Protocol C4471001

A TWO-PART, PHASE 1A/B, OPEN-LABEL, MULTICENTER TRIAL EVALUATING PHARMACOKINETICS, SAFETY AND EFFICACY OF PF-07284890 (ARRY-461) IN PARTICIPANTS WITH BRAF V600-MUTANT SOLID TUMORS WITH AND WITHOUT BRAIN INVOLVEMENT

Statistical Analysis Plan (SAP)

[redacted]

Version: 1

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[redacted]

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1. VERSION HISTORY

This is the first version.

2. INTRODUCTION

PF-07284890 (also known as ARRY-461) is a potent, selective, highly brain-penetrant small -molecule inhibitor of BRAF V600 mutations that is being investigated in participants with BRAF V600-mutant solid tumors with or without brain involvement. PF-07284890 is being developed to address the limited overall efficacy of approved BRAF inhibitors resulting from disease progression in the brain. By inhibiting BRAF V600-mutant enzyme in tumor cells both extracranially and intracranially, PF-07284890 has the potential to prolong the duration of overall disease control compared to approved BRAF inhibitors.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study PF 07284890. This document provides additional details for the planned analyses that are outlined in the protocol. This SAP was written in reference to amendment #1 of the protocol dated August 3, 2020. Any major modifications of the endpoints or analyses will be reflected in further amendments to the protocol and SAP.

2.1. Study Objectives and Endpoints

2.1.1. Primary Objectives

Phase 1a:

The primary objective for Phase 1a is to assess the safety and tolerability of PF-07284890 at increasing dose levels, to estimate the MTD, and to select the recommended dose for further study, as both a single agent and in combination with binimetinib, in participants with BRAF V600-mutated advanced solid tumor malignancies with and without brain involvement.

Phase 1b:

The primary objective for Phase 1b is to evaluate anti-tumor efficacy of PF-07284890 at the recommended dose for further study in combination with binimetinib in participants with BRAF V600-mutated advanced solid tumor malignancies with and without brain involvement.

2.1.2. Secondary Objectives

Phase 1a:

- To characterize the single- and multiple-dose PK of PF-07284890 as a single agent and in combination with binimetinib and of binimetinib in combination with PF-07284890.
- To evaluate preliminary clinical activity of PF-07284890 as a single agent and in combination with binimetinib.

Phase 1b:

- To confirm the safety and tolerability of PF-07284890 at the recommended dose for further study in combination with binimetinib.
- To evaluate single- and multiple-dose PK profiles of PF-07284890 at the recommended dose for further study in combination with binimetinib and of binimetinib in combination with PF-07284890.
- To assess additional measures of anti-tumor efficacy of PF-07284890 at the recommended dose for further study in combination with binimetinib.
- To evaluate the effect of repeated administration of PF-07284890 in combination with binimetinib on single dose PK of midazolam (Cohort 6 only).

2.1.3. Tertiary/Exploratory Objectives

Phase 1a:

- To explore the effect of CCI [redacted] on PF-07284890 exposures in participants treated with PF-07284890 as a single agent and in combination with binimetinib.
- To explore the brain penetration of PF-07284890 as a single agent and in combination with binimetinib.
- To evaluate tumor and blood-based biomarkers of response and resistance to PF-07284890 as a single agent and in combination with binimetinib.
- To assess the relationship between PF-07284890 concentrations and changes in QTcF.

Phase 1b:

- To explore the effect of CCI [redacted] on PF-07284890 exposures in participants treated with PF-07284890 in combination with binimetinib.
- To explore the brain penetration of PF-07284890 in combination with binimetinib.
- To evaluate tumor and blood-based biomarkers of response and resistance to PF-07284890 in combination with binimetinib.

2.2. Study Design

This is a Phase 1a/b, open-label, multicenter, dose-finding study of the safety, PK and preliminary clinical activity of PF-07284890 in adult participants with selected BRAF V600-mutant advanced or metastatic solid tumor malignancies and primary brain tumors. The study will be conducted in 2 parts, ie, Phase 1a (Dose Escalation) and Phase 1b (Dose Expansion and a DDI sub-study).

