Protocol C4431001

A PHASE 1 DOSE ESCALATION AND EXPANSION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETIC, PHARMACODYNAMIC, AND ANTI-TUMOR ACTIVITY OF PF-07260437 IN ADVANCED OR METASTATIC SOLID TUMORS

Statistical Analysis Plan
(SAP)

Version: 1

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1. VERSION HISTORY

This is the first version.

2. INTRODUCTION

PF-07260437 is a T cell redirecting B7-H4 x CD3 bispecific mAb with 2 binding domains: a domain that recognizes tumor antigen B7-H4 with high affinity and a domain that recognizes CCI, expressed on T cells, with moderate affinity. Co-engagement of B7-H4 on tumor cells and CCI on T cells leads to a tumor-localized T-cell cytotoxic response and reduces systemic CCI targeting and toxicity. This mechanism circumvents the need for T cells to recognize specific antigenic peptides in the context of CCI on malignant cells. Cytotoxicity is mediated by release and transfer of CCI from the T cell to the B7-H4 expressing target cell. PF-07260437 addresses a significant unmet medical need for BrCa, as its target is expressed in the majority of BrCas across all molecular subtypes.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study PF-07260437. This document provides additional details for the planned analyses that are outlined in the protocol. This SAP was written in reference to the protocol dated June 23, 2021. Any major modifications of the endpoints or analyses will be reflected in further amendments to the protocol and SAP.

2.1. Study Objectives, Endpoints and Estimands

2.1.1 Primary Estimand(s)

Primary Estimand (DLT) for Part 1:

DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period (28 days for regimen without priming; 42 days for the regimen with priming (priming doses plus 2 full doses)) in Part 1.

Variable: Occurrence of DLTs.

Analysis population:

For the dose escalation without priming, DLT-evaluable participants defined as participants:

- who receive at least 1 dose of study treatment and experience DLT during the DLT-evaluation period (28 days),

OR

- who complete the DLT-evaluation period without DLT. Participants without DLTs who withdraw from study treatment before receiving at least 2 full doses of study drug for reasons other than treatment-related toxicity are not evaluable for DLT.

For the dose escalation with priming, DLT-evaluable participants defined as participants:

- who receive at least 1 dose of study treatment and experience DLT during the DLT-evaluation period (priming doses plus 2 full doses, eg, 42 days),

OR

- who complete the DLT-evaluation period without DLT. Participants without DLTs who withdraw from study treatment before receiving at least the priming dose and 2 full doses of study drug for reasons other than treatment-related toxicity are not evaluable for DLT.

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.

Primary Estimand for Parts 1 and 2:

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.

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), timing, seriousness, and relationship to treatment.

2.2. Study Design

This is an open label, multi-center, first-in-human Phase 1 dose escalation and dose expansion study to evaluate the safety, tolerability, PK, PD, and preliminary antitumor activity of PF-07260437, a B7-H4 x CD3 bispecific mAb in advanced or metastatic selected solid tumors (BrCa, OvCa and endometrial cancer). This study contains 2 parts, dose escalation (Part 1) and dose expansion (Part 2).

Part 1 contains dose escalation in participants with locally advanced or metastatic BrCa, OvCa or endometrial cancer that is resistant or intolerant to standard therapy or for whom no standard therapy is available, to determine the MTD and select the RDE. Participants with other advanced or metastatic high B7-H4 expressing tumors may be considered after discussion with and approval from sponsor.

Once the PF-07260437 monotherapy RDE is selected, either with or without priming, Part 2 dose expansion cohorts may be initiated to further evaluate the safety and preliminary antitumor activity of PF-07260437 monotherapy in advanced or metastatic 2L+ HR+ HER2- BrCa with high B7-H4 expression (Part 2A) and 2L+ TNBC with high B7-H4 expression (Part 2C) as well as unselected HR+ HER2- BrCa or TNBC (Part 2B).

Part 1 Dose Escalation

Participants will receive escalating doses of PF-07260437 administered as SC injection with a starting dose level of 100 µg Q2W as monotherapy. Additional dosing frequency such as Q1W or Q3W may be considered if supported by emerging clinical PK, PD, and safety data. BLRM guided by EWOC principle will be used to guide the dose escalation process and determine the MTD/RDE. The maximum allowable PF-07260437 dose increment is 200% (dose tripling from the previous dose level) for cohorts but will be adjusted to no more than 100% (dose doubling from the previous dose level) following the observation of a DLT or if there are two Grade ≥2 clinically significant treatment-related AEs. For monotherapy without priming strategy, DLT will be assessed during the first 28 days. For monotherapy with priming, the DLT assessment period will extend to include priming doses plus 2 full doses (eg, first 42 days). Each dose level group will include approximately 3 participants, with at least 1 DLT evaluable participant per cohort in the first 2 cohorts and at least 2 DLT evaluable participants per dose level group in the remaining cohorts for Part 1. Per BLRM design, expanding additional participants at lower dose levels are allowed to assess safety. Dose escalation cohorts may be switched from SC administration to IV administration if SC administration is not considered as the preferred route due to severe skin toxicities, low PK exposure or other reasons. IV administration cohorts may initiate at a dose level that is no greater than 20% of the highest SC dose level that is deemed tolerable (eg, starting at 60 µg IV Q2W if 300 µg SC Q2W is deemed tolerable) depending on emerging PK and safety data.

