non-infectious) or uncontrolled lung diseases.

7. History of allogeneic transplant.

8. History of prior irAEs Grade ≥3.

9. Participants with central nervous system metastases; however participants who have undergone surgery and/or radiation for brain metastases who are asymptomatic and radiologically stable and are no longer taking corticosteroids. Participants with leptomeningeal metastases are not eligible.

10. Active inflammatory GI disease, known diverticular disease or previous lap-band surgery. Impairment of GI function or GI disease that may significantly alter the absorption of PF-07265028, such as history of GI surgery with may result in intestinal blind loops and participants with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhea of NCI CTCAE Grade >1. Proton-pump inhibitors are not allowed at least 7 days prior to C1D1 and throughout the study.

11. Hypertension that cannot be controlled by medications (>150/90 mm Hg despite optimal medical therapy).

12. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism; DVT; arterial occlusive disease; ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade that is uncontrolled, or QTcF interval >470 ms at screening.

13. Known or suspected hypersensitivity to active ingredient/excipients of study treatments.

14. 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 .

**Exceptions:**

- Limited, focal radiation therapy (including Gamma-Knife) require only a 3-day period before study entry and the absence of any radiation-induced complications.

- Palliative radiation therapy within 14 days of study entry (2 weeks in the case of immunotherapy) and the absence of any radiation-induced complications.

**Prior/Concomitant Therapy:**

15. Prior administration of HPK1 inhibitor.

16. Prior systemic anti-cancer therapy within 14 days (6 weeks for mitomycin C or nitrosoureas) prior to study treatment. Participant with prostate cancer are permitted to continue on LHRH agonists/antagonists.

17. Concomitant use or anticipated need for food (eg grapefruit juice), supplements (eg, St John's Wort), or drugs (eg, ketoconazole) that are known strong and/or moderate CYP3A4 inhibitors, or strong CYP3A4 inducers, including their administration within 10 days or 5 half-lives of the CYP3A4 inhibitor/inducer (whichever is longer) prior to the first dose of study intervention. Please see Section 10.8 for a comprehensive drug list.

18. Concomitant or anticipate use of sensitive substrates with NTI for CYP3A4, CYP2D6, UGT1A1, P-gp, and highly sensitive substrates for BCRP. Please see Section 10.8 for a comprehensive drug list.

19. Receipt of a live vaccine within 30 days of enrollment.

20. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.8 Concomitant Therapy.

21. Transfusion of RBCs or platelets or administration of hematopoietic growth factors within 2 weeks of C1D1.

**Prior/Concurrent Clinical Study Experience:**

22. Participation in other studies involving investigational drug(s) within 4 weeks or 5 half-lives (whichever is shorter) prior to planned first dose. Cases must be discussed with sponsor's medical monitor to judge eligibility.

**Diagnostic Assessments:**

23. Serum or urine pregnancy test (for WOCBP) positive at screening.

24. 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 for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2, he/she is excluded. See Section 10.10 for more information around SARS-CoV2

25. HBV, HCV, known HIV- or AIDS related illness. This protocol excludes participants with active infections but permits inclusion of participants who meet the following conditions:

    - Human immunodeficiency virus (HIV) infected participants must be on a protocol permitted antiretroviral therapy (ART) (See Appendix 10.8 for prohibited concomitant medications) and have a well-controlled HIV infection/disease defined as:

        - a CD4+ T cell count >350 cells/$mm^3$ at time of screening;

        - must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 copies/mL or the lower limit of qualification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening;

        - must have been on a stable regimen of ART, without changes in drugs or dose modification, for at least 4 weeks prior to study entry (Cycle 1 Day 1);

        - HIV screening tests are not required unless there is known history of HCV infection or as mandated by local health authority.

Participants who are hepatitis B surface antigen positive are eligible if they have received hepatitis B virus (HBV) antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to enrollment. Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention. Hepatitis B screening tests are not required unless there known history of HBV infection or as mandated by local health authority.

Participants with a history of hepatitis C virus (HCV) infection are eligible if HCV viral load is undetectable at screening. Note: Participants must have completed curative antiviral therapy at least 4 weeks prior to enrollment. Hepatitis C screening tests are not required unless there is a known history of HCV infection or as mandated by local health authority.

Japan only: Participant who are tested viral load positive for HBV at any time during the study will interrupt administration of PF-07265028 and should consider starting treatment immediately in parallel with consultation with hepatologist per local practice.

**Other Exclusions:**

26. 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 10.4.4) 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 Table 1), 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.

### 5.3.2. Photosensitivity

Participants will be advised to report any reaction to sun exposed skin. If a photosensitivity reaction occurs in a participant, special precautions should then be taken to limit any potential photo irritation effect, by minimizing the participants' exposure to light including sunlight, and exposure to high intensity UVA and UVB light sources such as tanning beds, tanning booths and sunlamps. Furthermore, for photosensitive participants, these individuals should be encouraged to apply sunscreen/sunblock daily and to wear clothing that covers areas of exposed skin when outdoors during daylight hours.

### 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 1 time. Rescreened participants should be assigned a new participant number.

## 6. STUDY INTERVENTIONS 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-07265028 and sasanlimab.

### 6.1. Study Interventions Administered

On days when study intervention is administered in clinic, PF-07265028 is administered first and then followed by sasanlimab.

| Study Interventions | | |
|---|---|---|
| **Intervention Name** | PF-07265028 | Sasanlimab Solution for Injection, 50 mg/mL |
| **ARM Name (group of participants receiving a specific treatment (or no treatment)** | All | Combination therapy (Parts 1B and Part 2A) |
| **Type** | Drug | Biologic |
| **Dose Formulation** | Tablet | Vial |
| **Unit Dose Strength(s)** | 5 mg, 25 mg, or 100 mg tablet | 50 mg/mL, 2 mL vial |
| **Dosage Level(s)** | Dose amount and frequency – reference the study scheme/figure or text below as appropriate | 300 mg Q4W |
| **Route of Administration** | Oral | SC |
| **Use** | Experimental | Experimental |
| **IMP or NIMP** | IMP | IMP |
| **Sourcing** | Provided centrally by the sponsor<br><br>See IP manual and/or IRT Guide for ordering the intervention | Provided centrally by the sponsor<br><br>See IP manual and/or IRT Guide for ordering the intervention |
| **Packaging and Labeling** | Study intervention will be provided in a 30-count HPD bottle. Each bottle will be open-labeled as required per country requirement. | Study intervention will be provided in a 2 mL vial. Each vial will be open-labeled as required per country requirement. |
| **Current/Former Names or Aliases** | PF-07265028, HPK1 | Sasanlimab, PF-06801591, or PD-1 inhibitor |

### 6.1.1. Administration

#### 6.1.1.1. PF-07265028

Participants will swallow PF-07265028 tablets whole with at least 8 ounces (240 mL) of water, and will not manipulate or chew the study intervention prior to swallowing. PF-07265028 will initially be administered QD by mouth for all cohorts on a continuous basis. Participants who are unable to swallow whole tablets may dissolve their dose in oral syringe(s) as outlined in the IP manual to allow for suspension administration either orally or via an NG tube. If supported by emerging data, BID continuous regimen may be considered. A cycle is defined as 28 days, regardless of missed doses or dose delays.

Participants will take PF-07265028 at approximately the same time within each dosing interval (ie, ±3 hours of nominal time). On site visit days, participants will take the drug at the site after performing predose assessment. On other days, participants will be instructed to self-administer the drug at home. A dosing diary will be given to each participant to support at home dosing. The participants will be requested to note the date and time of each dose, food consumption status at the time of drug administration.

If a participant misses a dose at the scheduled time, the participant can still take the dose within 4 hours of the scheduled time. If the participant missed taking a dose after 4 hours of the scheduled time, or day of treatment, they must be instructed not to "make it up" but resume subsequent doses as prescribed. This dose will be considered as a missed dose. In addition, if a participant vomits any time after taking a dose; they should not "make it up" but to resume subsequent doses as prescribed. Lastly, if a participant inadvertently takes 1 extra dose during a day, the participant should not take the next dose of PF-07265028.

**Food Requirements (Except for the Food-Effect Subset or Cohorts Evaluating Food Intake on Tolerability)**

Participants will take PF-07265028 orally with at least 8 oz (240 mL) of water on an empty stomach. No food or liquids other than water will be consumed for 2 hours before and 2 hour following each dose throughout the study).

These empty stomach requirements may be removed (via a letter to the investigators) if results from the food-effect subset indicate there is no clinically meaningful effect of food on the PK of PF-07265028. If food is demonstrated to improve tolerability for participants included in the cohorts where PF-07265028 is administered with food, participants in all cohorts may be instructed to take PF-07265028 with a meal.

**Food Requirements for the Food-Effect Subset**

Participants enrolled in the food-effect subset will take PF-07265028 under the fasted and fed conditions on Cycle 1 Day 15 and Day 16, respectively, and under empty stomach condition for the remaining portion of the study.

**Fasted condition:** Following an overnight fast of at least 6 hours, PF-07265028 will be administered and continue fasting for an additional 2 hours postdose. Water will be allowed ad libitum except for 1 hour before and 1 hour after drug administration.

**Fed condition:** Following an overnight fast of at least 6 hours, participants will start a high-fat/high-calorie breakfast in the clinical sites within 30 minutes prior to and finish breakfast before administration of PF-07265028. No additional food will be allowed until at least 2 hours postdose. Water will be allowed ad libitum except for 1 hour before and 1 hour after drug administration. The breakfast will be high-fat (approximately 50% of total caloric content of the meal) high-calorie (approximately 800-1000 calories with 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively) meal.

**Food Requirements for Cohorts Evaluating the Effect of Food on PF-07265028 Tolerability**

Each dose of PF-07265028 will be administered with a meal and with approximately 8 ounces (240 mL) of water.

#### 6.1.1.2. Sasanlimab (PF-06801591)

For participants in Part 1B and Part 2, qualified and trained investigator site personnel will administer sasanlimab at a fixed dose. See Section 8.2.7 for local site injection tolerability assessment. In the investigational combination therapy with PF-07265028, sasanlimab 300 mg (50 mg/mL), will be administered SC Q4W to the abdomen. Sasanlimab should be administered to 2 or more different quadrants of the abdomen (with preference given to the lower quadrants when possible); 1 or 2 injections per quadrant. 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. Sasanlimab SC injection will be administered at least 30 minutes after administration of PF-07265028. Additional guidance on SC injection site locations is provided in Appendix 16 Section 10.16. For specific instructions on the handling and preparation instructions of study intervention, refer to the Product Specific IP manual. See Section 8.2.7 for local site injection tolerability assessment.

Study staff should refer to the IP manual for specific instructions on the preparation and handling 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.

### 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. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. See the IP manual for storage conditions of the study intervention.

8. 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.

9. All PF-07265028 that is taken home by the participant, both used and unused bottles, must be returned to the investigator by the participant. Returned study intervention must not be re-dispensed to the participants.

10. 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

**Bottles and Vials:**

A qualified staff member will dispense the study intervention using the IRT system via unique container numbers in the bottles and vials provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant should be instructed to maintain the product in the bottle or vial provided throughout the course of dosing and return the [bottle, vials, or blister cards, as appropriate] to the site at the next study visit.

See the IP manual for instructions on how to prepare the 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.

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.