Participants will have experienced disease progression after prior treatment and have no acceptable alternative treatment options.

Participants must provide documented evidence of a BRAF V600 mutation in tumor tissue or blood ([redacted]) as previously determined by PCR or NGS-based laboratory assay in a CLIA or similarly certified laboratory at any time prior to Screening. Local testing is permitted (see Protocol Section 4.4.2). Participants are required to submit either archival or newly collected tissue sample (the latter if a biopsy is safe to perform; if not, participants may be eligible as long as they meet other eligibility criteria) and a blood sample prior to enrollment, which may be used for retrospective analysis of BRAF V600 mutation status but not to determine eligibility/enrollment.

Enrolled participants may be with or without brain involvement at baseline, with the allowed extent of and symptoms from intracranial disease determined by the degree of calculated BRAF V600E target coverage during dose escalation, and the specific cohort during dose expansion (see Protocol Section 5).

Phase 1a Dose Escalation

Approximately 35 participants will be enrolled to determine the MTD and/or recommended dose for further study of PF-07284890 alone and in combination with binimetinib 45 mg BID. Monotherapy dose escalation will initiate first.

A participant is classified as DLT evaluable if he/she experiences a DLT (See Protocol Section 4.3.3) or if he/she otherwise in the absence of a DLT receives at least 75% of the planned PF-07284890 doses (and at least 75% of the planned binimetinib doses if the participant is receiving combination treatment) and has received all scheduled safety assessments during the DLT observation window (first cycle of treatment, a 21-day cycle).

A BLRM will be used to model the DLT relationship of PF-07284890. This model, along with the EWOC, will guide the dose escalation of PF-07284890 after the completion of the DLT observation period of each cohort, until adequate DLT data has accumulated throughout the monotherapy dose escalation to inform the combination BLRM or until the determination of MTD/recommended dose for PF-07284890 monotherapy.

Cohorts of 2-4 evaluable participants will be treated at each dose level of PF-07284890 on an outpatient basis starting from 50 mg QD until the determination of MTD/recommended dose for further study. A minimum of 6 evaluable participants are expected to be treated at MTD/recommended dose for further study (ie, 6 participants each for both monotherapy and combination therapy) in order to evaluate safety, tolerability, PK as well as preliminary activity of PF-07284890 when given at the MTD/recommended dose for further study (both alone and in combination with binimetinib). The actual dose increases between dose levels will be determined by BLRM/EWOC, safety and observed PK as described in Protocol Section 4.3.2. In addition, an alternative schedule (eg, BID, dosing holiday) may be evaluated depending on safety and observed PK.

BLRM and EWOC will be used to model the DLT relationship of PF-07284890 in combination with binimetinib at the approved dose of 45 mg BID (monotherapy dose escalation will continue simultaneously). Based on preliminary PK and safety, the combination dose escalation phase of PF-07284890 with binimetinib may be started prior to the determination of the monotherapy PF-07284890 MTD/recommended dose for further study. The starting dose level for PF-07284890 in the combination dose therapy escalation will not be higher than previously studied doses in the monotherapy escalation and will satisfy EWOC criteria. The parameters will be derived from the combination BLRM by incorporating DLT data obtained from the PF-07284890 monotherapy escalation and historical data for binimetinib (see Protocol Section 9.4.1.1).

For both monotherapy and combination therapy dose escalations, toxicities will only be considered DLTs if they occur within the DLT window of the first cycle (21 days). However, overall safety, including later cycles, and PK data will be evaluated for the recommended dose for further study determination.

Phase 1b Dose Expansion and a DDI Sub-Study

After identification of the combination MTD/recommended dose for further study, approximately 40 participants will be enrolled to each of the Cohorts 1-4 and 20 participants to Cohort 5 of Phase 1b dose expansion based on tumor type, whether brain involvement is asymptomatic or symptomatic and measurable or non-measurable, prior treatment history and a history of or current leptomeningeal metastases. The participants intended for each cohort are described in Protocol Section 1.2 and Section 5. The dose expansion phase (Cohorts 1-5) will evaluate efficacy, safety and PK at the recommended dose for further study in combination with binimetinib.