A priming dose approach in the next dose level may be initiated if a dose level induces ≥ Grade 2 CRS (lasting for >24 hours) occurs in >1 participant despite treatment with tocilizumab and/or vasopressors. If the dose escalation has reached the MTD and a priming dose has not been previously incorporated to the dose regimen, a priming dose escalation cohort to minimize C_{max} may be initiated based on clinical safety, PK/PD, and clinical efficacy.

The DLT period for SC or IV dosing without priming will be 28 days. The DLT period with priming will extend to include the duration of the priming doses and 2 full doses after priming (eg, if a priming dose is given on Day 1 and the first full dose on Day 15, the total DLT observation period will be 42 days). A traditional 2-parameter BLRM will be used to model the DLT relationship to the drug and inform dose escalation with or without priming. The maximum dose level increase will be 200% (dose tripling from the previous dose level).

Part 2 Dose Expansion

The Part 2 dose expansion phase will enroll participants into 3 cohorts detailed as follows:

- **Part 2A (N=20):** PF-07260437 as monotherapy in participants with HR+ HER2- BrCa showing high B7-H4 expression, 2L+ who have progressed after at least 1 line of standard of care CDK4/6 inhibitor and 1 line of standard of care endocrine treatment. De novo paired pre- and on-treatment biopsies are mandatory for 5 participants.
- **Part 2B (N=20):** PF-07260437 as monotherapy in participants with HR+ HER2- BrCa, 2L+ who have progressed after at least 1 line of standard of care CDK4/6 inhibitor and 1 line of standard of care endocrine treatment, or 2L+ TNBC who have progressed after at least 1 line of SOC systemic therapy (eg 1L chemotherapy in combination with an immune checkpoint inhibitor if PD-L1+ or chemotherapy alone if PD-L1 negative/low). Approximately 10 HR+ HER2- BrCa and approximately 10 TNBC participants should be enrolled. De novo paired pre- and on-treatment biopsies are mandatory for approximately 5 HR+ HER2- BrCa participants and 5 TNBC participants. No biomarker selection based on B7-H4 expression.
- **Part 2C (N=20):** PF-07260437 as monotherapy in participants with TNBC showing high B7-H4 expression, 2L+ who have progressed after at least 1 line of SOC systemic therapy (eg, 1L chemotherapy in combination with an immune checkpoint inhibitor if PD-L1 positive or chemotherapy alone if PD-L1 negative/low). De novo paired pre- and on-treatment biopsies will be mandatory for 5 participants.

Depending on the results of preclinical combination in vivo efficacy data, emerging clinical monotherapy safety and efficacy, PF-07260437 combination cohorts may be added, including combination with CDK4/6 inhibitor and/or endocrine therapies in HR+ HER2- BrCa and combination with checkpoint inhibitors in TNBC.

All participants will undergo up to 28 days of screening prior to first dose. Eligible participants will then receive study intervention for up to 2 years, or until disease progression defined by irRECIST, unacceptable toxicities, a decision by the participant (withdrawal of consent or no longer willing to participate) or investigator to discontinue treatment, or study termination. Note: If a participant is classified as having PD during an on-treatment tumor assessment, then confirmation of PD by a second scan in the absence of rapid clinical deterioration is required per irRECIST.

Number of Participants

Total number of participants for Part 1 and Part 2 combined, is estimated to be approximately 100.

Approximately 35 participants are expected to be enrolled into 1 of 5-7 sequential dose levels in Part 1 including at least 6 participants treated at the MTD. The actual number of participants enrolled will depend on the tolerability of PF-07260437 and the number of dose levels that are required to determine MTD/RDE.

Approximately 60 participants are expected to be enrolled into 3 cohorts in Part 2: Part 2A, Part 2B and Part 2C, with approximately n=20 participants in each cohort. Twenty participants for each cohort is clinically sufficient to evaluate safety signals.

Intervention Groups and Duration

The total duration of the study from the beginning of screening to the safety follow-up visit is approximately 2 years.

Safety Review Committee

This study will use an SRC. The SRC will be comprised of participating investigators or their medically qualified designee(s) who have at least 1 participant enrolled in the study and the Pfizer medical monitor or designee. The SRC members will have voting rights for dose escalation decisions.

Statistical Methods

There is no formal hypothesis testing in this study.

Unless otherwise specified, summaries will be presented by dose group and overall. Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints. The rates of binary endpoints will be provided along with the corresponding 2-sided 95% CIs using an exact method. Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% CIs for each time-to-event endpoint will be provided.

The dose escalation in Part 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07260437. Dose toxicity is modelled using 2-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose.

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07260437 will be evaluated separately for cohorts with and without priming, taking into account the different DLT observation periods (28 days for the regimen without priming; priming doses plus 2 full doses for the regimen with priming). The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

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

Dosing decisions are guided by the EWOC principal (Rogatko et al, 2007). A dose may only be used for newly enrolled participants if the risk of overdosing at that dose is less than 25%.

Recommendation from the BLRM, along with safety (AEs, SAEs), laboratory, PK, biomarker, and other relevant data, will be used at the time of each dose escalation and for MTD/RDE determination.

A weakly informative prior was used as there were no relevant human historical DLT data available.. For details, please see C4431001 Technical Supplement to Appendix 10.9.

For Part 2, the expansion arms will be conducted to assess efficacy as well as safety and tolerability of PF-07260437.

