Protocol C4731001

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

Statistical Analysis Plan
(SAP)

Version: **1**

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1. VERSION HISTORY

This is the first version. This section will be updated if a SAP amendment is to be written.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in study C4731001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. This SAP was written in reference to the original version of the protocol dated October 5, 2021 and the protocol amendment 1 dated November 22, 2021.

Note: in this document any text taken directly from the protocol is *italicized*.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1. Part 1 Primary Estimands

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* Protocol *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.*

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* Protocol *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.*

2.1.2. Part 2 Primary Estimands

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.*

For the primary estimand of incidence of AEs, see Section 2.1.1.

2.2. Study 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:

- *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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Part 1 Primary Endpoints

- *First cycle DLTs.*
- *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.*
- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.*

3.2. Part 1 Secondary Endpoints

- *PK parameters of PF-07265028:*
  - *SD: C_{max}, T_{max}, AUC_{last}, AUC_{tau}, and as data permit, $t_{1/2}$, AUC_{inf}, CL/F, and V_z/F.*
  - *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} ($AUC_{tau,ss}/AUC_{tau,\ sd}$).*
  - *For food effect subset only: PK parameters of PF-07265028 (including C_{max}, T_{max}, AUC_{tau}, AUC_{last}) under fasted and fed conditions*
- *PK of sasanlimab:*
  - *C_{min} in selected cycles.*
- *Incidence and titers of ADA and NAb against sasanlimab.*
- *OR, as assessed using the RECIST version 1.1 and irRECIST and proportion of participants with PR and irPR, as appropriate.*

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3.4. Part 2 Primary Endpoints

- *OR, as assessed using the RECIST version 1.1 and irRECIST.*
- *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.*
- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.*

3.5. Part 2 Secondary Endpoint(s)

- *Time-to-event endpoints: eg, DoR, PFS, OS.*
- *PK parameters of PF-07265028 (ie, $C_{ss,max}$ and $C_{ss,min}$) and sasanlimab (ie, C_{min} in selected cycles).*
- *For food effect subset only: PK parameters of PF-07265028 (including C_{max}, T_{max}, AUC_{tau}, AUC_{last}) under fasted and fed conditions.*
- *Incidence and titers of ADA and NAb against sasanlimab.*

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3.7. Baseline Variables

Baseline characteristics will be collected according to Schedule of Activities as specified in the protocol. No baseline variable will be used for stratification or as covariates for the primary statistical analysis. Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, starting the study intervention administration in the first cycle.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population.

Table 1. Analysis Sets

Participant Analysis Set	Description
Full Analysis Set (FAS)	*All enrolled participants who have been assigned to treatment. Participants are analyzed according to the treatment they were assigned .*
Safety Analysis Set (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.*

Table 1. Analysis Sets

Participant Analysis Set	Description
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.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There will be no formal hypothesis testing in this study.

Decision Rules for Part 1 Dose Escalation:

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.

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]*

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%.

Weakly informative prior distributions based on preclinical/expert opinion information will be chosen for the logistic parameters, see Protocol *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.

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 Protocol *Appendix 11 Section 10.11.*

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.*

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.

Decision Rules for Part 2 Dose Expansion:

The main objective is to evaluate the RDE for PF-07265028 in combination with sasanlimab for safety and preliminary efficacy. Summary statistics will be provided for safety and efficacy endpoints, without formal hypothesis testing.

Sample Size Consideration:

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.

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.

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.

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5.2. General Methods

Whilst every effort has been made to pre-specify all analyses in this statistical analysis plan, CCI [redacted], the analyses and the reasons for them will be detailed in the clinical study report (CSR).

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration in the first cycle. All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the case report form (CRF).

The data will be summarized by dose level, defined by the initial dose of the study intervention administered to participants. If a dose level has more than 1 cohort, data from these cohorts will be combined. DLT rates at the study dose levels will be presented via mean and medians and a Bayesian credible interval based on the posterior density from the full probability model. This information will also be used for the dose level review meetings (DLRM) to guide the dose escalation.