### 6.3. Measures to Minimize Bias: Randomization and Blinding

#### 6.3.1. Allocation to Study Intervention

This is an open-label Phase 1 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.

No participant will receive study intervention until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the participant's enrollment;
- Specification of the dose level for that participant and;
- Permission to proceed with dosing the participant.

Study intervention will be dispensed at the study visits summarized in the SoA Table 1.

Returned study intervention must not be redispensed to the participant.

Allocation of participants to treatment groups will proceed through sponsor or designee and will include the participant number and randomization number. The site staff will e-mail a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a participant identification number and supply this number to the site. The form must be stored in the site's files. The participant identification number will be used on all study-related documentation at the site.

Returned study intervention must not be re-dispensed to the participants.

This is an open-label study; the study intervention dose will be determined by the sponsor and dispensed to the participant using an IRT. The IRT will assign a kit number for study intervention administration for each participant.

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 the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff. 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.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed counting returned tablets/capsules during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of tablets/capsules/ dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

### 6.5. Dose Modification

Dose modifications may occur in 1 of 3 ways:

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

The decision to proceed to the next dose level of PF-07265028 (either an increase or a decrease) will be made by the study team and the investigators based on safety, tolerability, and preliminary PK and/or pharmacodynamics data obtained in all participants at the prior dose level.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, PK, and/or pharmacodynamics findings at a given dose level or to add cohorts to evaluate additional dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as that described for other study participants/cohorts.

Every effort should be made to administer study intervention on the planned dose and schedule. In the event of significant toxicity, dosing of PF-07265028 may be delayed and/or reduced 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 modifications, investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Toxicities potentially related to PF-07265028 should be managed according to the dose modifications described in Table 8.

**Table 8. Dose Modifications for PF-07265028-Related Toxicity**

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Nonhematologic | Continue at the same dose level. | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator. | Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator. |
| Hematologic | Continue at the same dose level. | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level. | Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment or discontinue at the discretion of the investigator. |

Specific GI toxicities potentially related to PF-07265028 should be managed according to the dose modifications described in Table 9.

**Table 9. Dose Modifications for PF-07265028 Related GI Toxicity**

| Grade 1 | Grade 2 | Grade 3* | Grade 4 |
|---|---|---|---|
| Continue at the same dose level and, institute standard of care supportive measures at the discretion of the investigator. | Continue at the same dose level and institute standard of care supportive measures at the discretion of the investigator.<br>If recurrent and intolerable, withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the next lower dose level | Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.<br><br>If recurrent, withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level. | Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.<br><br>If recurrent, permanently discontinue treatment |

*Nausea, vomiting, or diarrhea must persist at Grade 3 despite optimal supportive care to require dose modification.

Note: Cycle will not be extended to cover for the missing dose.

Note: For management of GI iRAEs see Appendix 3 Section 10.3.

Note: Participants with confirmed Hy's Law must be discontinued.

**Table 10. Dose Modifications for PF-07265028 Related QTcF Prolongation**

| QTcF >480 ms ≤500 ms | QTcF >500 ms | Recurrent QTcF>500 ms | QTcF >500 ms or >60 ms change from baseline, and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia |
|---|---|---|---|
| Reduce the dose of drug by one level without interruption of dosing. Following dose reduction, the drug dose may be resumed at the previous level in the next cycle if the QTcF has decreased to within 30 ms of baseline or <450 ms but subject must be monitored closely for QT prolongation for the first cycle at the increased dose. | Withhold dose for up to 14 days. If QTcF returns to within 30 ms of baseline or <450 ms within 14 days, resume and reduce by 1 dose level. | Permanently discontinue treatment if QTcF >500 ms recurs despite appropriate dose reduction and correction/elimination of other risk factors (eg, serum electrolyte abnormalities, concomitant QT prolonging medication) | Permanently discontinue treatment |

Note:For all episodes of QTc prolongation, regardless of grade, check electrolyte (potassium, calcium, and magnesium) levels and correct any abnormalities. If possible, stop any medications that may prolong the QT interval (see Section 8.2.4 for management of QTc prolongation).

### 6.5.1. Sasanlimab Dose Modifications

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 11).

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

**Table 11. 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.<br>• Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline.<br>• 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.<br>• Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline.<br>• 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.<br>• Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline.<br>• Permanently discontinue sasanlimab if thrombocytopenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. |
| **Nonhematologic toxicities** | |
| **Grade 1 and Grade 2** | • Continue as per schedule. |
| **Grade 3** | • Hold sasanlimab.<br>• Resume sasanlimab at the next scheduled dose after recovery to Grade ≤1 or baseline.<br>• Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.<br>• **Exceptions are:** laboratory values that do not have any clinical correlate.<br>• For suspected immune-related toxicity follow guidance in Section 10.3.5. |
| **Grade 4** | • Permanently discontinue sasanlimab.<br>• **Exceptions are:** laboratory values that do not have any clinical correlate.<br>• For suspected immune-related toxicity follow guidance in Section 10.3.5. |

To facilitate the early recognition and prompt intervention in the event of clinically meaningful sasanlimab immune-related AEs, management algorithms have been developed for suspected pulmonary, GI, liver, endocrine, skin, neurological and renal toxicities (see Appendix 3 Section 10.3.5).

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 Section 10.3.5.

### 6.5.2. Dose Reductions

No dose reductions are permitted for sasanlimab.

Following dosing interruption or cycle delay due to treatment-related toxicity, the PF-07265028 dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1 or 2 treatment-related toxicity. However, investigators should always manage their participants according to their medical judgment based on the particular clinical circumstances.

Participants experiencing recurrent and intolerable treatment-related Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Dose reduction of PF-07265028 by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Participants requiring more than 2 dose reductions will be discontinued from the treatment and entered into the Follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at the reduced dose level, unless further dose reduction is required. Intraparticipant dose re-escalation is not allowed.

Participants experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved, and in the opinion of the investigator and sponsor, the participant is benefiting from therapy.

### 6.5.3. Dosing Interruptions

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in the Dose Delays (Section 6.5.4).

Doses may be held up to 4 weeks until toxicity resolution for PF-07265028 and held up to 8 weeks for sasanlimab. Depending on when the AE resolved, a treatment interruption may lead to the participant missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the AE that led to the treatment interruption recovers within the same cycle, then redosing with PF-07265028 in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions Section 6.5.2, unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the participant may need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

### 6.5.4. Dose Delays

Retreatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC $\geq$1,000/mm$^3$.
- Platelets count $\geq$50,000/mm$^3$.
- Hemoglobin $\geq$10 g/dL.
- Nonhematologic toxicities have returned to baseline or Grade $\leq$1 severity (or, at the investigator's discretion, Grade $\leq$2 if not considered a safety risk for the participant).

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

If these conditions are met within 4 weeks of treatment interruption, PF-07265028 may be resumed. Refer to the Dose Reductions (Section 6.5.2) for AEs requiring dose reduction at the time of treatment resumption.

If participants require discontinuation of PF-07265028 for more than 4 weeks at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the sponsor. If participants require discontinuation of sasanlimab for more than 8 weeks at any time during the study, then study treatment should be permanently discontinued.

If a treatment interruption continues beyond Day 28 (1 cycle) of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

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

As this is a FIH clinical trial, 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-07265028 any dose greater than the assigned dose within a 24-hour time period 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 medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07265028 (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 within 7 days from the date of the last dose of study intervention if requested by the 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 30 days prior to 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, antiemetic treatment and prophylaxis), drugs used to treat AEs or chronic diseases, and nondrug 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.

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.

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. Potential Drug-Drug Interactions

Inhibition of CYP3A4/5 isoenzymes may increase PF-07265028 exposure leading to potential increases in toxicities. Induction of CYP3A4/5 isoenzymes may decrease PF-07265028 exposure leading to potential decrease in efficacy. Therefore, the use or food (eg, grapefruit juice), supplements (eg St John's Wort), or drugs (eg ketoconazole) that are known strong and/or moderate CYP3A4 inhibitors, or strong CYP3A4 inducers is prohibited within 10 days or 5 half-lives of the CYP3A4 inhibitor/inducer (whichever is longer) prior to the first dose of study intervention. Please see Appendix 9 for a comprehensive drug list.

Concomitant use of PF-07265028 and a substrate of CYP3A4, CYP2D6, UGT1A1, P-gp or BCRP may increase the systemic exposure of that substrate. Therefore, concomitant use of PF-07265028 with sensitive substrates with NTI for CYP3A4, CYP2D6, UGT1A1, P-gp, and highly sensitive substrates for BCRP is prohibited.

For HMG CoA reductase inhibitors (statins): Atorvastatin (limit dose to 10 mg daily), fluvastatin (limit dose to 20 mg daily), rosuvastatin (limit dose to 5 mg daily), simvastatin (avoid usage).

Please see Appendix 8 Section 10.8 for a comprehensive list for prohibited drugs or use with caution due to DDI.

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

Prior systemic anti-cancer therapy within 14 days (6 weeks for mitomycin C or nitrosoureas) prior to study treatment are excluded.

### 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.[50]

#### 6.8.3.1. 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. AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using MedDRA, except CRS, which will be graded by ASTCT criteria[51] (see Appendix 15 Section 10.15). AE data will be reported in tables and listings. Summaries of AE by mapped terms, appropriate thesaurus level, 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. If local standard of care is a different regimen, this should be utilized.

The decision to incorporate pre-medication (ie, corticosteroids) for CRS prophylaxis for all participants will be made following discussions between the sponsor and the investigators and the MTD identified. The pre-treatment medication will not be supplied by Pfizer.

#### 6.8.3.2. Supportive Care for Hypersensitivity Reactions Type 1

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein.

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.

#### 6.8.3.3. Supportive Care for Immune-Related Adverse Events

For immunotherapeutic agents, treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade version 5.0). In general, Grade 1 or 2 irAEs are treated symptomatically with persistent Grade 2, Grade 3 or Grade 4 irAEs managed with moderate to high corticosteroids.

Guidelines for the management of irAEs are provided in Appendix 3, Section 10.3.5.

### 6.8.4. Hematopoietic Growth Factors

Primary **prophylactic** use of colony stimulating factors is not permitted during the first 28 days of Cycle 1 Part 1, but they may be used to treat treatment-emergent neutropenia as indicated by the current ASCO guidelines.[52]

For Japan only: since the indication and dosage of G-CSF compounds approved in Japan may differ from ASCO guidelines, please refer to Japanese package insert.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia. Erythropoietin is not approved in some countries, including Japan, 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

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.

### 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. Proton pump inhibitors, Antacids or H2-Receptor Antagonists

In the absence of in vitro data evaluating the PF-07265028 solubility in acidic pH, participants are prohibited from using acid reducing agents as described below:

a. Patient should not use proton pump inhibitors, eg, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, or dexlansoprazole, at least 7 days prior to C1D1 and throughout the study.

b. When concurrent use of an H2 blocking agent is necessary, eg, ranitidine, famotidine, or cimetidine, it must be administered only between 2 and 3 hours after the dose of PF-07265028. If not taken during this time, the dose of H2 blocking agents should not be taken again until 2–3 hours after the next dose of PF-07265028.

c. When concurrent use of an antacid is necessary, eg, aluminum hydroxide/magnesium hydroxide/simethicone or calcium carbonate, it must be administered 2 or more hours before and/or 2 or more hours after the dose of PF-07265028.