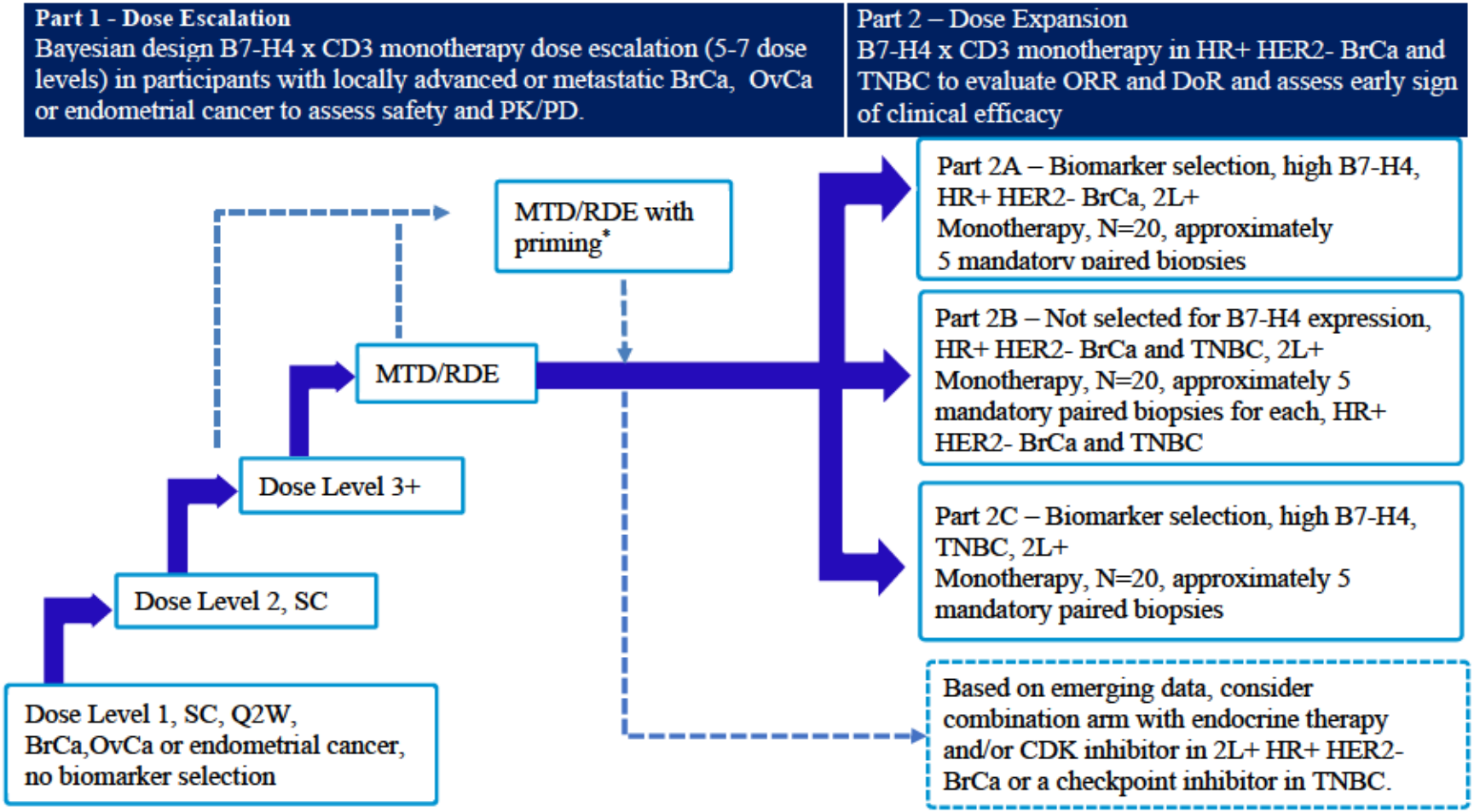
In Part 2, the secondary endpoint of overall response by RECIST version 1.1 and by irRECIST will be summarized and listed by expansion cohort and disease type. The secondary endpoints of DOR (RECIST version 1.1, irRECIST) , PFS (RECIST version 1.1, irRECIST), TTP (RECIST version 1.1, irRECIST), and OS will be summarized (graphically where appropriate) and listed by expansion cohort and disease type.

AEs will be graded by the investigator according to the NCI CTCAE version 5.0 and coded using the MedDRA. 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 on the entire study period.

2.3. Schema

A diagram of the study design is displayed in
Figure 1.

Figure 1. Study Schema



* A priming dose escalation may be initiated if criteria is met.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1 PRIMARY ENDPOINT(S)

Part 1

Determination of MTD will be performed using Per-protocol analysis set (evaluable for MTD). The dose escalation in Part 1 of the study will be guided by a Bayesian analysis of DLT data for PF-07260437. Dose toxicity is modelled using 2-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose for the monotherapy and using BLRM model specifically developed for combinations separately for regimens with and without priming. A weakly informative prior distribution based on nonclinical/expert opinion information will be used to define the prior distribution for the PF-07260437 monotherapy dose escalation.

Dosing decisions are guided by the EWOC principal (Rogatko et al, 2007). A dose may only be used for newly enrolled participants if the risk of overdosing at that dose is less than 25%.

Recommendation from the BLRM, along with safety (AEs, SAEs), laboratory, PK, biomarker, and other relevant data, will be used at the time of each dose escalation and for MTD/RDE determination.