For Part 1A and Part 1B, when there are multiple dose levels, in addition to data presentation by dose level, the overall summary combining all dose levels may also be presented.

5.2.1. Analyses for Binary Endpoints

Binary data will be summarized using number of unique participant incidence, proportion in the analysis set, and the 2-sided 95% exact confidence interval for the proportions. The confidence interval will be based on the Clopper-Pearson exact method.

Binary data in this study include complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and objective response rate (ORR), based on RECIST 1.1 and irRECIST.

5.2.2. Analyses for Continuous Endpoints

Continuous data will be summarized with the mean, median, minimum, maximum, standard deviation, and 2-sided 95% confidence interval of the mean if the sample size permits and deemed necessary.

Continuous data in this study include, but not limited to, certain laboratory measurements, vital signs, ECG, certain PK parameters or biomarkers.

5.2.3. Analyses for Categorical Endpoints

Categorical data will be summarized by number of unique participant incidence and proportion of participant in each category, and 2-sided 95% confidence interval of the proportion if the sample size permits and deemed necessary.

An example of categorical data presentation is adverse events or laboratory abnormalities graded by NCI CTCAE v5.0, where each grade is considered as a category.

5.2.4. Analyses for Time-to-Event Endpoints

The time-to-event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves may be displayed graphically when needed. Graphs will describe the number of participants at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method, when possible based on the number of observed events. Confidence intervals for medians and quartiles, based on the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982), may be presented. Confidence intervals for the estimated probability of an event at a particular time point may be generated using the Greenwood formula.

Time to event endpoints include duration of response(DoR), progression-free survival (PFS), and overall survival (OS) when the event numbers are sufficient for reasonable interpretation.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied based on the Safety Rulebook.

5.3.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of onset cannot be prior to day one date). In this case, the date resulting in 0 time duration will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration). This excludes the pharmacokinetic and ECG analyses, which will only use the actual date collected or if date not available deem the data missing.

5.3.2. Efficacy Analysis

For tumor assessment that will be used in the binary efficacy endpoint, every effort will be made to retrieve data in the CRF, however missing data will be left as is, no imputation will be performed. The reasons for missing tumor assessment will be collected

For the time-to-event endpoints, the missing data handling method will be censoring. Censoring rules for time-to-event endpoints are detailed in Section 6.2.2.

5.3.3. Pharmacokinetics

5.3.3.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ (i.e. lower limit of quantification) will be replaced with the value for the LLQ.)

5.3.3.2. Deviations, Missing Concentrations and Anomalous Values

Participants who experience events that may affect their PK (eg, incomplete dosing) may be excluded from the PK analysis.

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (i.e., not done) or NS (i.e., no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other subjects. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

5.3.4. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (i.e., not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues.)

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter (due for example to dosing error), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.5. Pharmacodynamic Parameters

Missing data for the pharmacodynamic parameters will be treated as such and no imputed values will be derived.

5.3.6. QTc

For the corrected QT (QTc) analyses, no values will be imputed for missing data.

5.4. Statistical Considerations of COVID-19 Impacted Data

In March 2020, the World Health Organization (WHO) announced a global pandemic of the virus SARS-CoV-2 and the resulting disease COVID-19. During the conduct of this trial, if any participant's data is impacted by this pandemic, the following considerations will be given in the data analyses:

a. If a participant dropped out of the study during the DLT evaluation window in Parts 1A and 1B due to COVID-19, a replacement participant may be added.

b. Death caused by COVID-19 is still considered as an "event" in the analysis of PFS (Parts 1 and 2) and OS (Part 2). If deemed necessary, a sensitivity analysis may be performed where COVID-19 driven death is censored at the death date.

c. If a scheduled tumor radiographic scan is *delayed* out of the Schedule of Activity allowable window, or is *missing* (i.e. participant skipped a scheduled tumor radiographic scan) due to any reasons related to the pandemic, this delay or missingness does not alter the censoring rules for PFS or TTP as described in Section 6.2.2. A censoring reason of "COVID-19" may be added to the PFS or TTP summary if the specific reason of tumor scan delay or missing can be attributed to COVID-19. If deemed necessary, a sensitivity analysis may be performed where participants would be censored on the date of COVID-19 diagnosis.