In addition, approximately 10 participants will be enrolled to a sub-study (Cohort 6) to evaluate the effect of PF-07284890 in combination with binimetinib on CYP3A activity using midazolam as a probe CYP3A4 substrate.

Treatment with study intervention will continue until either disease progression, participant refusal, unacceptable toxicity occurs, or up to 2 years, whichever occurs first. Participants who have disease progression but are deriving clinical benefit may continue if criteria are met and the participant consents to continue treatment (see Protocol Section 7.1.1). Participants who complete 2 years on study intervention and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study intervention will be given the opportunity to continue treatment upon agreement between investigator and sponsor, using the same safety assessments as were being performed most recently, but with efficacy monitored at intervals consistent with clinical practice.

Number of Participants

An expected number of approximately 175-225 participants will be enrolled to study intervention. Refer to Protocol Section 9.2 for sample size determination.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent

process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

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. For details, please see October 7, 2020 Protocol Administrative Changes and Clarifications for Study C4471001.

Statistical Methods

Adaptive Bayesian approach: The dose escalation in the Phase 1a of the study will be guided by a BLRM analysis of the first 21 days (Cycle 1) of DLT data for PF-07284890. Toxicity is modelled using a logistic regression for the probability of a participant experiencing a DLT at the given dose. A similar approach will be used to guide the combination dose escalation for the PF-07284890 with binimetinib.

Assessment of participant risk: After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07284890 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

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

The EWOC principle: Dosing decisions are guided by the EWOC principal. A dose may only be used for newly enrolled participants if the risk of over-dosing at that dose is less than 25%.

Prior distributions: MAP prior distribution based on clinical/expert opinion information will be chosen for the logistic parameters. For details, please see C4471001 Technical Supplement to Appendix 10.9.

For Phase 1b, the expansion arms will be conducted to assess efficacy as well as safety and tolerability of PF-07284890 in combination therapy with binimetinib.

In Phase 1b, the primary endpoint of overall response by RECIST version 1.1 and intracranial response by mRECIST version 1.1 (RANO for primary brain tumors) will be summarized and listed by expansion cohort and disease type. The secondary endpoints of