Prior distributions:

Weakly informative prior distributions based on pre-clinical/expert opinion information will be chosen for the logistic parameters for prior distribution in Part 1.

A MAP approach will be used to derive the prior distribution for model parameters used in Part 1 with priming based on the data collected in Part 1 without priming. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data (Neuenschwander et al, 2010; Schmidli et al, 2014). MAP priors are derived from hierarchical models, which take into account possible differences between the studies.

Starting dose:

The starting dose for the monotherapy PF-07260437 is SC injection 100 µg Q2W. This dose satisfies the EWOC criterion.

Stopping criteria:

The sponsor estimates that the maximum number of participants in the Part 1 dose escalation portion of the trial is 40 participants. However, the actual number may be more or less based on observed PK and safety. The dose escalation will stop when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD or RDE.
- The dose d for PF-07260437 satisfies 1 of the following conditions for the mono-escalation part:

- The probability of target toxicity at dose d exceeds 50%, ie, Pr (0.16 $\leq \pi d < 0.33$) $\geq$50%, or
- A minimum of 15 participants have been treated in Part 1.

Part 1 and Part 2

Incidence of AEs estimated in the safety 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 Section 8.3.
- **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), timing, seriousness, and relationship to treatment.

3.2 Secondary Endpoint(s)

Part 1 and Part 2

irAEs

irAEs as characterized by type, frequency, severity (as graded by NCI CTCAE v5) timing, seriousness, and relationship to study therapy.

Single-Dose and Steady-State PF-07260437 Pharmacokinetic Analysis

Serum concentrations of PF-07260437 will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and its associated coefficient of variation) by dose, cycle, day, and nominal time.

Individual participant serum concentration-time data within a dose interval after Cycle 1 Day 1 and Cycle 2 Day 1 will be analyzed using noncompartmental methods to determine single and multiple dose PK parameters.

Single dose PK parameters to be estimated will include the serum C_{max}, T_{max} and AUC_{last}, and as data permit, AUC from time 0 extrapolated to infinity (AUC_{inf}), $t_{½}$, clearance (CL/F for SC dosing and CL for IV dosing) and volume (V_z/F for SC dosing and V_{ss} for IV dosing).

Multiple dose PK parameters to be estimated will include $C_{max,ss}$, $T_{max,ss}$, $AUC_{ss,\tau}$, $C_{min,ss}$, clearance (CL_{ss}/F for SC and CL_{ss} for IV) and as data permit, volume (V_z/F for SC or V_{ss} for IV), $t_{½}$, and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$). The single dose and steady-state PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and its associated coefficient of variation) by dose level and cycle.

Dose normalized AUC_{inf} (AUC_{τ} at steady state) and C_{max} will be plotted against dose (using a logarithmic scale) by cycle. These plots will include individual participant values and the geometric means for each dose.

Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of participants with positive ADA and neutralizing antibodies each 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.

Part 2

Efficacy Analysis

Response Evaluable Set will be used for all response-related analyses including ORR, DoR, PFS, and TTP (RECIST, irRECIST). Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, tumor response at each visit, and best overall response. OS will be reported on the Full Analysis Set as well as on the mITT.

Data will be summarized (also graphically where appropriate) and listed by expansion cohort.

3.3 Tertiary/Exploratory Endpoint(s)

Part 1

Efficacy Analysis

Response Evaluable Set will be used for ORR and PFS (RECIST, irRECIST). Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, tumor response at each visit, and best overall response.

Data will be summarized (also graphically where appropriate) and listed by dose level.

Part 1 and 2

Analysis of Pharmacodynamics

Results of exploratory endpoint analyses will be described in the CSR to the extent possible. Due to the exploratory nature of the endpoints, the associated data analyses may not be complete at the time of CSR preparation. If results of exploratory endpoint analyses cannot be included in the CSR, they will be disseminated to the scientific community to the extent possible through presentation at scientific meetings and/or publication in peer-reviewed scientific journals.

3.4 Baseline Variables

Baseline characteristics will be collected according to Schedule of Activities as specified in the protocol. For the primary analyses, no baseline variable will be used for stratification or as covariates in the 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.

Laboratory baseline will be the last predose measurement taken before the first dose of any component of the study intervention.

3.5 Safety Endpoints

The on-treatment period will be used for all safety assessments. The on-treatment period is defined as the period that starts with the first dose of study treatment and ends at minimum (last dose of study treatment + 30 days, start of new anti-cancer therapy - 1 day).

3.5.1 Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5 and coded using MedDRA. AE data will be reported in tables and listings. Summaries of AE by appropriate MedDRA terms, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death and premature withdrawal from study treatment. The number and percentage of participants who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).When a priming dose is used, the full 42 day period will be reported separately, instead of Cycle 1. Listings of DLTs and deaths will be provided.

A similar approach will be used for irAEs.

3.5.2 Laboratory Data

Details of the laboratory tests can be found in Appendix 10.2 of the protocol.

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 prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Table 1. Analysis Sets

Participant Analysis Set	Description
Full Analysis Set (FAS)	All enrolled participants.