   In the confirmed ORR analysis, as described in Section 6.2.2, if a response can't be confirmed by a subsequent tumor scan because of the pandemic (i.e. the subsequent tumor scan wasn't performed), then the initial response will be considered as

unconfirmed. This is a conservative approach. No sensitivity analysis will be performed.

d. Any COVID-19 related symptoms are to be captured as adverse events in the case report form. Those adverse events will be summarized in the same manner as other adverse events. If a label or phrase of COVID-19 can be identified in the investigator provided adverse event term, then a separate AE listing may be provided for just the COVID-19 related events.

e. If identifiable, the COVID-19 related data points, including missing data where the reason of missing is identified as COVID-19 related (site closure hence data could not captured; participants skipped a visit because of concern over the pandemic), protocol deviations driven by COVID-19, safety events caused by COVID-19 may be separately listed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints for Part 1

6.1.1. Dose-Limiting Toxicities (DLTs)

- Analysis set: Per protocol analysis set.

- Analysis methodology:

  For the purpose of dose escalation, the DLT observation period will be during the first cycle (28 days after the start of study treatment), or DLT window, in each participant. According to the design, cohort sizes are planned to be approximately 3, but it is required to have at least 2 DLT-evaluable patients in the dosing cohorts. The participants who cross over from Part 1A monotherapy to Part 1B combination therapy will be excluded from the DLT assessment in Part 1B.

  Whether an adverse event a participant experienced during the DLT window is determined as a DLT or not is based on the DLT definitions provided in Section 4.3.3 of the protocol. A DLT yes/no checkbox will be provided in the case report form, where the investigator provides his/her judgement if an event is a DLT or not. However, the final determination will be reached between the investigators and the sponsor during the dose level review meeting (DLRM). These final decisions will be documented.

  The DLT events will be summarized by dose level. A listing of the DLTs events will also be provided in which the participant primary diagnosis (malignancy), dose level the participant was enrolled to, DLT event start day and stop day relative to the cycle 1 day 1 dose date, the DLT event term, NCI CTCAE grade, relatedness to the investigational product (PF-07265028), or sasanlimab (Part 1B), outcome of the event, along with other variables deemed important, will be included.

- Missing data: All enrolled participants in Part 1 should have an indicator variable derived to be either 1 (yes) or 0 (no) based on the DLT definitions and participant's

safety data during the DLT observation window. If a participant fails to have a value on the indicator variable because the participant being non-DLT-evaluable, the participant may be replaced.

6.1.2. Adverse Events

- Analysis set: Safety analysis set.
- Analysis methodology:

  Adverse Events (AEs) will be graded by the investigator according to NCI CTCAE version 5.0 and coded using the MedDRA. The focus of AE summaries will be on Treatment Emergent Adverse Events (TEAEs). TEAE is defined as any adverse event that occurs during the on-treatment period, on or after the first dose of study treatment, and before the last dose of study treatment + 28 days, or the start of any other anti-cancer therapy, whichever is earlier. AEs that occurs after the on-treatment period may still be recorded in the clinical database and will be included in the AE listings, but will not be included in the AE summaries.

  The number and percentage of participants who experienced any AE, serious AE (SAE), treatment related AE (i.e. related to any of the study treatment PF-07265028, or sasanlimab), and treatment related SAE will be summarized by system organ class (SOC) and preferred terms (PT) according to worst toxicity grades. The summaries will present AEs for the entire on-treatment period and for the various parts of the study (by dose level for Parts 1A and 1B, by arm for Part 2), and will not be presented by treatment cycle. In the summary tables for Parts 1A and 1B, a "Total" column, summarizing data across all dose levels, will be presented. Additionally summaries of adverse events leading to death and premature withdrawal from study treatment will be provided.