### 6.8.9. Surgery

Caution is advised for any surgical procedures during the study. The appropriate interval of time between surgery and PF-07265028 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-07265028 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-07265028 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

### 6.8.10. Radiotherapy

Palliative radiotherapy to specific sites of disease will be permitted if considered medically necessary by the treating physician. All attempts will be made to rule out progressive disease in the event of increased localized pain. Palliative radiotherapy to baseline target lesions should be avoided.

### 6.8.11. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07265028; standard medical supportive care must be provided to manage the AEs.

The study site will supply rescue medication that will be obtained locally.

### 6.8.12. COVID-19 Vaccines

COVID-19 vaccines with authorization/approval are considered concomitant medications and standard AE collection and reporting processes should be followed. The timing of vaccine dosing relative to the dosing of study medications is at the discretion of the investigator although, if applicable, it is best to avoid the DLT observation period.

## 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:

- Disease progression;
- Lack of clinical benefit;
- 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 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 safety up to 90 days (see Section 8.2.9). See the SoA Table 1 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:**

Follow-up at 30 days (±3 days) after discontinuation of study intervention, participants will return to the site for a safety follow up visit (see SoA Table 1 and Section 8.2.9). Subsequent follow-up is required at 60 and 90 days (±7 days) and may be a telephone follow-up. The investigator may conduct these follow-up visits in clinic if any concerns are noted during the remote contact. Participants continuing to experience treatment-related AEs at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

### 7.1.1. Request to Continue Treatment

Participants with radiological progression per RECIST will be permitted to continue on study treatment while PD is confirmed, 4 or more weeks later as per irRECIST if the investigator believes that it is in the best interest of the participant. Participants who have confirmed progression per irRECIST may continue on therapy if, after discussion with the sponsor, the investigator considers that the participant is deriving clinical benefit from treatment; participants with rapid progression or sites of disease adjacent to or invading major blood vessels are not eligible for treatment beyond progression

Criteria that must be met to ensure that participants are not exposed to unreasonable risks by continued use of the investigational agent in spite of progression of disease may include the following:

- Absence of symptoms and signs indicating clinically significant progression of disease.
- No decline in ECOG performance status.
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression).

At the time of radiographic progression of disease, obtain the re-consent of participants using a written informed consent document that details all FDA-approved therapy, and potential clinical benefit, that the participant may be foregoing in order to continue receiving the study intervention.

### 7.1.2. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN/Urea 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/Urea, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, magnesium 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.

## 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 follow-up;
- Death;
- Study terminated by sponsor;
- Withdrawal of consent;

- Investigator discretion.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA Table 1 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 follow-up, 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 14 days prior to signing of the ICD.

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.

All assessments are relative to start of study intervention (Cycle 1 Day 1). All assessments to be completed prior to administration of study intervention unless otherwise noted per study visit.

## 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 for participants with known or suspected bone metastases. For participants with known computed tomography contrast allergy, a non-contrast CT 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.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the schedule of activities, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks). Investigator (local) assessment of response will be made using RECIST version 1.1 and irRECIST (see Sections 10.12 and 10.13).

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

## 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), injection site 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 as per the SoA.

A complete physical examination will include, at a minimum, assessments of the 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.

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.

**When should it be done:**

Physical examination should precede blood draw for clinical laboratory tests.

### 8.2.3. Vital Signs

BP and pulse rate measurements will be assessed either in the sitting position with feet supported (ie, not dangling) or the semi-recumbent/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.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

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). The method of temperature measurement should be noted in the CRF.

**When should it be done:**

Vital sign assessments should precede blood draw for clinical laboratory tests.

### 8.2.4. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. All 12 lead ECGs should be confirmed by a qualified individual at the institution or use a fully validated automated ECG analysis. All ECGs in a single participant should be analyzed by the same reader. 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 10 minutes in recumbent or semi-recumbent position and before blood draws or vital signs.

At each time point (see SoA) except screening and EOT, 3 consecutive ECGs (ie, triplicate ECGs) will be performed at approximately 2 minutes apart to determine the mean QTcF interval. ECG assessments should precede blood collection for clinical laboratory tests. When coinciding with blood sample draws for PK, plan the timing of ECG well so that the PK collection afterwards can be around the intended time.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms 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 until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. In addition, if verified QTcF values continue to exceed the criteria above, immediate correction for reversible causes including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval should be performed.

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). If in that timeframe the QTcF intervals rise above the threshold values, the study intervention will be held until the QTcF interval decreases to below the threshold values. Participants may resume study intervention at the current dose level or next lower dose level after discussion

with the sponsor If at any time a participant has a QTcF interval >515 ms or becomes symptomatic, the participant will be discontinued from study treatment. Additional triplicate ECGs may be performed as clinically indicated.

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.

### 8.2.5. 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. Confirmation of eligibility is required at Cycle 1 Day 1. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. For laboratory collection volumes see the laboratory manual. 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 30 days (±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 7 days prior to that date (SoA).

### 8.2.6. 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 intervention. 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 end of the study. 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.

### 8.2.7. Local Site Injection Tolerability Assessment

Assessments to monitor local tolerability to sasanlimab SC injections will be performed as outlined in the respective SoA.

Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported; otherwise details of these assessments will not be recorded on the CRF. When appropriate, at the discretion of the investigator, a participant with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR. If injection site reaction is noted, site tolerability assessments should continue until the symptoms resolve.

### 8.2.8. EOT Visit

Participants who discontinue study treatment will undergo the EOT visit and obtain assessments per the SoA. The EOT assessments will be conducted at the visit that the participant is discontinued from study treatment or no longer than 1 week after the decision to discontinue the participant from study intervention and prior to the initiation of new anticancer therapy. The tumor assessments must be completed if not completed in the last 8 weeks and prior response is other than PD. Laboratory assessments must be completed if not completed in the prior 7 days.

If the EOT visit falls within 7 days of the 30-day follow-up visit, the EOT visit can be used to satisfy the requirements for both visits.

### 8.2.9. 30/60/90 Day Follow-Up Visit

The initial safety follow-up visit will be conducted in the clinic 30 days after last dose of study intervention. The 60-day and 90-day follow-up visits will be performed via remote contact (eg, telephone). The investigator may conduct these follow-up visits in clinic if any concerns are noted during the remote contact.

## 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/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 30 calendar days after the last administration of the study intervention or initiate a new systemic-anti-cancer therapy. All irAEs and treatment-related AEs must be collected for 90 days after the last dose of 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.

#### 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.

#### 8.3.5.1. Exposure During Pregnancy

An 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 ingestion, inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, 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

preprocedure 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 ingestion, 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.

### 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

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.

#### 8.3.8.1. Lack of Efficacy

This study is primarily designed to investigate the safety of PF-07265028; 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:

- 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.

Other examples include, but are not limited to:

- 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

### 8.4.1. Blood for PK Analysis for PF-07265028 and Sasanlimab

Blood samples of approximately 3 mL, to provide a minimum of 1 mL of plasma, will be collected for measurement of plasma concentrations of PF-07265028 as specified in the SoA. Separate blood samples of approximately 3 mL will be collected for PK analysis of serum concentration of sasanlimab. 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 the Pharmacokinetic and Biomarker Sampling table (see SoA Table 2) 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 emerging PK data support BID dosing, the sampling time will shift. 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, participant, and sponsor.

Samples will be used to evaluate the PK of PF-07265028 and sasanlimab, and may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, biomarker, or for other internal exploratory purposes.

Genetic analyses may be performed on these whole blood samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentration of PF-07265028, serum concentration of sasanlimab, will be analyzed using validated analytical methods in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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 procedures (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.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from participants experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

CCI

[redacted]

## 8.5. Genetics

### 8.5.1. Specified Genetics

There are no specified genetics assessment.

### 8.5.2. Retained Research Samples for Genetics

A 4-mL whole 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 cancer under study. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples. See Appendix 5 Section 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in laboratory manual.

### 8.6. Biomarkers

A key element of this study is measurement of cellular and molecular biomarkers that might be modified by PF-07265028 alone and in combination with sasanlimab. Biomarker studies will be used to help elucidate the in vivo mechanism of action of PF-07265028 alone an in combination with sasanlimab by quantifying its impact on CCI [redacted], the tumor microenvironment, tumor infiltrated lymphocytes, and evaluating potential mechanisms of resistance. CCI [redacted]

[redacted]

**Table 12. Biomarker Collections and Analyses**

| Assay | Sample Type |
|---|---|
| CCI [redacted] | [redacted] |
| Tumor neo-antigen prediction through comparison of tumor mutation to germline DNA | Whole blood |
| Measurement of changes in intra-tumor PD-L1 and immune cell infiltration | Fresh pre-, on-, post-treatment tumor biopsies |
| Measurement of T cell activation, and T cell repertoire changes, CCI [redacted] | Whole Blood |
| CCI [redacted] | [redacted] |
| [redacted] | [redacted] |

#### 8.6.1. Tumor Biopsies

Tumor biospecimens from recent archival, de novo pre-treatment, on-treatment, and end of treatment samples will be used to examine candidate CCI [redacted] and cellular biomarkers. Analysis of pre-treatment biospecimens as well as comparison to those collected during and after treatment will be used to establish proof-of-mechanism, identify those participants who are most likely to benefit from treatment with PF-07265028 alone and in

combination with sasanlimab, and identify acquired mechanisms of resistance. Biomarkers may include, but are not limited to, PD-L1, DNA, RNA, DNA mutations, CCI , as well as cell types and constituents of the tumor microenvironment (such as CD8 T cells, macrophages, myeloid derived suppressor cells, and other cell types).

In all parts of the study, optional second on-treatment and/or end of treatment biopsies are encouraged to confirm responses or understand disease progression as clinically indicated throughout treatment for all participants.

Biopsies should be representative of the participant's metastatic disease. All fresh biopsy collections (pre-treatment and on-treatment) should attempt to obtain 6 core biopsies, with a minimum of preferably 3 cores. Fine needle aspiration is unacceptable for submission and bone biopsy are not preferred. If biopsy is to be completed the same day as CT scan, it must be completed after the CT scan, and should not be collected from a target lesion.

When paired pre-treatment and on treatment samples are collected, on treatment samples should preferably be collected from the same tumor lesion as the pre-treatment sample or when this isn't possible, be collected from the same metastatic site, if available.

CCI [redacted]

For all tumor samples, tissue blocks are requested and preferable, but freshly cut paraffin sections are acceptable. Sites should contact sponsor for approval to submit slides, or samples originating from a bone biopsy, and refer to Laboratory Manual for instructions and minimum requirement for submitting slides.

The biopsy requirements during the study are summarized in Table 13.

**Table 13. Summary of Tumor Biopsy Requirements for C4731001**

| Study Part | Archival Tumor Tissue Sample | Fresh Tumor Tissue Samples | | |
|---|---|---|---|---|
| | Screening | Screening | On-Treatment Biopsy Cycle 2, Day 15 (±7 days) | EOT or Second On-Treatment |
| Part 1 Dose levels 1 & 2 | Mandatory (<6 months old) | Optional/Required if archival >6 months old[a] | Optional | Optional |
| Part 1A, 1B Dose levels 3 or higher | Requested if available | Mandatory[a] | Mandatory[a] | Optional |
| Part 2 | Requested if available | Mandatory[a] | Optional / Mandatory for approximately 10 participants | Optional |

a. If a new biopsy represents a significant risk in the opinion of the investigator, the participant may be considered for enrollment with the submission of archival tissue, after discussion with the sponsor.