Participant Analysis Set	Description
Safety Analysis Set (SAS)	All enrolled participants who receive at least 1 dose of study intervention. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses.
Per Protocol Analysis Set	All enrolled participants who do not have major protocol deviations during the course of the study
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 and received either 100% of dosing in cycle 1 (no priming regimen) or 100% of dosing in cycle 1 and cycle 2 (priming regimen)..
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;
Response Evaluable set	The response evaluable population will include all participants who received at least one dose of study treatment and had measurable disease at baseline and at least one post baseline disease 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.

5.GENERAL METHODOLOGY AND CONVENTIONS

5.1 Hypotheses and Decision Rules

There will be no formal hypothesis testing in this study.

5.2 General Methods

The data are summarized by dose level cohort, defined by the initial dose of the study intervention administered to participants. 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 escalation decision meetings. Unless otherwise specified, all other summaries will be presented by dose level cohort and overall. Additionally, summary tables will include the total sample size and number missing/not reported. Lastly, missing data may be imputed according to section 0 and unless otherwise specified missing values that are not imputed will be excluded from the analysis.

5.2.1 Analyses for Binary Endpoints

Binary data will be summarized using number of unique patient incidence, and confidence interval for binomial proportions will be presented if warranted using Clopper-Pearson exact method.

Binary endpoints in this study include complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), disease control rate (DCR) ,objective response rate (ORR) based on RECIST v1.1, and irCR, irPR, irSD, irPD and irDCR based on irRECIST. Descriptive statistics along with the corresponding 2-sided 95% confidence intervals (CI) using Clopper-Pearson exact method will be provided for these endpoints if the sample size per cohort permits.

5.2.2 Analyses for Continuous Endpoints

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

5.2.3 Analyses for Categorical Endpoints

Categorical data will be summarized by number of unique patient incidence.

5.2.4 Analyses for Time-to-Event Endpoints

The time-to-event data will be presented for individual patient, by dose level cohort, and overall when applicable. Time-to-event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. 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 are based on the Brookmeyer-Crowley method. Confidence intervals for the estimated probability of an event at a particular time point will be generated using the Greenwood formula.

5.3 Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied. See Clinical Data Interchange Standards Consortium (CDISC) and Pfizer data standard (PDS) Safety Rulebooks for details.

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

No imputation will be performed for tumor assessments that will be used for the binary efficacy endpoints. Every effort will be made to retrieve data in the CRF, however missing data will be left as is. The reasons for missing tumor assessments will be collected.

For the time-to-event endpoints, the missing data handling method will be censoring.

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 will be replaced with the value for the lower limit of quantification.)

5.3.3.2 Deviations, Missing Concentrations and Anomalous Values

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 participants. 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 be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

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 Part 1 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 and OS. 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 Appendix 1. 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 at the date of their last scan prior to their COVID-19 diagnosis.

   In the confirmed ORR analysis, 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. 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 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 Endpoint(s)

6.1.1 DLTs (Part 1)

Determination of MTD will be performed using Per-protocol analysis set (evaluable for MTD) as described above in Section 3.

6.1.2 **Adverse Events** (Part 1 and Part 2)

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

    AEs will be characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0, except CRS, which will be graded by ASTCT criteria (Lee et al., 2019)) timing, seriousness, and relationship to study therapy. Further description is given in Section 0. The primary focus will be on TEAEs. TEAEs is defined as any AE that occurs during the on-treatment period. AEs that occur 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 on-treatment emergent AE summaries.

    See Section 0 for details on the specific AE summaries to be provided.

  - Missing data: If an AE start or stop date is missing, imputation will be performed. 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** (Part 1 and Part 2)

- Analysis methodology:

  Laboratory abnormalities will be presented as tables and characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal high/low, or not done. The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. Shift tables of baseline grade to worst post-baseline grade will be provided. Quantitative summaries for change from baseline and percent change from baseline for the laboratory tests may be provided, if deemed necessary. These summaries will be

presented for the entire on-treatment period and for the various subgroups of the study (by dose level for Part 1 and by expansion cohort for Part 2).

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.

- Missing data: Missing lab values will not be imputed.

6.2 Secondary Endpoints

Part 1 and Part 2

6.2.1 irAEs

- Analysis methodology:

  irAEs will be characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0, except CRS, which will be graded by ASTCT criteria (Lee et al., 2019)) timing, seriousness, and relationship to study therapy. Further description is given in Section 0. ir AEs that occur after the on-treatment period may still be recorded in the clinical database and will be included in the irAE listings, but will not be included in the on-treatment emergent AE summaries.

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

6.2.2 Single-Dose and Steady-State PF-07260437 Pharmacokinetic Analysis

- Analysis set: PK analysis set

Serum concentrations of PF-07260437 will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and its associated coefficient of variation) by dose, cycle, day, and nominal time.

Individual participant serum concentration-time data within a dose interval after Cycle 1 Day 1 and Cycle 2 Day 1 will be analyzed using noncompartmental methods to determine single and multiple dose PK parameters.

Single dose PK parameters to be estimated will include the serum C_{max}, T_{max} and AUC_{last}, and as data permit, AUC from time 0 extrapolated to infinity (AUC_{inf}), $t_{½}$, clearance (CL/F for SC dosing and CL for IV dosing) and volume (V_z/F for SC dosing and V_{ss} for IV dosing).

Multiple dose PK parameters to be estimated will include $C_{max,ss}$, $T_{max,ss}$, $AUC_{ss,\tau}$, $C_{min,ss}$, clearance (CL_{ss}/F for SC and CL_{ss} for IV) and as data permit, volume (V_z/F for SC or V_{ss} for IV), $t_{½}$, and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$). The single dose and steady-state PK parameters will be

summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and its associated coefficient of variation) by dose level and cycle.