- Missing data: If AE start or stop date is missing, impution will be performed according to Section 5.3. The imputed dates will be used to determine whether the AE is to be included in the TEAE summary. The missing AE start or stop dates will be listed as is in AE listings. When the CTCAE grade is missing for an AE, the AE will be excluded from the CTCAE grade summary table.

6.1.3. Laboratory abnormalities

- Analysis set: Safety analysis set.
- Analysis methodology:

  Laboratory tests in this study include several panels: hematology, chemistry, serology, coagulation, urinalysis, and pregnancy test.

  The frequency and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade (based on NCI CTCAE version 5.0) observed for each laboratory assay. Summaries of laboratory

tests results by visit may be provided. Summaries for change from baseline and percent change from baseline for the laboratory tests may be provided, if deemed necessary. Shift tables may be provided for selected laboratory tests.

The summaries will be presented for the entire on-treatment period and for the various parts of the study (by dose level for Parts 1A and 1B, by arm for Part 2), and will not be presented by treatment cycle.

Hematology, serology, and coagulation lab results can be combined into one summary output. Separate summaries will be created for chemistry tests. Urinalysis and pregnancy tests will not be summarized and will only be listed in data listings. Shift tables may be provided for selected laboratory tests.

- Missing data: Intermediate missing values (ie, values collected between baseline and the last study measurement) will not be imputed.

6.1.4. Vital Sign Abnormalities

Vital signs including temperature, pulse rate, respiratory rate, and blood pressure, will be assessed.

- Analysis set: Safety analysis set.
- Analysis methodology:

  The vital signs will be generally considered as continuous endpoints. However the summaries of vital signs as continuous variables will not be provided as they may not be clinically meaningful. Instead, vital signs during the on-treatment period will be summzried by the categories of abnormality as specified in Appendix 1. Shift tables will not be provided unless deemed necessary.

- Missing data: Intermediate missing values (ie, values collected between baseline and the last study measurement) will not be imputed.

6.1.5. Heart rate corrected QT interval

- Analysis set: Safety analysis set.
- Analysis methodology:

  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 (Table 2) *will be tabulated by treatment:*

Table 2. 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. Additional analysis may be performed if needed.

- Missing data: Intermediate missing values (ie, values collected between baseline and the last study measurement) will not be imputed.

6.2. Secondary Endpoints for Part 1

6.2.1. Pharmacokinetic Analysis

6.2.1.1. PK Parameter Analysis

- Analysis set: PK Parameter Set

- Analysis methodology:

In Part 1, following single dose administration of PF-07265028, plasma PK parameters including the C_{max}, T_{max}, AUC_{last}, $AUC_{tau,sd}$ 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 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) 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.

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.

- Missing data: missing parameter data will be handled according to Section 5.3.4.

6.2.1.2. PK Concentration Analysis

- Analysis set: PK Concentration Set
- Analysis methodology:

Presentations for plasma PF-07265028 and serum sasanlimab will include:

- A listing of all concentrations sorted by dose, subject ID, cycle, and nominal time post-dose. The listing of concentrations will include the actual sample collection times, and the time of dosing. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by dose, cycle, and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- Plots of median concentrations against nominal time post-dose by dose (based on the summary of concentrations by dose, cycle, and time post-dose), with all doses presented on the same plot. Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.
- Plots of geometric mean concentrations against nominal time post-dose by dose (based on the summary of concentrations by dose, cycle, and time post-dose), with all doses presented on the same plot. Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.
- Plots of individual concentrations against actual time post-dose (separate plots for each dose). Two plots per dose will be generated, so that the concentrations can be presented on linear and logarithmic scales.
- Plots of concentration against actual time post-dose by subject (separate line for each dose). Two plots per subject will be generated, so that the concentrations can be presented on linear and logarithmic scales.