### 8.6.2. Whole Blood and Serum Samples

Peripheral blood and derivatives may be used to characterize cell phenotypes, measure target engagement, CCI [redacted] to support study objectives. Examples may include but are not limited to tumor exosomes, cell free DNA, T cells receptor sequencing, CCI [redacted], CTCs, CCI [redacted], and CCI [redacted]. Additional analyses may be warranted based on emerging data.

CCI [redacted]

In Part 2, blood for Antigen Responses analysis may measure T cell responses to known tumor associated cancer/testis and tissue differentiation antigens and those specific to a participant's tumor as determined by neo-antigen predictions from analysis of tumor mutations.

Blood samples for TCR sequencing may measure if there are changes in the repertoire of T cells including possibly the specificity against tumor-associated antigens after treatment with PF-07257876 alone and in combination with sasanlimab.

A blood sample will be collected at screening for isolation of baseline germline DNA. This sample will be used to enable subtraction of germline DNA variants from somatic mutations that may be identified in tumor in order to make tumor neo-antigen predictions.

Instructions for sample collection, including collection of unscheduled blood samples if a participant is suspected to be experiencing an irAE or CRS, processing, storage, and shipment will be provided in the Laboratory Manual.

### 8.7. Immunogenicity Assessments

Blood samples will be collected from participants receiving sasanlimab combination therapy for determination of serum ADA and NAb of sasanlimab 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. Samples determined to be positive for ADA may be further characterized for NAb.

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.

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

As part of understanding the immunogenicity of the sasanlimab combination, samples may be used for additional characterization of an observed immunogenicity response and/or evaluation of the bioanalytical methods. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

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.

### 8.8. 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 statistical hypothesis testing in this study.

### 9.1.1. Estimands

#### 9.1.1.1. DLT

Primary Estimand: DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period (Cycle 1) in Part 1.

- Variable: Occurrence of DLTs. DLTs are defined in Section 4.3.3.
- Analysis population: DLT-evaluable participants defined as participants who receive at least 1 dose of study treatment, and either 1) received at least 75% of the planned doses of the study intervention and have received all scheduled safety assessments during the DLT-observation period or 2) have experienced a DLT regardless of the percentage of planned doses received. Participants without DLTs who withdraw from study treatment in the DLT-evaluation period for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.
- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants in the DLT-evaluation period.

#### 9.1.1.2. Incidence of AEs

Primary Estimand: Incidence of AEs estimated in the analysis population during the AE-evaluation period, defined as the time from the first dose to earliest of (28 days post last dosing date and day of new anti-cancer therapy -1 day).

- Variable: Occurrence of AEs. AEs are defined in Appendix 3 Section 10.3.
- Analysis population: Safety analysis set defined as participants who receive at least 1 dose of study treatment without regard to tolerability or duration of treatment.
- Population-level summary measure: Incidence of AEs defined as the number of participants with AEs in the AE-evaluation period divided by the number of participants in the analysis population. AEs will be summarized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to treatment.

#### 9.1.1.3. OR

Estimand: The treatment effect of PF-07265028 in combination with sasanlimab assessed by ORR using the RECIST version 1.1 and irRECIST in the analysis population.

- Variable: Objective response defined as CR or PR according to RECIST v1.1 and irRECIST, from the date of first dose until the date of the first documentation of PD, death, or start of new anticancer therapy. Both CR and PR must be confirmed by

repeat assessments performed no less than 4 weeks after the criteria for response are first met.

- Analysis population: The response evaluable set defined as all enrolled participants who received at least 1 dose of study treatment and had adequate baseline disease assessment. Participants who discontinued early or died will be included.

- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with OR and 2-sided 95% CI for ORR using the Clopper-Pearson/Wilson method. Participants who do not have a post-baseline tumor assessment due to early progression of disease, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, have PD, or stop tumor assessments for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR.

### 9.2. Analysis Sets

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

| Participant Analysis Set | Description |
|---|---|
| FAS | All enrolled participants who have been assigned to treatment. Participants are analyzed according to the treatment they were assigned . |
| SAS | All enrolled participants who receive at least 1 dose of study treatment. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses. |
| Per-Protocol Analysis Set (DLT-Evaluable Set) | All enrolled participants who had at least 1 dose of study treatment and either experienced DLT or do not have major protocol deviations during the DLT observation period. |
| mITT Population | All enrolled participants who have received at least 1 dose of study medication; have a baseline assessment and at least 1 post-baseline assessment. |
| PK Parameter Set | All enrolled participants treated who do not have protocol deviations influencing PK assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest. |
| PK Concentration 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 1 dose of study treatment and had adequate baseline disease assessment. Participants who discontinued early or died will be included. |
| Pharmacodynamic/ Biomarker Analysis Sets | The Pharmacodynamic/Biomarker analysis population is defined as all enrolled participants with at least 1 of the Pharmacodynamic/Biomarkers evaluated at pre- and/or postdose. |
| Immunogenicity Analysis Set | The immunogenicity analysis set is a subset of the safety analysis set and includes participants who have at least 1 analyzed sasanlimab ADA/NAb sample. |

### 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

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, PK, immunogenicity measurements, and biomarker measurements.

#### 9.3.2. Primary Endpoints

For Part 1, determination of MTD will be performed using the Per-Protocol analysis set (evaluable for MTD).

For Part 2, the response evaluable set will be used for all response-related analysis, including ORR and DoR. See more details in Section 9.3.3.

**Bayesian adaptive approach:**

The dose escalation in the Part 1 of the study will be guided by a Bayesian analysis of Cycle 1 DLT data for PF-07265028. A traditional 2-parameter BLRM will be used to model the DLT relationship of PF-07265028 monotherapy, and a more complex BLRM model specifically designed for combinations will be used to model the dose toxicity relationship of PF-07265028 given in combination with sasanlimab. Using DLT data at all tested dose levels and pre specified prior distribution of model parameters, the posterior distribution for probability of having a DLT will be calculated for all dose levels.

**Assessment of participant risk:**

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07265028 monotherapy and combination therapy will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

- Underdosing: [0, 0.16];
- Targeted dosing: [0.16, 0.33];
- Overdosing: [0.33, 1].

**The EWOC principle:**

Dosing decisions are guided by the escalation with overdose control principle.[1] A dose may only be used for newly enrolled participants if the risk of excessive toxicity at that dose is less than 25%.

**Prior distributions:**

Weakly informative prior distributions based on preclinical/expert opinion information will be chosen for the logistic parameters, see Appendix 11 Section 10.11.

A MAP approach may be used to derive the prior distribution for model parameters used in Part 1B based on the data collected in Part 1A and historical DLT data on sasanlimab as monotherapy. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data. MAP priors are derived from hierarchical models, which take into account possible differences between the studies. A full description of the application of the MAP approach to derive the prior distributions of the model parameters is given in Technical Supplement.

**Starting dose:**

The starting dose is 25 mg PF-07265028. For this dose the prior risk of overdosing is 7.1%, which satisfies the EWOC criterion. A full assessment of the prior risk to participants is given in Appendix 11 Section 10.11.

**Stopping criteria:**

The number of participants in Part 1 dose escalation of the trial may be approximately 60. The trial for Part 1A and Part 1B will be stopped when the following criteria are met:

At least 6 participants have been treated at the MTD/RDE.

The dose $\tilde{d}$ satisfies one of the following conditions:

- The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$.
- A minimum of 12 participants have been treated for Part 1A, or a minimum of 9 participants have been treated for Part 1B.

**Sensitivity analysis:**

To mitigate the risk of dichotomizing and misclassifying DLTs, a sensitivity analysis that uses weighted DLT/AE data (in equivocal cases) into the BLRM model estimation will also be performed. 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. See Appendix 11 Section 10.11 for more details.

### 9.3.3. Secondary Endpoints

The 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 and irRECIST will also be presented.

The Kaplan-Meier method will be used to analyze time-to-event efficacy endpoints.

The detailed analyses will be described in the SAP.

#### 9.3.3.1. Pharmacokinetic Analysis

##### 9.3.3.1.1. Single Dose and Steady State PF-07265028 and Sasanlimab Pharmacokinetic Analysis (with the Exception of Food Effect Assessment)

The plasma concentration time data of PF-07265028 and serum $C_{min}$ for 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. Exclusions or separate summaries for dose modifications and concomitant medications may be considered in data summaries.

In Part 1, following single dose administration of PF-07265028, plasma PK parameters including the $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC_{tau}$ and if data permit, $AUC_{inf}$, CL/F, $V_z$/F, and $t_{½}$ will be estimated. Following multiple doses of PF-07265028, steady-state PK parameters including $C_{max,ss}$, $T_{max,ss}$, $AUC_{last,ss}$, $AUC_{tau,ss}$, $C_{min,ss}$, $CL_{ss}$/F, and if data permit, $V_{ss}$/F, $t_{½}$, and $R_{ac}$ ($AUC_{tau,ss}$/$AUC_{tau,sd}$) will be estimated. In Part 2 participants Not in food-effect subset, following multiple doses of PF-07265028, $C_{min}$ will be reported. In Part 2 participants in food-effect subset, steady-state PK parameters including $C_{max,ss}$, $T_{max,ss}$, $AUC_{last,ss}$, $AUC_{tau,ss}$, $C_{min,ss}$, $CL_{ss}$/F under fasted and fed conditions will be estimated. In Part 1 and Part 2, following multiple doses of sasanlimab, $C_{min}$ in selected cycles will be reported.

The single-dose and steady-state PK parameters will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, and day.

Trough concentrations ($C_{min}$) will be plotted for each cohort using a box-and-whisker plot by cycle and day within cycle in order to assess the attainment of steady state. Dose normalized $C_{max}$, $AUC_{last}$, $AUC_{tau}$ (at steady state) and $AUC_{inf}$ (if estimated), and will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual participant values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

#### 9.3.3.1.2. Effect of Food on PF-07265028 Pharmacokinetics

For the evaluation of the food effect, PF-07265028 plasma concentration-time data will be compared on days taken under fasted (Reference) and fed conditions (Test). PK parameters ($C_{max,ss}$, $T_{max,ss}$, $AUC_{last,ss}$, $AUC_{tau,ss}$) of PF-07265028 given under fasted and fed conditions will be summarized descriptively. Natural log transformed AUC and $C_{max}$ values will be analyzed using an analysis of variance model and treatment as fixed effects. Estimates of the mean differences (Fed-Fasted) and corresponding 90% CI will be obtained from the model. The mean differences and 90% CI for the differences will be exponentiated to provide estimates of the ratios of geometric means (Fed/Fasted) and 90% CI for the ratios.

#### 9.3.3.2. Immunogenicity Analysis

For the immunogenicity data, the percentage of participants with positive ADA and Nab for each of sasanlimab combination dosing cohort will be summarized. For participants with positive ADA or neutralizing antibodies, the magnitude (titer), time of onset, and duration of ADA or neutralizing antibodies response will also be described, if data permit. The potential impact of immunogenicity on PK and CCI [redacted], safety/tolerability, and efficacy will be explored, if warranted by the data.