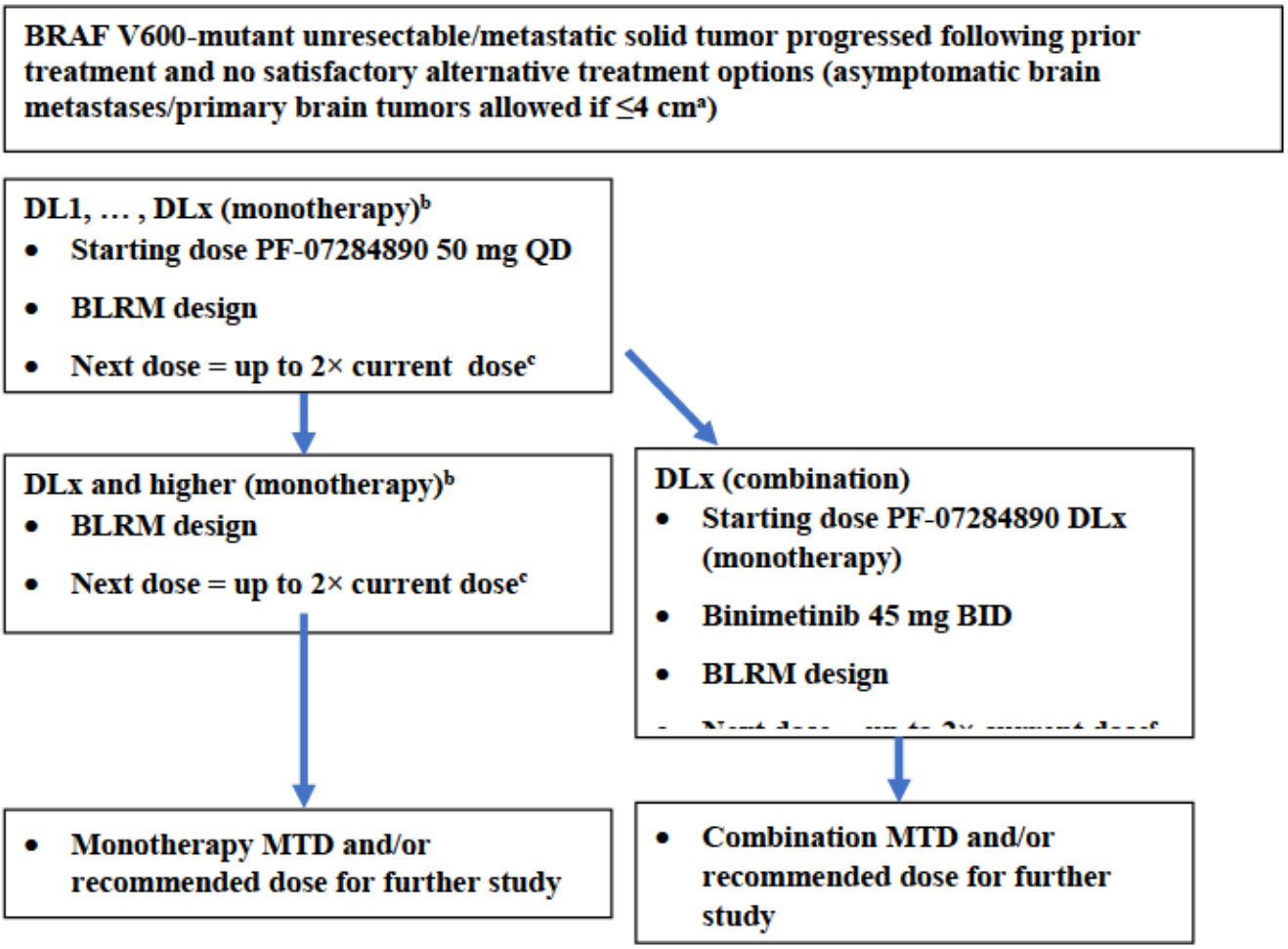
DCR (overall and intracranial), PFS (overall and intracranial), OS, DoR (overall and intracranial) and TTR (overall and intracranial) will be summarized (graphically where appropriate) and listed by expansion cohort and disease type.

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 and Figure 2.

Figure 1. Study Schema for Phase 1a Dose Escalation (Approximately 35 Participants)