Dose normalized AUC_{inf} (AUC_{τ} at steady state) and C_{max} will be plotted against dose (using a logarithmic scale) by cycle. These plots will include individual participant values and the geometric means for each dose.

6.2.3 Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of participants with positive ADA and neutralizing antibodies each 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.

Part 2

6.2.4 Efficacy Analysis

Response Evaluable Set will be used for all response-related analyses including ORR, DoR, PFS, and TTP (RECIST, irRECIST). Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, tumor response at each visit, and best overall response. Immune related response by irRECIST will be calculated and reported similarly to RECIST response. OS will be reported on the Full Analysis Set as well as on the mITT.

Data will be summarized (also graphically where appropriate) and listed by expansion cohort.

- **Overall Response Rate (ORR)**
  - Overall response rate (ORR) is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR by Investigator assessment in intracranial metastasis and extracranial lesions per mRECIST v1.1 (or RANO for glioblastomas) and RECIST v1.1, respectively.
- **Duration of Response (DOR)**
  - Duration of response is defined as the time from start date (which is the date of first documentation of PR or CR) to date of first documentation of objective progression or death. Both confirmed DOR and unconfirmed DOR (uDOR) will be determined and reported separately for the subset of participants with a confirmed and unconfirmed objective response of CR or PR (defined below). DOR will be derived for Intracranial/RANO response rate, extracranial response rate and ORR.
- **Best Overall Response (BOR)**

- **Complete Response (CR)**: Two objective statuses of CR a minimum of 4 weeks apart documented before PD.

- **Partial Response (PR)**: Two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of 4 weeks apart documented before PD, but not qualifying as CR. Sequences of PR- Stable- PR are considered PRs as long as the two PR responses are observed at a minimum of 4 weeks apart.

- **Stable Disease (SD)** (applicable only to patients with measurable disease at baseline): At least one objective status of stable disease or better documented at least 6 weeks after start of treatment and before PD but not qualifying as CR or PR.

- **Non-CR/non-PD** (applicable only to patients with non-measurable disease at baseline): at least one non-CR/non-PD assessment (or better) documented at least 5 weeks after start of treatment and before first documentation of PD (and not qualifying for CR or PR).

- **Progressive Disease (PD):** Progression documented within 12 weeks after 'start date' and not qualifying as CR, PR or SD.

- **Not Evaluable (NE):** All other cases. Note that reasons for NE should be summarized and the following reasons could be used:

  - No adequate baseline assessment

  - No evidence of disease at baseline

  - No post-baseline assessments due to early death, i.e., death prior to 6 weeks after 'start date'.

  - No post-baseline assessments due to other reasons

  - All post-baseline assessments have overall response NE

  - New anti-cancer therapy started before first post-baseline assessment

  - SD of insufficient duration (<5 weeks after 'start date' without further evaluable tumor assessments)

  - PD too late (>12 weeks after start of treatment)

  - Special and rare cases where BOR is NE due to both SD of insufficient duration ('too early') and late PD will be classified as 'SD of insufficient duration.

- Unconfirmed CR (uCR) is defined as one objective status of CR documented before PD.

- Unconfirmed PR (uPR) is defined as one objective status of PR documented before PD but not qualifying as uCR.

Note: An objective status of PR, SD, or Non-CR/Non-PD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR – SD – PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Patients with a BOR of "Not Evaluable" (NE) based on confirmed responses will be summarized by reason for having unknown status. The following reasons will be used:

- No adequate baseline assessment.
- No post-baseline assessments due to early death .
- No post-baseline assessments due to COVID-19 (ie, patients miss tumor assessment visits due to COVID-19 pandemic).
- No post-baseline assessments due to other reasons.
- All post-baseline assessments have overall response NE.
- New anticancer therapy started before first post-baseline assessment.
- SD of insufficient duration (<6 weeks after date of the first dose without further evaluable tumor assessments).
- PD >12weeks after date of the first dose (ie, tumor assessment of PD was >12 weeks after date of the first dose and there was no tumor assessment in between).

Special and rare cases where BOR is NE due to both SD of insufficient duration (SD <6 weeks after date of the first dose) and late PD (PD >12 weeks after date of the first dose) will be classified as "SD of insufficient duration".

- 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 graphical representation (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: Data after the study intervention is discontinued and rescue will be excluded; intermediate missing values (ie, values collected between baseline and the last study measurement) will not be imputed.

Progression-free Survival (PFS)

- Analysis set: Response Evaluable

Progression-free survival (PFS) is defined as the time from date of the first dose of study treatment to the earliest documented disease progression by Investigator assessment, or death due to any cause, whichever occurs first. If a patient has not had a PFS event at the time of the analysis cutoff or at the start of any new anticancer therapy, PFS is censored at the date of last adequate tumor assessment.

PFS will be calculated as follows:

PFS (months) = (date of event or censoring – date of first dose +1)/30.4375

The censoring and event date options to be considered for PFS analysis are presented in Table 2.

PFS time will be estimated using the Kaplan-Meier method. The PFS rate at 3, 6, 9, 12, 15 and 18 months will be estimated with corresponding 2-sided 95% CIs.

Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented along with the overall event and censor rates. Reasons for censoring will be summarized according to the categories in Table 3. In addition, time to progression/censoring, event, and censoring reasons will be listed.

Table 2 PFS and DOR Outcome and Event Dates

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment [a]	Date of first dose [a]	Censored [a]
PD or death - after at most one missing or inadequate postbaseline tumor assessment, or - ≤8 weeks (±3-day window) after date of first dose	Date of PD or death	Event
PD or death - after >=2 missing or inadequate postbaseline tumor assessment	Date of last adequate tumor assessment[b] documenting no PD prior to new anticancer therapy, or missed tumor assessments	Censored
No PD		
New anticancer therapy given prior to PD or death		

[a] This criterion only applies to PFS censoring. If the participant dies ≤6 weeks after date of first dose and and did not initiate new anticancer therapy, the death is an event with date on death date (6 weeks is 2 times the length of the first 2 tumor assessment intervals).

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

Table 3 PFS Censoring Reasons and Hiearchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anticancer therapy before event	Start of new anticancer therapy
3	Event after 2 or more missing or inadequate postbaseline tumor assessment/start date	Event after missing or inadequate assessments
4	No event and [withdrawal of consent date ≥ date of first dose OR End of study (EOS) = Subject refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and lost to follow-up in any disposition page	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

Time to Progression (TTP)

Time to progression (TTP) is defined as the time from date of the first dose of study treatment to the earliest documented disease progression by Investigator assessment.

TTP will be calculated in months as follows:
TTP (months) = (date of progression or censoring – date of first dose +1)/30.4375

TTP will be estimated using the Kaplan-Meier method. The TTP rate at 3, 6, 9, 12, 15 and 18 months will be estimated with corresponding 2-sided 95% CIs.

Overall Survival (OS)

- Analysis set: Full Analysis Set

OS will be calculated in months as follows:
OS (months) = (date of death or censoring – date of first dose +1)/30.4375

OS time will be estimated using the same Kaplan-Meier method. The OS rate at 6, 12, 18, 24, 30 and 36 months will be estimated with corresponding 2-sided 95% CIs.

Frequency (number and percentage) of patients with death events and censoring reasons will be presented by cohort along with the overall event and censor rates. The event and ensoring reasons are as follows:

- Death:
  - Death due to COVID-19.
- Ongoing and no death.
- Withdrawal of consent.
- Lost to follow-up.

- The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Phenotypes, and quantity of TIL before and after PF-07260437 treatment (eg, CD3, CD8, Granzyme B, Ki67 IHC)

6.3 Tertiary/Exploratory Endpoint(s)

Part 1

Efficacy Analysis

Response Evaluable Set will be used for ORR and PFS (RECIST, irRECIST). Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, tumor response at each visit, and best overall response.

Data will be summarized (also graphically where appropriate) and listed by dose level.

Part 1 and 2

Analysis of Pharmacodynamics

Results of exploratory endpoint analyses will be described in the bSAP and CSR to the extent possible. Due to the exploratory nature of the endpoints, the associated data analyses may not be complete at the time of CSR preparation. If results of exploratory endpoint analyses cannot be included in the CSR, they will be disseminated to the scientific community to the extent possible through presentation at scientific meetings and/or publication in peer-reviewed scientific journals.

6.5 Baseline and Other Summaries and Analyses

6.5.1 Baseline Summaries

Baseline characteristics such as demographics, prior medication, and primary diagnosis will be tabulated and listed. The Safety Analysis Set will be used.

6.5.2 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.

6.5.3 Study Treatment Exposure

The Safety Analysis Set will be used.

Dose modifications are described in the protocol. The following will be summarized by treatment dose level and overall:

- Number of subjects;
- Median and range of number of treatment cycles started;
- Number (%) of subjects starting a treatment cycle (1, 2, 3…);
- Number (%) of dose interruptions (include both known and unknown dates). Dose interruptions is defined as as a planned dosing day with 0 mg total dose administered. Missing doses on unknown dates will be included in the summary. Note: Dose interruptions apply to unexpected dose interruptions and not the one-week treatment holiday given in each treatment cycle;
- Number (%) of dose interruptions related to AEs, defined as "Was the Actual Dose adjusted from planned?" = "ADVERSE EVENT(S)" and "Latest Action Taken with Study Treatment:" = "DOSE INTERRUPTED";
- Number (%) of subjects with dose reductions. A dose reduction is defined as a day when the actual dose is less than the planned dose at enrollment and the acutal dose is greater than 0 mg (i.e., missed doses are not counted as a reduction);
- Number (%) of dose reductions related to AEs, defined as "Was the Actual Dose adjusted from planned?" = "ADVERSE EVENT(S)" and "Latest Action Taken with Study Treatment:" = "DOSE REDUCED";
- Number (%) of participants with dose reductions or interruptions for each reason (AE vs insufficient clinical response vs Other);
- Days on treatment (median, range).
- Number of treatment cycles received per subject (median, range);
- Number of treatment cycles received before 1st reduction (median, range);
- Number of treatment cycles received before 1st interruption (median, range).

The following will be summarized for cumulative dose by dose level:

- Summary statistics (mean, median, standard deviation and range) of cumulative dose and cumulative percent of administered dose (compared to planned dose);
- Actual dose intensity (mg/day): Defined as cumulative actual dose received (mg) divided by the number of doses scheduled per protocol during treatment period;
- Ratio of actual dose intensity to planned dose intensity. Where planned dose intensity is defined as a participant's planned starting dose.