CCI [redacted]

#### 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 will be tabulated by treatment:

**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.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/pharmacodynamics modeling approach. If a PK/pharmacodynamics relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on-treatment ECG data. Baseline ECG is defined as the most recent ECG prior to 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 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. 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. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

### 9.3.6. Other Analyses

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

### Population PK/PD

PK and PD data from this study may be analyzed using modeling approaches. Participants who provide at least 1 postdose drug concentration measurement and have no major protocol deviations influencing the PK assessment will be included in the population PK analysis. The population PK model may be further combined with data on biomarkers and relevant efficacy and safety endpoints for population PK/PD analysis. The population PK and PK/PD analysis, if performed, will be reported separately.

## 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/pharmacodynamic modeling, and/or supporting clinical development.

### 9.5. Sample Size Determination

A maximum sample size of 240 participants will be enrolled in the study including approximately 60 participants in Part 1 dose escalation and up to 180 participants in Part 2 dose expansion.

#### 9.5.1. Part 1 Dose Escalation

Approximately 60 participants will be enrolled in the Part 1 dose escalation portion of the study, including approximately 30 participants in Part 1A and 30 participants in Part 1B. The actual number of participants enrolled in Part 1 will depend on the tolerability of PF-07265028 as monotherapy and in combination with sasanlimab and the number of dose levels required to identify the MTD/MAD or RDE.

#### 9.5.2. Part 2 Dose Expansion

In Part 2A for combination therapy (4 cohorts in total), up to 40 participants will be enrolled for each expansion cohort. If the expansion cohort as monotherapy is explored based on emerging clinical, safety, PK, or PD data, then 20 additional participants will be enrolled for Part 2B. The sample size is based on practical consideration that the stated sample size will provide sufficient evidence of preliminary efficacy of PF-07265028 alone and in combination with sasanlimab. For an expansion cohort in Part 2A, for example, if minimal or no anti-tumor activity is observed in the first 15 participants in each cohort, the enrollment for that cohort may be discontinued.

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 participant-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. Participant-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 study monitoring plan.

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.

Description of the use of the computerized system is documented in the Study Management Plan, 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.

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 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 safety laboratory tests will be performed at times defined in the SoA section of this protocol (see Table 14). 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.

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.

**Table 14. Core Laboratory Tests**

| Phase 1 |
|---|
| **Hematology** |
| Hemoglobin |
| Platelets |
| WBC |
| Absolute Neutrophils |
| Absolute Lymphocytes |
| Absolute Monocytes |
| Absolute Eosinophils |
| Absolute Basophils |
| |
| **Chemistry** |
| ALT |
| AST |
| Alkaline Phosphatase |
| Sodium |
| Potassium |
| Magnesium |
| Chloride |
| Bicarbonate or $CO_2$ (venous) |
| Total Calcium |
| Total and indirect Bilirubin* |
| BUN or Urea |
| Creatinine |
| Uric Acid |
| Glucose (non-fasted) |
| Albumin |
| Phosphorus or Phosphate |
| Amylase |
| Lipase |
| |
| **Coagulation** |
| PT or INR |
| PTT or aPTT |
| |

**Table 14. Core Laboratory Tests**

| Phase 1 |
|---|
| **Endocrinology** |
| TSH |
| Free T3 and free T4 |
| |
| **Serology** |
| HBV (HBsAg, HbcAb, anti-HBs) |
| HCV (HCVAb) |
| HIV (if applicable) |
| |
| **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) |
| Urine dipstick for bilirubin |
| |
| **Pregnancy Test** |
| For female participants of childbearing potential, on serum or urine (to be specified in the protocol |

## 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.<br><br>• 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 Meeting 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:<br><br>  • Is associated with accompanying symptoms;<br><br>  • Requires additional diagnostic testing or medical/surgical intervention;<br><br>  • 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.<br><br>• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.<br><br>• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.<br><br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br><br>• 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.<br><br>• 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.<br><br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br><br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br><br>• 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.<br><br>• 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**<br><br>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**<br><br>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 |

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:** |
|---|
| serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br><br>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**<br><br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br><br>• 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.**<br><br>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:**<br><br>• Grade 4 laboratory abnormalities.<br><br>• 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.<br><br>• 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. |

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:** |
|---|
| • 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 SoA 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<br><br>**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) *<br><br>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.

| Assessment of Causality |
|---|
| • The causality assessment is one of the criteria used when determining regulatory reporting requirements.<br><br>• 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.<br><br>• New or updated information will be recorded in the originally submitted documents.<br><br>• 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 an Electronic Data Collection Tool |
|---|
| • The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.<br><br>• If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.<br><br>• The site will enter the SAE data into the electronic system as soon as the data become available.<br><br>• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. |

| SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool |
| --- |
| • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone. |

| 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.<br><br>• 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.<br><br>• 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 Management of Immune-Related Adverse Events

| Gastrointestinal irAEs | | |
|---|---|---|
| **Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Diarrhea: <4 stools/day over Baseline<br><br>Colitis: asymptomatic | -Continue study treatment<br><br>-Symptomatic treatment (eg, loperamide) | -Close monitoring for worsening symptoms<br><br>-Educate participant to report worsening immediately<br><br>-If worsens:<br>Treat as Grade 2, 3 or 4. |
| **Grade 2**<br>Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; limiting instrumental ADL<br><br>Colitis: abdominal pain; blood in stool | -Withhold study treatment<br><br>-Symptomatic treatment | -If improves to Grade ≤1:<br>Resume study treatment<br><br>-If persists >5-7 days or recurs:<br>Treat as Grade 3 or 4. |
| **Grade 3 to 4**<br>Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 hours; interfering with ADL<br><br>Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs<br><br>Grade 4: life-threatening, perforation | -Withhold for Grade 3.<br><br>-Permanently discontinue study treatment for Grade 4 or recurrent Grade 3.<br><br>-1.0 to 2.0 mg/kg/day prednisone IV or equivalent<br><br>-Add prophylactic antibiotics for opportunistic infections<br><br>-Consider lower endoscopy | -If improves:<br>-Continue steroids until Grade ≤1, then taper over at least 1 month; resume study treatment following steroids taper (for initial Grade 3).<br><br>-If worsens, persists >3 to 5 days, or recurs after improvement:<br>-Add infliximab 5 mg/kg (if no contraindication).<br><br>-Note: infliximab should not be used in cases of perforation or sepsis. |

| Dermatological irAEs | | |
|---|---|---|
| **Grade of Rash (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1 to 2**<br>Covering ≤30% body surface area | -Continue study treatment<br>-Symptomatic therapy (for example, antihistamines, topical steroids) | -If **Grade 2** persists >1 to 2 weeks or recurs:<br>-Withhold study treatment<br>-Consider skin biopsy<br>-Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study treatment following steroids taper.<br>-If worsens: Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br>Grade 3: Covering >30% body surface area;<br>Grade 4: Life threatening consequences | -Withhold study treatment for Grade 3.<br>-Permanently discontinue for Grade 4 or recurrent Grade 3.<br>-Consider skin biopsy<br>-Dermatology consult<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent<br>-Add prophylactic antibiotics for opportunistic infections | -If improves to Grade ≤1:<br>-Taper steroids over at least 1 month; resume study treatment following steroids taper (for initial Grade 3). |

| Pulmonary irAEs | | |
|---|---|---|
| **Grade of Pneumonitis (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Radiographic changes only | -Consider withholding study treatment<br>-Monitor for symptoms every 2 to 3 days<br>-Consider Pulmonary and Infectious Disease consults | -Re-assess at least every 3 weeks<br>-If worsens: Treat as Grade 2 or Grade 3 to 4. |
| **Grade 2**<br>Mild to moderate new symptoms | -Withhold study treatment<br>-Pulmonary and Infectious Disease consults<br>-Monitor symptoms daily; consider hospitalization<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent<br>-Add prophylactic antibiotics for opportunistic infections<br>-Consider bronchoscopy, lung biopsy | -Re-assess every 1 to 3 days If improves:<br>-When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume study treatment following steroids taper<br>-If not improving after 2 weeks or worsening: Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br>Grade 3: Severe new symptoms; New/worsening hypoxia;<br>Grade 4: Life-threatening | -Permanently discontinue study treatment.<br>-Hospitalize.<br>-Pulmonary and Infectious Disease consults.<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent<br>-Add prophylactic antibiotics for opportunistic infections<br>-Consider bronchoscopy, lung biopsy | -If improves to Grade ≤1:<br>-Taper steroids over at least 1 month<br>-If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil) |

| Hepatic irAEs | | |
|---|---|---|
| **Grade of Liver Test Elevation (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| Grade 1<br>Grade 1 AST or ALT > ULN to 3.0 x ULN if baseline was normal, >1.5-3.0 x baseline if baseline was abnormal; and/or Total bilirubin > ULN to 1.5 x ULN if baseline was normal, >1.0-1.5 x baseline if baseline was abnormal | -Continue study treatment | -Continue liver function monitoring<br>-If worsens: Treat as Grade 2 or 3 - 4. |
| **Grade 2**<br>AST or ALT >3.0 to ≤5 x ULN if baseline was normal, >3.0-5.0 x baseline if baseline was abnormal; and/or total bilirubin >1.5 to ≤3 x ULN if baseline was normal, >1.5-3.0 x baseline if baseline was abnormal | -Withhold study treatment<br>-Increase frequency of monitoring to every 3 days. | -If returns to Grade ≤1:<br>-Resume routine monitoring; resume study treatment.<br>-If elevation persists >5 to 7 days or worsens:<br>-Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br>AST or ALT >5 x ULN if baseline was normal, >5.0 x baseline if baseline was abnormal; and/or total bilirubin >3 x ULN if baseline was normal, >3 x baseline if baseline was abnormal | -Permanently discontinue study treatment<br>-Increase frequency of monitoring to every 1 to 2 days<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent<br>-Add prophylactic antibiotics for opportunistic infections<br>-Consult gastroenterologist/ hepatologist<br>-Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted | -If returns to Grade ≤1:<br>-Taper steroids over at least 1 month<br>-If does not improve in >3 to 5 days, worsens or rebounds:<br>-Add mycophenolate mofetil 1 gram (g) twice daily<br>-If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines. |

| Renal irAEs | | |
|---|---|---|
| **Grade of Creatinine Increased (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Creatinine increased > ULN to 1.5 x ULN | -Continue study treatment | -Continue renal function monitoring<br>-If worsens: Treat as Grade 2 to 3 or 4. |
| **Grade 2 to 3**<br>Creatinine increased >1.5 and ≤6 x ULN | -Withhold study treatment<br>-Increase frequency of monitoring to every 3 days<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>-Add prophylactic antibiotics for opportunistic infections<br>-Consider renal biopsy | -If returns to Grade ≤1:<br>-Taper steroids over at least 1 month, and resume study treatment following steroids taper.<br>-If worsens:<br>-Treat as Grade 4. |
| **Grade 4**<br>Creatinine increased >6 x ULN | -Permanently discontinue study treatment<br>-Monitor creatinine daily<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>-Add prophylactic antibiotics for opportunistic infections Consider renal biopsy<br>-Nephrology consult | -If returns to Grade ≤1:<br>Taper steroids over at least 1 month. |

| Cardiac irAEs | | |
|---|---|---|
| **Myocarditis** | **Initial Management** | **Follow-up Management** |
| New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin I, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis. | -Withhold study treatment.<br><br>-Hospitalize.<br><br>-In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management.<br><br>-Consult cardiologist to establish etiology and rule-out immune-mediated myocarditis.<br><br>-Guideline based supportive treatment as per cardiology consult.*<br><br>-Consider myocardial biopsy if recommended per cardiology consult. | -If symptoms improve and immune-mediated etiology is ruled out, re-start study treatment.<br><br>-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.<br><br>-Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent<br><br>-Add prophylactic antibiotics for opportunistic infections. | -Once improving, taper steroids over at least 1 month.<br><br>If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A, abatacept). |