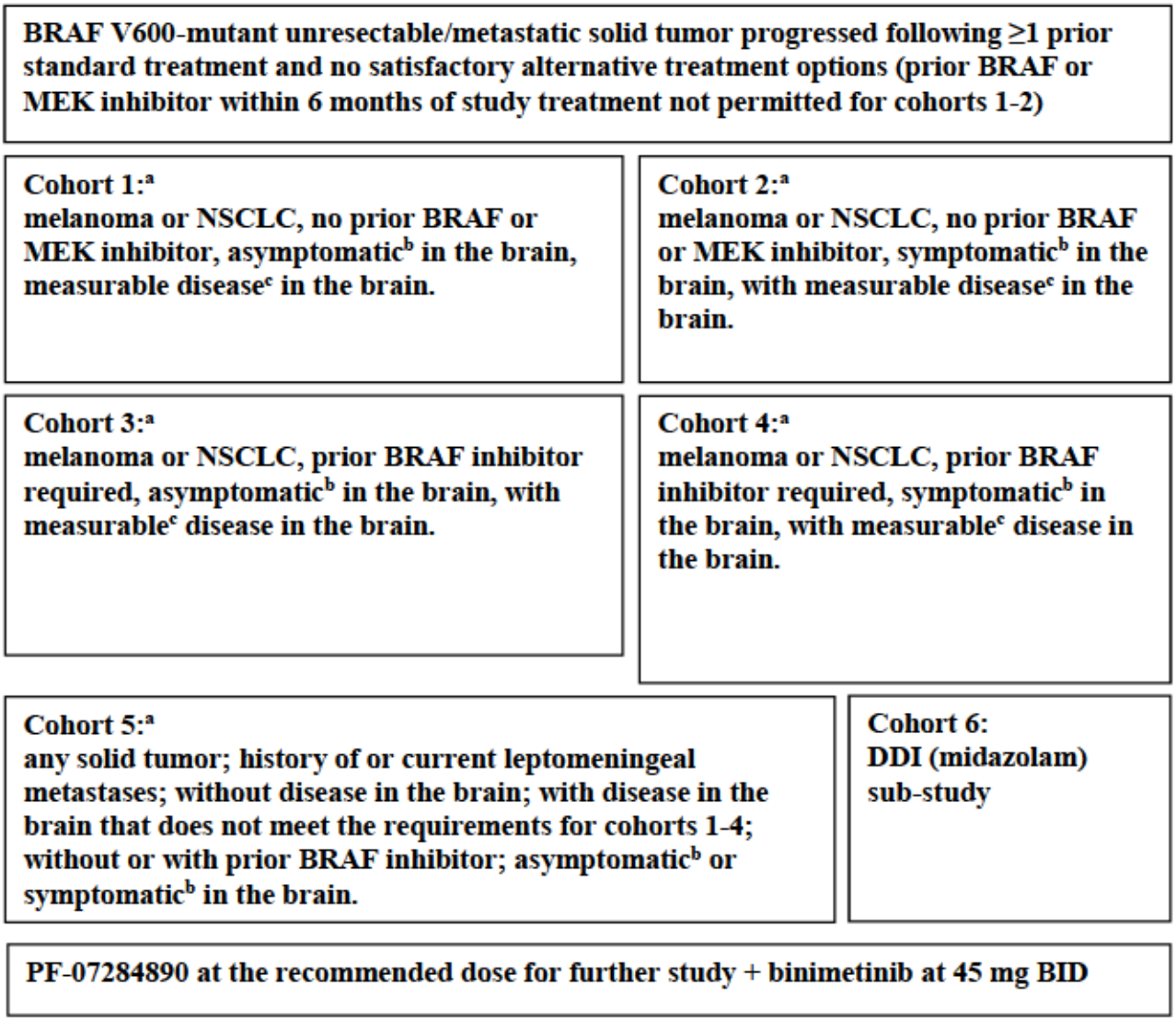


a. Once the trough concentration of PF-07284890 at steady state is ≥0.168 µg/mL (equal to the fu-adjusted IC_{70} for inhibition of BRAF V600E) in at least two-thirds of participants at the same dose level (a level at which anti-tumor activity in the brain and systemically may be expected), subsequent participants entering the study during dose escalation may have a lesion(s) >4 cm and/or be symptomatic in the brain as defined in Protocol Section 5.1.

b. Intrapatient dose escalation and/or addition of binimetinib may be allowed after 12 weeks of monotherapy or disease progression. See Protocol Section 4.3.2.3.

c. If no DLTs at the current and all prior dose levels, and if the observed trough concentration at steady state with the current dose is < the calculated IC_{50} of PF-07284890 in at least two-thirds of participants, the next dose will not exceed 3× the current dose level. See Protocol Section 4.3.2.

Figure 2. Study Schema for Phase 1b Dose Expansion and a DDI Sub-Study (Approximately 40 Participants Per Cohort for Cohorts 1-4, 20 Participants for Cohort 5 and 10 Participants for Cohort 6)



a. Each cohort will be analyzed for efficacy as a whole and by tumor type (eg, melanoma, NSCLC).

b. Asymptomatic in the brain is defined as, within 14 days of the start of study: no neurological symptoms due to brain metastases/primary brain tumor; not requiring initiation of or an increase in steroid dosing to control neurological symptoms due to brain metastases/primary brain tumor; and not requiring initiation of or an increase in anti-epileptic dosing to control seizure activity due to brain metastases/primary brain tumor. Symptomatic in the brain is defined as any of the above within 14 days of the start of study treatment.

c. For Cohorts 1-4: a measurable lesion must be at least 0.5 cm and ≤4 cm in long axis and evaluable by mRECIST v1.1; if all disease in the brain was previously irradiated, at least 1 lesion must demonstrate progression by RECIST v1.1 since irradiation.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Phase 1a:

- Incidence of Cycle 1 DLTs.
- MTD/recommended dose determination for further study.
- AEs 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.
- Incidence of dose interruptions, dose modifications and discontinuations due to AEs.