Listings by subject (ordered by dose level): 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, and cycle number relative to the dosing period.

Listings by subject and cycle (ordered by dose level): cycle length, total planned dose, total actual dose received, percentage of planned dose, dose reduction (yes/no), and dose interruption (yes/no).

6.5.4 Concomitant Medications and Nondrug Treatments

Prior, concomitant, and further therapies (drug and non-drug treatments) will be coded by the World Health Organization (WHO) medical dictionary. Listings of prior, concomitant, and further therapies will be provided separately.

6.6 Safety Summaries and Analyses

All safety analyses will be performed on the Safety Analysis Set.

Summaries and analyses of safety parameters will include all participants in the safety analysis set.

AEs, ECGs, blood pressure (BP), pulse rate, ophthalmic examinations 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 pulse rate 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/or neurological examinations 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.

6.6.1 Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1). Adverse event data will be reported in tables and listings. Summaries of adverse event by system organ class and preferred terms, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of adverse events 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 across the entire study period. A table summarizing whether deaths were on (i.e., death ≤ 30 Days From Last Dose of Study Treatment) or off study treatment (i.e., death > 30 Days From Last Dose of Study Treatment) will be provided. Additionally, listings of DLTs and deaths will be provided. Death and SAE information will be based on the data captured from the CRF.

A similar approach will be used for irAEs.

6.6.2 Clinical Safety Laboratory Assessments

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

The data may be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and biomarker measurements.

6.6.3 Vital Signs

Vital signs will consist of systolic and diastolic blood pressure, and pulse ratemeasurements. Criteria for clinically relevant abnormal findings are provided in Appendix 2. Measurements that meet these criteria will be listed.

6.6.4 Electrocardiograms

The analysis of ECG results will be based on participants in the Safety Analysis Set with baseline and on-treatment ECG data. Baseline is defined as measurements taken at Cycle 1 Day 1 pre-dose (see SoA in protocol for details).

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, pulse rate 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 cohort:

Safety QTcF Assessment

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

In addition, the number of participants with QTcF values >500 msec will be summarized.

Electrocardiogram (ECG) measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations.

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 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTcF value and 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/pharmacodynamic modeling approach. If a PK/pharmacodynamic 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.

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 heart rate (HR) (QTc) using the standard correction factor of Fridericia. Data will be summarized and listed for QT, HR, RR, pulse rate, QRS, QTcF, time and dose. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment, by dose and time point.

6.6.5 Physical Examination

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

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 study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PKmodeling, and/or supporting clinical development.

8. REFERENCES

Neuenschwander B, Matano A, Tang Z, Roychoudhury S, Wandel S and Bailey S. A Bayesian Industry Approach to Phase I Combination Trials in Oncology. In *Statistical Methods in Drug Combination Studies*. Zhao W and Yang H (eds), Chapman & Hall/CRC, 2014.

Rogatko A1, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of innovative designs into phase I trials. J Clin Oncol. 2007 Nov 1;25(31):4982-6.

9. APPENDICES

Appendix 1 Time to Event Data Analysis Censoring Rules

Table 4 OS Outcome and Event Dates

Situation	Date of Death/Censoring	Outcome
Alive	Date of Last Contact	Censored
Death due to any cause	Date of Death	Event

Appendix 2 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.

Appendix 3 Abbreviations

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

Abbreviation	Term
AE	adverse event
ASTCT	American society for transplantation and cellular therapy
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time versus time curve from time 0 to infinity

Abbreviation	Term
AUC_{last}	area under the concentration-time curve from time 0 to time of last measurable concentration
$AUC_{tau,ss}$	area under the steady state dose concentration-time curve over dosing interval tau
BLQ	below the limit of quantification
BLRM	Bayesian logistic regression model
BOR	best overall response
BP	blood pressure
bpm	beats per minute
bSAP	biomarker statistical analysis plan
CDISC	clinical data interchange standards consortium
CI	confidence interval
CL	total clearance of drug from eg, plasma
C_{max}	maximum observed concentration
COVID	corona virus disease
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography/clinical trial
CTCAE	common terminology criteria for adverse events
ctDNA	circulating tumor DNA
DC	disease control
DCR	disease control rate
DDI	drug-drug interaction
DLRM	dose level review meeting
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
EWOC	escalation with overdose control
FIH	first in human
HR	heart rate
ITT	intention to treat
LLQ	lower limit of quantification
MAP	meta-analytic-predictive
MedDRA	medical dictionary for regulatory activities
mg	milligrams
mITT	modified-intent-to-treat
mm	millimeters
MRI	magnetic resonance imaging
msec	millisecond
MTD	maximum tolerated dose
NC	not calculated
NCI	national Cancer Institute

Abbreviation	Term
ND	not done
NE	not evaluable
NS	no sample
NSCLC	non-small cell lung cancer
OR	overall response
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics(s)/progressive disease
PDS	Pfizer data standard
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
QTc	corrected QT
QTcF	QTc corrected QT (Fridericia method) using Fridericia's formula
R_{ac}	accumulation ratio based on AUC (observed)
RECIST	response evaluation criteria in solid tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
$t_{½}$	terminal phase half-life
TEAE	treatment emergent adverse events
T_{max}	time to reach C_{max}
TTP	time to progression
WHO	world health organization