For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used. Exclusions or separate summaries for dose modifications and concomitant medications may be considered in data summaries.

- Missing data: missing concentration and BLQ values will be handled according to Section 5.3.3.

6.2.2. Immunogenicity Analysis

- Analysis set: Immunogenicity Analysis Set.
- Analysis methodology:

  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.*

- Missing data: no imputed values will be derived.

6.2.3. Objective Response

In Part 1, objective response per RECIST 1.1 and irRECIST is a secondary endpoint. The proportion of participants with PR and irPR, as appropriate, will be derived.

- Analysis sets: Safety analysis set and response evaluable set, respectively.
- Analysis methodology:

  Both confirmed ORR and unconfirmed ORR (uORR) will be determined based on the confirmed and unconfirmed CR and PR. ORR will be based on the best overall response (BOR) of a participarnt, according to RECIST 1.1 and irRECIST. In the BOR derivation, the minimu duration of SD as the best overall response is set as 5 weeks.

  Unconfirmed CR (uCR) is defined as one objective status of CR documented before PD, while confirmed CR requires two objective statuses of CR a minimum of four weeks apart documented before PD. Sequences of CR - Non-evaluable - CR are considered confirmed CR as long as the two CR responses are observed at a minimum of 4 weeks apart. Simillarly, unconfirmed PR (uPR) is defined as one objective status of PR documented before PD but not qualifying as uCR. Confirmed PR is defined as two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of four weeks apart documented before PD, but not qualifying as CR. Sequences of PR - Stable Disease or Non-evaluable - PR are considered PRs as long as the two PR responses are observed at a minimum of 4 weeks apart. Based on these definitions, the unconfirmed ORR analysis will include both confirmed CR or PR and unconfirmed CR or PR as responders, whereas the confirmed ORR analysis will only include confirmed CR or PR as responders.

  Consider there may be some participans who cross over from Part 1A monotherapy to Part 1B combination therapy, two methods will be used for Part 1 ORR calculation. The primay one will only include (censor) the tumor response data by the cross over

date for those participants. The additional analysis will combine the participant who cross over from monotherapy to combination therapy with Part 1B participants for ORR calculation, in which only the tumor response data after the cross over date will be considered for the evaluation of best overall response. The re-baseline method may be considered if needed.

ORR and its 95% exact confidence interval as described in Section 5.2.1 will be presented for each dose level and the total across all dose levels.

Tumor response will be presented in the form of participants data listings that include, but are not limited to: tumor type, actual received day 1 dose, tumor response at each assessment, and best overall response. Progression date, death date, date of first response, last assessment date, and date of last contact will also be listed.

- Additionally, a swimmer plot will be provided to display tumor response overtime and a waterfall plot displaying the best percentage change in tumor size will be provided.Missing data: missing tumor data will not be imputed.

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6.3. Exploratory and Other Endpoints for Part 1

6.3.1. Physical Examination

Participants will have physical examinations according to the study protocol. The physical examinations may include weight, vital signs, assessment of ECOG performance status and height, assessments of the cardiovascular, respiratory and gastrointestinal systems, skin, lungs etc. Physical examination generally will not be summarized or listed except vital signs or ECG. Any change from baseline considered by the investigation to be clinically significant should be recorded as an adverse event in the CRF, thus will be analyzed in the adverse events data.

6.3.2. Concomitant Medications and Nondrug Treatments

Concomitant, and further therapies (drug and non-drug treatments) will be coded by the World Health Organization (WHO) medical dictionary. This data will not be summarized. Data listings of concomitant medications and further therapies may be provided.

6.3.3. Exploratory Endpoints

For the tertiary and exploratory endpoints as described in Protocol *Section 3, summary statistics will be presented. Results from tertiary/exploratory analyses will be reported in the CSR where possible. However, given the exploratory nature of exploratory objectives and endpoints, the analyses may not be complete at the time of the CSR. Results from exploratory analyses that are not included in the CSR are expected to be shared with the scientific*

community through publication at a scientific conference and/or in a peer-reviewed scientific journal.