*Local guidelines, or eg. ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

| Endocrine irAEs | | |
|---|---|---|
| **Endocrine Disorder** | **Initial Management** | **Follow-up Management** |
| Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, Type 1 diabetes mellitus) | -Continue study treatment<br>-Endocrinology consult if needed<br><br>-Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type 1 diabetes mellitus) as appropriate<br><br>-Rule-out secondary endocrinopathies (ie, hypopituitarism/hypophysitis) | -Continue hormone replacement/suppression and monitoring of endocrine function as appropriate. |
| Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, Type 1 diabetes mellitus) | -Withhold study treatment<br>-Consider hospitalization<br>-Endocrinology consult<br><br>-Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type 1 diabetes mellitus) as appropriate.<br><br>-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).<br><br>-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):<br>-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)<br><br>-Hormone replacement/suppressive therapy as appropriate<br><br>-Perform pituitary MRI and visual field examination as indicated<br><br>**-If hypophysitis is confirmed:**<br>-Continue study treatment if mild symptoms with normal | -Resume study treatment once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement).<br><br>-In addition, for hypophysitis with abnormal MRI, resume study treatment only once shrinkage of the pituitary gland on MRI/CT scan is documented.<br><br>-Continue hormone replacement/suppression therapy as appropriate. |

| Endocrine irAEs | | |
|---|---|---|
| **Endocrine Disorder** | **Initial Management** | **Follow-up Management** |
| | MRI. Repeat the MRI in 1 month<br><br>-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.<br><br>-Add prophylactic antibiotics for opportunistic infections. | |

| Other irAEs (not described above)** | | |
|---|---|---|
| **Grade of other irAEs (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| 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<br>-If irAE is confirmed, treat as Grade 2 or 3 irAE. |
| Grade 2 irAE or first occurrence of Grade 3 irAE | -Withhold study treatment<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent<br>-Add prophylactic antibiotics for opportunistic infections<br>-Specialty consult as appropriate | -If improves to Grade ≤ 1:<br>-Taper steroids over at least 1 month and resume study treatment following steroids taper. |
| Recurrence of same Grade 3 irAEs | -Permanently discontinue study treatment<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent<br>-Add prophylactic antibiotics for opportunistic infections<br>-Specialty consult as appropriate | -If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month. |
| Grade 4 | -Permanently discontinue study treatment<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed<br>-Add prophylactic antibiotics for opportunistic infections<br>-Specialty consult. | -If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month |

| Other irAEs (not described above)** | | |
|---|---|---|
| **Grade of other irAEs (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| | | |
| 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<br><br>Persistent Grade 2 or 3 irAE lasting 12 weeks or longer | - Permanently discontinue study treatment<br><br>-Specialty consult | |

** 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/professionals/physician_gls/pdf/immunotherapy.pdf.

## 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 93 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study interventions (eg, 5 terminal half-lives) ***plus*** an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse 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 when engaging in any activity that allows for passage of ejaculate to another person 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.

### 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 6 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention. As for participants using a highly effective method that is user dependent, this contraception method must be used together with a second effective method of contraception, as described below. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. 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 1 of the non-estrogen 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.
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.

    *not approved in Japan.

**Highly Effective Methods That Are User Dependent**

1. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal*;
    - Transdermal*.
2. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral*;
    - Injectable*.
3. 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).

  * not approved in Japan.

## 10.5. Appendix 5: Genetcs

**Use/Analysis of DNA**

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07265028 alone and in combination with sasanlimab or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Retained samples for banking will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

    - Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

## 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."

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 May Qualify as AE |
|---|
| • Marked sinus bradycardia (rate <40 bpm).<br>• New PR interval prolongation >280 ms.<br>• New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms from baseline.<br>• New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.<br>• New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.<br>• Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes. |
| **ECG Findings That May Qualify as Serious AE** |
| • QTcF prolongation >500 ms.<br>• New ST-T changes suggestive of myocardial ischemia.<br>• New-onset left bundle branch block (QRS >120 ms).<br>• New-onset right bundle branch block (QRS >120 ms).<br>• Symptomatic bradycardia.<br>• Asystole:<br>  • 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.<br>  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.<br>  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.<br>• 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: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with PF-07265028 for the period of time at least equal to the required washout period listed in the table, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgement on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with PF-07265028 may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

| Drug Category | Drugs | Required Washout Period requirement |
|---|---|---|
| **Strong CYP3A4 Inhibitor** | Grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos), amprenavir, Boceprevir, ceritinib, clarithromycin, conivaptan, cobicistat (GS-9350), fosamprenavir, itraconazole, indinavir, idelalisib, ketoconazole, lopinavir/ritonavir, LCL161, miconazole, mibefradil, nefazodone, nelfinavir, ritonavir, ribociclib, saquinavir, telaprevir, troleandomycin, telithromycin, voriconazole, posaconazole | 10 days<br>or<br>5 half-lives<br>whichever is longer |
| **Moderate CYP3A4 Inhibitor** | Amprenavir, aprepitant, atazanavir/ritonavir, ACT-178882, crizotinib, casopitant, cyclosporine, ciprofloxacin, cimetidine, darunavir, duvelisibm diltiazem, darunavir/ritonavir, delavirdine, dronedarone, erythromycin, fluconazole, fedratinib, fluvoxamine, FK1706, letermovir, GSK2647544, lefamulin, faldaprevir, imatinib, istradefylline, isavuconazole, magnolia vine (Schisandra sphenanthera), netupitant, nilotinib, palbociclib, ravuconazole, tofisopam, voxelotor, verapamil | 10 days<br>or<br>5 half-lives<br>whichever is longer |
| **Strong CYP3A4 Inducer** | Apalutamide, avasimibe, carbamazepine, clevidipine, enzalutamide, lumacaftor, mitotane, rifampin, rifabutin, rifapentine, phenytoin, phenobarbital, St John's Wort extract | 10 days<br>or<br>5 half-lives<br>whichever is longer |

| Drug Category | Drugs | Required Washout Period requirement |
|---|---|---|
| **CYP3A4 Sensitive Substrate** | Amiodarone, alfentanil (excluding transdermal patch), astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl (excluding transdermal patch), pimozide, quinidine, rifampin, sirolimus, terfenadine, tacrolimus, valproate | 10 days<br>or<br>5 half-lives<br>whichever is longer |
| **CYP2D6 Sensitive Substrate** | Desipramine, flecainide, nortriptyline, quinidine, thioridazine, pimozide, trimipramine | 10 days<br>or<br>5 half-lives<br>whichever is longer |
| **UGT1A1 Sensitive Substrate** | Belinostat, irinotecan | 10 days<br>or<br>5 half-lives<br>whichever is longer |
| **BCRP Highly Sensitive Substrate** | Paritaprevir, pemafibrate | 10 days<br>or<br>5 half-lives<br>whichever is longer |
| **P-gp Sensitive Substrate** | Sirolimus, temsirolimus | 10 days<br>or<br>5 half-lives<br>whichever is longer |

**The following drugs need to be used with caution or lower the dose:**

- P-gp substrate: Digoxin (monitoring of serum digoxin level is recommended and dose reduction of digoxin may be needed).
- Statins: Atorvastatin (limit dose to 20 mg daily), fluvastatin (limit dose to 20 mg daily), rosuvastatin (limit dose to 10 mg once daily), simvastatin (limit dose to 10 mg daily).
- BCRP substrates: apixaban, glecaprevir, letermovir, pibrentasvir, rivaroxaban, sofosbuvir, sulfasalazine, tenofovir.
- OCT-1/MATE2K substrate: Metformin.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

## 10.9. Appendix 9: Country-Specific Requirements

### 10.9.1. Japan Specific Requirement

#### 10.9.1.1. Condition to Be Met for Discharge

When a participant is discharged from the hospital during the DLT evaluation period, the following conditions (tests, medical examinations, etc.) should be performed on the day of the scheduled discharge by the investigators, and the propriety of discharge should be determined. The tests/medical examinations which are needed to confirm the participant's status will be conducted per clinical practice in the study site as appropriate.

- There are no current clinically significant adverse or side effects, or medical reasons that require monitoring in a hospital setting.
- If a clinically significant adverse or side effect has occurred or continues to be present, the investigator will determine that the event is manageable by appropriate treatment or prophylaxis in an out of the hospital setting.
- Overall physical condition is stable and acceptable.
- In case of emergency, the participant may return to the clinical study site or other medical institution. If participants go to a medical institution other than the clinical study site, the clinical study site asks that the participants contact the study site, study investigator and the doctor at the medical institution who will communicate to discuss appropriate treatments. A study site keeps framework to ready for emergency situations that is available even during nights and holidays, and the sponsor will ensure that the selected study site will thoroughly follow all participants according to study procedures.

#### 10.9.1.2. Eligibility

Exclusion Criterion 24: Participants with positive HBsAb or positive HBcAb are allowed to participate in the study if they have negative HBV DNA test at screening but HB viral load should be monitored for re-activation every 12 weeks.

- Participants with positive HBsAb who have been vaccinated with HBV are exempted from the testing of HB viral load.
- If a participant tests positive for HBV (positive viral load) at any time during the study, study treatment will be interrupted and investigator should consider starting nucleoside antagonist immediately in parallel with consultation with hepatologist in accordance with the JSH Guidelines for the management of Hepatitis B Virus infection.[53]

#### 10.9.1.3. Vital Signs

To screen and monitor interstitial lung disease/pneumonitis for early detection, $SpO_2$ test should be done at the same time as vital signs collection.

#### 10.9.1.4. Generics and Biomarkers

Given the genetic testing is for exploratory purposes only and following Pfizer process, there is no expectation to disclose these genetic testing results to the study participants, at any time.

A study participant's participation in a clinical study shall not be conditioned on his or her informed consent for the use of biospecimens that is not related to a clinical endpoint, the drug being investigated in the trial, or the inclusion/exclusion criteria for the study.

## 10.10. Appendix 10: 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).

### 10.10.1. 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 #24. When the infection resolves, the participant may be considered for re-screening.

### 10.10.2. 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 SOA 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 10.10.3.1 of this appendix regarding pregnancy tests.

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

### 10.10.3. Alternative Facilities for Safety Assessments

#### 10.10.3.1. 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 (see Section 10.2.)

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.

#### 10.10.3.2. 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.

#### 10.10.3.3. 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.

### 10.10.4. 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.

PF-07265028 may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the PF-07265028. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of PF-07265028 must be kept in the participant's source documents/medical records.

The following is recommended for the administration of PF-07265028 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, PF-07265028 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 6.8.1 for any concomitant medication administered for treatment of SARS-CoV2 infection.

### 10.10.5. 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:

- Laboratory assessments;
- Vital signs;
- Others as appropriate.

### 10.10.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or 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.

### 10.10.7. Efficacy Assessments

Please contact the sponsor should a participant need to use alternative measures for efficacy assessments. A plan will be devised in discussion with the sponsor and investigator.

### 10.10.8. Independent Oversight Committees

This is an open-label, non-randomized Phase 1 study. This study will not use a DMC.

## 10.11. Appendix 11: Detailed Dose Escalation/De-Escalation Scheme for BLRM Design

This appendix provides the details of the statistical model, the description of prior distribution of the model parameters, and sensitivity analysis. 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 could be found in the separate Technical Supplement.

### 10.11.1. Statistical Model

Let $\pi\ (d\ )$ be the risk of DLT for PF-07265028 given as a single agent at dose $d$. The dose-DLT model is logistic:

$$\text{Logit}\ (\pi\ (d\ ))\ \ = \log(\alpha\ ) + \beta\ \log(d\ /\ d*\ )$$

$d*$= 600 mg QD and used to scale the doses of PF-07265028. Hence, $\alpha$ (>0) is the odds of a DLT at PF-07265028 $d*$ mg; and $\beta$ (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

Statistical model to be used in Part 1B along with prior specifications based on currently available data is described in the separate Technical Supplementary material to this appendix.

### 10.11.2. Prior Specifications for Part 1A

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 was used as there were no relevant human historical DLT data available. It was assumed that model parameters will follow a BVN distribution

$$(\log(\alpha), \log(\beta\ )) \sim N_2\ (m, S)$$

with prior means $m = (m_1, m_2)$, and prior covariance matrix $S$ composed of standard deviations $s_1, s_2$ and correlation $cor$. It was assumed that:

$$(m_1, m_2, s_1, s_2, cor) = (\text{logit}(p^*), 0, 2, 1, 0)$$

Here, $p^*$ is the anticipated DLT rate at the scaling dose $d*$. It was assumed based on pre-clinical data that DLT rate at 600 mg QD dose was 0.2.

This prior is considered to be weakly informative.

The prior distributions of the model parameters are provided in Table 15. Table 16 summarizes the resulting prior distribution of DLT rate derived from the prior, which is also illustrated in Figure 1. Based on the available information the starting dose of 25 mg QD satisfies the EWOC criteria.

**Table 15 Prior Distribution for the Model Parameters**

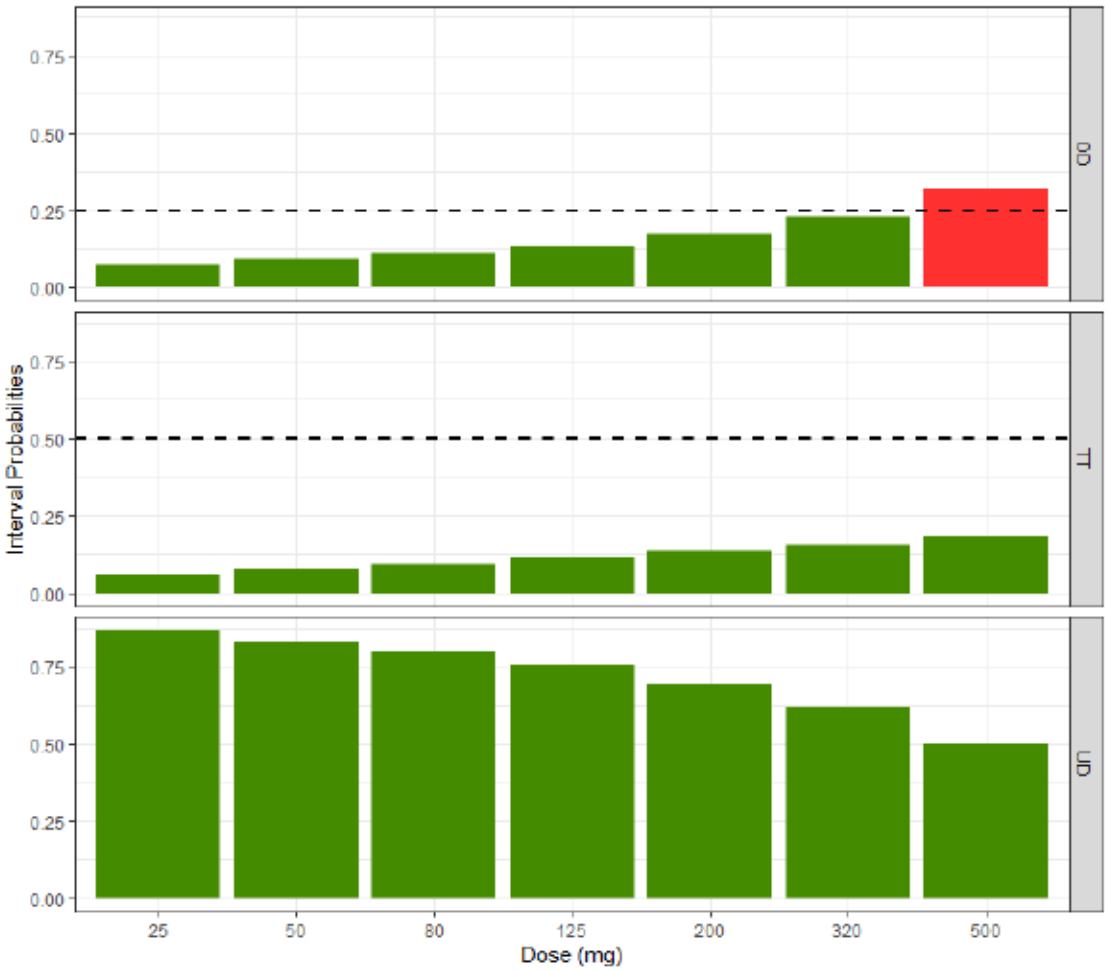
| PF-07265028 Single Agent Parameters: BVN Weakly Informative Prior | | | |
|---|---|---|---|
| **Parameters** | **Means** | **Standard Deviations** | **Correlation** |
| $(\log(\alpha), \log(\beta))$ | -1.386, 0 | 2, 1 | 0 |

**Table 16 Summary of Prior Distribution of DLT rates for PF-07265028**

| PF-07265028 (mg QD)* | Prior Probabilities that DLT Rate is in the Interval | | | Mean | Standard Deviation | Quantiles | | |
|---|---|---|---|---|---|---|---|---|
| | [0, 0.16) | [0.16, 0.33) | [0.33,1] | | | 2.5% | 50% | 97.5% |
| 25 | 0.867 | 0.062 | 0.071 | 0.073 | 0.158 | 0.000 | 0.007 | 0.623 |
| 50 | 0.831 | 0.078 | 0.091 | 0.091 | 0.175 | 0.000 | 0.013 | 0.688 |
| 80 | 0.797 | 0.094 | 0.109 | 0.107 | 0.189 | 0.000 | 0.021 | 0.731 |
| 125 | 0.754 | 0.111 | 0.135 | 0.128 | 0.204 | 0.000 | 0.033 | 0.773 |
| 200 | 0.696 | 0.133 | 0.171 | 0.158 | 0.222 | 0.000 | 0.054 | 0.815 |
| 320 | 0.616 | 0.154 | 0.230 | 0.201 | 0.244 | 0.001 | 0.092 | 0.862 |
| 500 | 0.500 | 0.183 | 0.317 | 0.264 | 0.268 | 0.003 | 0.160 | 0.905 |

*Dose levels in this table are provisional and subject to change during the study.

**Figure 1. Interval Probabilities**




Interval probabilities of UD, TT, and OD. Note the dashed horizontal line in the TT panel displays the probability threshold that a dose must meet to be selected as the MTD, while the dashed line in the OD panel displays the probability threshold for the EWOC design.

### 10.11.3. 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 $d$ with m unequivocal DLTs and r equivocal DLTs/AEs, and the weight w for the equivocal data, then based on the power prior,

$$\text{Posterior}(\alpha, \beta \mid d, m, r, w) \propto L(m \mid \alpha, \beta, d, w) \times L(r \mid \alpha, \beta, d, w)^{w} \times \text{prior}(\alpha, \beta)$$

$$\propto p(\alpha, \beta, d)^{m} \times [1 - p(\alpha, \beta, d)]^{n-r-m} \times p(\alpha, \beta, d)^{rw} \times \text{prior}(\alpha, \beta),$$

where L is the likelihood of the observed DLT data, and p ($\alpha$, $\beta$, 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.

## 10.12. Appendix 12: RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from Eisenhauer EA, et al (2009).[54]

### CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least 1 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 2 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 1 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 (SEE Table 17)**

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:
  - 1 or more target measurable lesions have not been assessed.
  - or assessment methods used were inconsistent with those used at baseline.
  - or 1 or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure).
  - or 1 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 1 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

Participants 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 17. 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 participants with only non-target disease, the following Table 18 will be used:

**Table 18 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 |

## 10.13. Appendix 13: Immune-related RECIST (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics.

This is particularly true for immunotherapeutic agents such as anti-CTLA-4 and anti PD-1/anti-PD-L1 antibodies which exert the anti-tumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects.[55-57] Clinical observations of participants with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as RECIST and WHO criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of participants who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria.[58-60]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare type responses into the RECIST v1.1 (irRECIST).

For irRECIST, only target and measurable lesions are taken into account. In contrast to RECIST v1.1, irRECIST:

- Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented; and
- Does not necessarily score the appearance of new lesions as PD if the sum of lesion diameters of target lesions (minimum of 10 mm longest diameter per non-nodal lesion and 15 mm shortest diameter per nodal lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial.

irRECIST is defined as follows:

- Overall irCR: Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.
- Overall irPR: Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.

- Overall irSD: Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions is neither irCR, irPR, (compared to baseline) nor immune related progressive disease (irPD, compared to nadir).

- Overall irPD: Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir) with a minimum absolute increase of 5 mm, confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (ie, added to the target lesion measurements). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements at each assessment time point.

New non measurable lesions: Do not define progression but preclude irCR.

CCI

[redacted]

## 10.15. Appendix 15: Suggested Cytokine Release Syndrome Management Algorithm and Revised CRS Grading System

*Adapted from Lee DW, et al: ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells 2019.25: 625-638.*

ASTCT CRS Consensus Grading

| CRS Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Fever**[*] | Temperature ≥38°C | Temperature ≥38°C | Temperature ≥38°C | Temperature ≥38°C |
| | | With | | |
| **Hypotension** | None | Not requiring vasopressors | Requiring a vasopressor with or without vasopressin | Requiring multiple vasopressors (excluding vasopressin) |
| | | And/or[†] | | |
| **Hypoxia** | None | Requiring low-flow nasal cannula[‡] or blow-by | Requiring high-flow nasal cannula[‡], facemask, nonrebreather mask, or Venturi mask | Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation) |

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[*] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients 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.