Detailed methodology for summary and statistical analyses of exploratory endpoints in this study will be further detailed in a biomarker statistical analysis plan (bSAP), which will be maintained by the sponsor.

6.4. Primary Endpoints for Part 2

6.4.1. Objective Response

OR is considered as a primary endpoint in Part 2. This endpoint in Part 2 will be analyzed in the same manner as described in Section 6.2.3.

6.4.2. Safety Endpoints

Adverse events, laboratory tests, vital signs, and ECG including heart rate corrected QT interval are the safety primary endpoints for Part 2. The analysis set, analysis methodology will be same as described in Section 6.1.

6.5. Secondary Endpoints for Part 2

6.5.1. Efficacy Endpoints

The secondary efficacy endpoints for Part 2 include multiple time-to-event endpoints such as DoR, PFS and OS.

- Progression-Free Survival (PFS): PFS will be summarized using the Kaplan-Meier method, as described in Section 5.2.4. And PFS may also be displayed graphically when appropriate.

  Participants without an event or with an event after 2 or more inadequate or missing tumor assessments will be censored on the date of the last adequate tumor assessment that documented no progression; deaths within 17 weeks after the first dose date for participants who did not initiate new anti-cancer therapy will still be considered an event. If a new anti-cancer therapy is started prior to an event, the participant will be censored on the date of the last adequate tumor assessment that documented no progression prior to the start of the new anti-cancer therapy.

  Participants with no baseline tumor assessment (including participants with an inadequate baseline assessment) or with no adequate post-baseline tumor assessments within 17 weeks after the first dose date will be censored on the first dose date, unless the participant dies within 17 weeks of the first dose date, in which case, death will be an event on date of death.

  PFS outcome and censoring rules are summaries in Table 3. Any additional censoring rules that may affect data analysis will be documented in the Analysis Programming Specification (a separate document).

  Any tumor scan or response data impacted by COVID-19 will be handled according to Section 5.4.

Table 3. PFS and TTP Censoring Rules

Situation	Date of Event/Censoring	Outcome
No adequate baseline assessment	First dose date	Censored [a]
PD or death - after at most one missing or inadequate post-baseline tumor assessment, or - ≤ 17 weeks after the first dose date	Date of PD or death	Event
PD or death - after 2 or more missing or inadequate tumor assessments	Date of last adequate tumor assessment [b] documenting no PD prior to new anti-cancer therapy or missed tumor assessments	Censored
No PD		
New anti-cancer therapy given prior to PD or death		

a If the participant dies ≤17 weeks after the first dose date and did not initiate new anti-cancer therapy, the death is an event with date on death date.

b If there are no adequate post-baseline tumor assessments prior to the PD or death, then the time without adequate assessment should be measured from the first dose date; if the criteria were met the censoring will be on the first dose date.

- Duration of Response (DoR): DoR is defined as the time from first documentation of CR or PR to date of first documentation of PD or death due to any cause. The responders who have not disease progressed at the time of analysis will be censored at the last available tumor scan date. Both confirmed DoR and unconfirmed DoR (uDOR) will be determined separately for the subset of participants with a confirmed and unconfirmed objective response of CR or PR.

  If there is a relatively large number of objective response, DoR may be analyzed using the Kaplan-Meier approach. The outcome, event dates and reasons for censoring for DoR will be the same as for those in the analysis of PFS except that participants will not be censored for inadequate baseline assessment or for no adequate post-baseline assessment, as only participants with an objective response are included in the analysis.

- Overall Survival (OS): OS will be analyzed with the Kaplan-Meier approach. Participants last known to be alive are censored at date of last contact. The date of last contact will be derived for participants not known to have died at the analysis data cutoff date using the latest complete date (non-imputed) among AE collection date, vital sign date, tumor assessment date, date of follow up anti-cancer therpay etc. This is not an exclusive list of possible dates. Any retrievable last contact date from the clinical database will be used.

- Missing data: For time-to-event endpoints, missing data will be handled by the censoring rules and no imputation will be performed.

6.5.2. Pharmacokinetic Analysis

Pharmacokinetic analysis for Part 2 will be carried out in the same manner as described in Section 6.2.1

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6.7. Subset Analyses

There are no planned subset analyses.

6.8. Baseline and Other Summaries and Analyses

6.8.1. Baseline Summaries

Baseline characteristics will be summarized and/or listed in participant level data listings:

- Demographics: will be summarized by dose level (Part 1) and overall across all dose levels, or by arm (Part 2). This will be based on the Full analysis set. Demographic data will also be listed in a data listing.
- Primary diagnosis: will be listed for all enrolled participants.
- Baseline signs and symptoms: will be summarized by dose level (Part 1) or by arm (Part 2) using the full analysis set. This data will also be listed for all enrolled participants.
- ECOG performance status: will be summarized by dose level (Part 1) or by arm (Part 2) using the full analysis set.

Prior medication, medical history, physical examinations will not be summarized or listed, unless it's deemed necessary.

6.8.2. Study Conduct and Participant Disposition

An accounting of the study participants will be tabulated. The participant dose level cohort will be listed. The Full Analysis Set will be used.

Participant discontinuation from treatment and study will be tabulated and listed for each participant separately with their reason for discontinuation. The Safety Analysis Set will be used.

6.8.3. Study Treatment Exposure

The Safety Analysis Set will be used for the anlaysis of treatment exposure.

Treamtent exposure will be assessed with the following approaches:

- Duration of Treatment (DOT): defined as the last active dose date minus the first active dose date + 1. DOT will be summarized, as a continuous variable, by dose level for Part 1 and overall across all dose levels; or by arm for Part 2. DOT may also be categorized into different intervals (≥ 1 cycle; ≥ 2 cycles; ≥ 3 cycles etc.). Frequency and percentage of participants for each interval may be descriptively summarized by dose level for Part 1 and overall across all dose levels; or by arm for Part 2. DOT, when it is derived at participant level, will be derived for PF-07265028 and sasanlimab separately.

- Treatment Compliance: defined as the proportion of cumulative actually taken dose over the cumulative planned dose for cycle 1 (for the purpose of defining the per-protocol population for the MTD evaluation) and over the entire treatment period (i.e. between the first active dose date and the last active dose date). Treatment compliance will be calculated for PF-07265028 and sasanlimab separately.

- Dose interruption will be listed, reasons for dose interruption (e.g. AE), if available, will be included in the listing. Dose interruption is defined as a situation when the actual dose was adjusted from the planned dose (as collected in the case report form).

- Listing by participant level of dosing administration data: cycle number, start date and stop date of dosing period within each cycle (including records with 0 mg), total daily dose received for each dosing period, any missed doses with unknown dates (yes/no), number of missed doses with unknown dates, reason for any dosing changes, total planned dose, total actual dose received, percentage of planned dose, dose reduction (yes/no), and dose interruption (yes/no).

7. INTERIM ANALYSES

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

8. REFERENCES

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9. APPENDICES

9.1. Appendix 1: Categorical Classes for ECG and Vital Signs

Clinically Relevant Categories for QTcF

QTcF (msec)	max. ≤450	450< max. ≤480	480< max. ≤500	max. >500
QTcF (msec) increase from baseline	30≤ max. <60	max. ≥60		

Clinically Relevant Categories for Pulse Rate and QRS

Pulse Rate (msec)	max. ≥300	
Pulse Rate (msec) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (msec)	max. ≥200	
QRS (msec) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Clinically Relevant Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	≥160 max.
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	≥100 max.
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfil these criteria are to be listed in the study report.