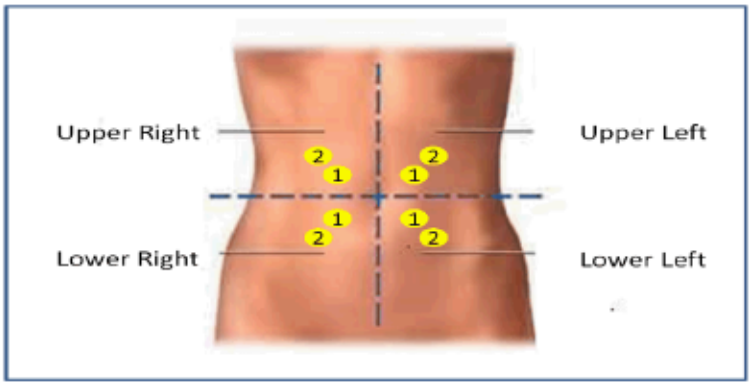
[†] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[‡] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

*Note – Hypoxia requiring low-flow simple facemask defined as oxygen delivered at ≤6 L/minute is Grade 2 CRS, whereas hypoxia requiring high-flow simple facemask defined as oxygen delivered at >6 L/minute is Grade 3 CRS.

## 10.16. Appendix 16: Subcutaneous Injection Site Locations

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 number of injections in the following order:

1. Abdomen- Right Lower Quadrant Location 1;
2. Abdomen- Right Lower Quadrant Location 2;
3. Abdomen- Left Lower Quadrant Location 1;
4. Abdomen- Left Lower Quadrant Location 2;
5. Abdomen- Right Upper Quadrant Location 1;
6. Abdomen- Right Upper Quadrant Location 2;
7. Abdomen- Left Upper Quadrant Location 1;
8. Abdomen- Left Upper 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.

For participants in the combination arm receiving PF-07265028 and sasanlimab on the same dosing day, injections for sasanlimab should be administered in different quadrants to facilitate assessment of ISRs. If a particular quadrant is not available for injection, move to the next quadrant, in sequential order. Injecting sasanlimab diagonally by quadrant to maximize the distance is preferred when applicable.

Track the participant's injection sites(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 and time of each injection and any ISR in the participant's source records and study CRF. See eCRF guidelines for more information.

## 10.17. Appendix 17: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

| Abbreviation | Term |
|---|---|
| ACTH | adrenocorticotropic hormone |
| ADA | antidrug antibodies |
| ADL | activities of daily living |
| ADME | absorption, distribution, metabolism, and excretion |
| AE | adverse event |
| CCI | [redacted] |
| AESI | adverse events of special interest |
| AHA | American Heart Association |
| AIDS | acquired immunodeficiency syndrome |
| ALL | Acute Lymphocytic Leukemia |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AML | Acute Myeloid Leukemia |
| ANC | absolute neutrophil count |
| aPTT | activated partial thromboplastin time |
| ART | antiretroviral therapy |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| AT | aminotransferase |
| AUC | area under the curve |
| $AUC_{inf}$ | area under the concentration-time curve from time zero extrapolated to infinite time |
| $AUC_{last}$ | area under the concentration-time curve from time zero to the last quantifiable time point prior to the next dose |
| $AUC_{last, ss}$ | area under the concentration-time curve from time zero to the last quantifiable time point prior to the next dose steady state |
| $AUC_{ss}$ | steady state AUC |
| $AUC_{tau}$ | AUC during the dosing interval tau |
| $AUC_{tau}$ | AUC during the dosing interval tau steady state |
| AV | atrioventricular |
| BCRP | breast cancer resistance protein |
| BID | twice daily |
| BLRM | Bayesian logistic regression model |
| BNP | B-type natriuretic peptide |
| BP | blood pressure |
| Bpm | beats per minute |
| BSC | best supportive care |
| BUN | blood urea nitrogen |

| Abbreviation | Term |
|---|---|
| BVN | bivariate normal |
| C | cycle |
| $C_{ave,ss}$ | average concentration steady state |
| CD8 | cluster of differentiation 8 |
| C1D1 | cycle 1 day 1 |
| cfDNA | cell 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 |
| CL/F | apparent total clearance after oral administration |
| $CL_{ss}/F$ | steady-state apparent total clearance |
| CLK | Cdc2-like kinase |
| CCI | [redacted] |
| $C_{max}$ | maximum observed concentration |
| $C_{max,ss}$ | maximum observed concentration at steady state |
| $C_{min,ss}$ | minimum observed concentration at steady state |
| $CO_2$ | carbon dioxide |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | coronavirus disease 2019 |
| CPI | checkpoint inhibitor |
| CPS | combined positive score |
| CR | complete response |
| CRF | case report form |
| CRO | contract research organization |
| CRP | c-reactive protein |
| CRS | cytokine release syndrome |
| CSF | cerebrospinal fluid |
| CSR | clinical study report |
| CT | clinical trial, computed tomography |
| CT-Ag | cancer/testis antigens |
| CTC | circulating tumor cells |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA-4 | cytotoxic T lymphocyte-associated protein-4 |
| CTMS | clinical trial management system |
| CV | coefficient of variation |
| CYP | cytochrome P450 |
| D | Day |
| DDI | drug-drug interaction |
| DILI | drug-induced liver injury |

| Abbreviation | Term |
|---|---|
| DL | dose level |
| DLRM | dose level review meeting |
| DLT | dose-limiting toxicity |
| DMC | data monitoring committee |
| dMMR | deficient mismatch repair |
| DNA | deoxyribonucleic acid |
| DoR | duration of response |
| DVT | deep venous thrombosis |
| DU | dispensable unit |
| EC | ethics committee |
| $EC_{50}$ | half maximal effective concentration |
| ECC | emergency contact card |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| EDP | exposure during pregnancy |
| EMA | European Medicines Agency |
| EOT | end of treatment |
| ER | efflux ratio |
| ESC | European Society of Cardiology |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| EWOC | escalation with overdose control |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FFPE | formalin-fixed paraffin-embedded |
| FIH | first in human |
| FSH | follicle-stimulating hormone |
| F/U | follow-up |
| GC | gemcitabine and cisplatin |
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony-stimulating factor |
| GEJ | gastroesophageal junction |
| GEMM | genetically-engineered mouse model |
| GGT | gamma-glutamyl transferase |
| GH | growth hormone |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| GVHD | graft versus host disease |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |

| Abbreviation | Term |
|---|---|
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HED | human equivalent dose |
| HIV | human immunodeficiency virus |
| HMG CoA | 3-hydroxy-3-methylglutaryl coenzyme A |
| HNSCC | head and neck squamous cell carcinoma |
| HNSTD | highest non-severely toxic dose |
| HPK1 | hematopoietic progenitor kinase 1 |
| HR | heart rate |
| HRT | hormone replacement therapy |
| H2 | histamine H2-receptor |
| IB | investigator's brochure |
| $IC_{50}$ | half-maximal inhibitory concentration |
| ICB | Immune checkpoint blockade |
| ICD | informed consent document |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICI | immune checkpoint inhibitor |
| ID | identification |
| IFN-γ | interferon-gamma |
| IGF-1 | insulin-like growth factor 1 |
| IHC | immunohistochemistry |
| IL | interleukin |
| IMP | investigational medicinal product |
| IND | investigational new drug |
| INR | international normalized ratio |
| IO | immuno-oncology |
| IP manual | investigational product manual |
| IPAL | Investigational Product Accountability Log |
| irAE | immune-related adverse events |
| IRB | institutional review board |
| irPR | immune-related partial response |
| irRECIST | immune-related RECIST |
| irSD | immune-related stable disease |
| IRT | interactive response technology |
| ISR | injection site reaction |
| IV | intravenous |
| IWR | interactive Web-based response |
| JAK | Janus kinase |
| JSH | Japan Society of Hepatology |
| LAG-3 | lymphocyte-activation gene 3 |
| LCMV | lymphocytic choriomeningitis virus |

| Abbreviation | Term |
|---|---|
| LFT | liver function test |
| LH | luteinizing hormone |
| LHRH | luteinizing hormone-releasing hormone |
| MAD | maximum administered dose |
| MAP | meta-analytic-predictive |
| MATE2 | multidrug and toxin extrusion 2 |
| MD | multiple dose |
| MDR | medical device regulation |
| MEC | molar extinction coefficient |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| MRI | magnetic resonance imaging |
| MSI-H | high levels of microsatellite instability |
| MTD | maximum tolerated dose |
| MVAC | methotrexate, vinblastine, doxorubicin (adriamycin), and cisplatin |
| N/A | not applicable |
| NAb | neutralizing antibodies |
| NCI | National Cancer Institute |
| NG | nasogastric |
| NIMP | non-investigational medicinal product |
| NK | natural killer |
| NOAEL | no-observed-adverse-effect level |
| NSCLC | non-small-cell lung cancer |
| NTI | narrow therapeutic index |
| OCT | octamer-binding transcription factor |
| OD | overdosing |
| OR | objective response |
| ORR | objective response rate |
| OS | overall survival |
| $P_{app,AB}$ | apical-to-basolateral permeability |
| PBMC | peripheral blood mononuclear cell |
| PD | pharmacodynamics(s), progressive disease |
| PD-1 | programmed death-1 |
| PD-L1 | programmed death ligand-1 |
| PDx | PD-1, PD-L1, or PD-L2 |
| PFS | progression-free survival |
| PGE2 | prostaglandin E2 |
| P-gp | P-glycoprotein |
| PGx | pharmacogenomics |
| PK | pharmacokinetic(s) |
| PKA | protein kinase A |
| PR | partial response, pulse rate |

| Abbreviation | Term |
|---|---|
| PRL | prolactin |
| PS | performance status |
| CCI | [redacted] |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| PVC | premature ventricular contraction/complex |
| Q4W | every 4 weeks |
| Q12W | every 12 weeks |
| QD | every day |
| QTc | corrected QT |
| QTcB | corrected QT (Bazett method) |
| QTcF | corrected QT (Fridericia method) |
| QTL | quality tolerance limit |
| Rac | accumulation ratio |
| RBC | red blood cell |
| RDE | recommended dose expansion |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | ribonucleic acid |
| RP2D | recommended phase 2 dose |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV2 | severe acute respiratory syndrome coronavirus 2 |
| SAS | safety analysis set |
| SC | subcutaneous |
| SCr | serum creatinine |
| SD | single dose, stable disease |
| SLP76 | SH2 domain-containing leukocyte protein 76 kDa |
| SoA | schedule of activities |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| $SpO_2$ | percent saturation of oxygen |
| STD | severely toxic dose |
| SUSAR | suspected unexpected serious adverse reaction |
| $t_{1/2}$ | terminal elimination half-life |
| T4 | thyroxine |
| TBili | total bilirubin |
| TCR | T cell receptor |
| TGF-β | transforming growth factor beta |
| TIGIT | T cell immunoreceptor with Ig and ITIM domains |
| TNFα | tumor necrosis factor alpha |
| $T_{max}$ | time to maximum concentration |
| $T_{max,ss}$ | time to maximum concentration steady state |

| Abbreviation | Term |
|---|---|
| TMB | tumor mutational burden |
| TME | tumor microenvironment |
| TSH | thyroid-stimulating hormone |
| TT | target toxicity |
| TYK | tyrosine kinase |
| UC | urothelial cancer |
| UD | underdosing |
| UGT | UDP-glucuronosyltransferase |
| ULN | upper limit of normal |
| US | United States |
| UVA | ultraviolet A |
| UVB | ultraviolet B |
| $V_{ss}/F$ | apparent volume of distribution at steady state |
| $V_z/F$ | apparent volume of distribution during terminal phase after oral administration |
| WBC | white blood cell |
| WNL | within normal limit |
| WOCBP | woman/women of childbearing potential |

## 10.18. Appendix 18: Protocol Amendment History

| | |
|---|---|
| Original protocol | 05 October 2021 |

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