Phase 1b:

- Overall response by RECIST version 1.1 and intracranial response by mRECIST version 1.1 (RANO for primary brain tumors).

3.2. Secondary Endpoint(s)

Phase 1a:

- PK parameters of PF-07284890 and binimetinib:
  - Single dose: C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F.
  - Multiple dose (assuming steady state is achieved): $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,min}$, and as data permit, CL_{ss}/F, V_{ss}/F, $t_{½}$ and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$).
- Overall response by RECIST version 1.1 and intracranial response by mRECIST version 1.1 (RANO for primary brain tumors).

Phase 1b:

- AEs 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.
- Incidence of dose interruptions, dose modifications and discontinuations due to AEs.
- PK parameters of PF-07284890 and binimetinib:
  - Single dose - C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F.
  - Multiple dose (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,min}$, and as data permit, CL_{ss}/F, V_{ss}/F, $t_{½}$ and R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$).
- DCR (overall and intracranial).

- PFS (overall and intracranial), OS, DoR (overall and intracranial) and TTR (overall and intracranial).

- PK parameters of CYP3A4 probe substrate midazolam:
  - C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F.

3.3. Other Endpoint(s)

Phase 1a:

- PF-07284890 PK parameters (single dose C_{max} and AUC_{last}; multiple dose $C_{ss,max}$, $AUC_{ss,\tau}$) in participants CCI.
- CSF concentrations of PF-07284890 (in participants in whom CSF is obtained as SOC).

CCI [redacted]

- Maximal changes in QTcF estimated using a linear mixed effect model.

Phase 1b:

CCI [redacted]

- CSF concentrations of PF-07284890 (in participants in whom CSF is obtained as SOC).

CCI [redacted]

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

Severity of adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment-emergent AE are defined as AEs with onset date during the on-treatment period.

For the purpose of dose escalation, any of the following AEs occurring in the DLT observation period (ie, first cycle of treatment, a 21-day cycle) for DLT-evaluable participants, that are attributable to the study intervention, will be classified as DLTs.

DLT related AEs can be found in section 4.3.3 of the protocol, while definitions of an AE and an serious adverse event (SAE) can be found in Appendix 3 of the protocol.

3.5.2. Vital Signs

Vital signs include temperature, systolic and diastolic blood pressure, and pulse rate. Details on the collection of vital signs can be found in section 8.2.6 of the protocol.

3.5.3. Laboratory Data

Details of the laboratory tests can be found in Appendix 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

Population	Description
Full analysis set	The full analysis set includes all enrolled participants. "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety analysis set	The safety analysis set includes all enrolled participants who receive at least one 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 (Evaluable for MTD)	The per protocol analysis set includes all enrolled participants who had at least one dose of study treatment and either experienced DLT or do not have major treatment deviations during the DLT observation period.

Table 1. Analysis Sets

Population	Description
Modified Intent to Treat (mITT)	The per protocol analysis set includes all enrolled participants who had at least one dose of study treatment and either experienced DLT or do not have major treatment deviations during the DLT observation period. To be DLT evaluable, a participant must have received at least 75% of their planned doses of each study drug for the first cycle and has received all scheduled safety assessments during the DLT window.
PK analysis sets	The PK concentration population is defined as all enrolled participants who are treated and have at least 1 analyte concentration. The PK parameter analysis population is defined as all enrolled participants treated who do not have protocol deviations influencing PK parameter assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest. As such, the PK parameter analysis population is a subset of the PK concentration population.
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.
PD/Biomarker analysis set	The PD/Biomarker analysis population is defined as all enrolled participants with at least 1 of the PD/Biomarkers evaluated at pre and/or post dose.

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 5.3 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 intracranial response rate based on mRECIST v 1.1/RANO for primary brain tumors (details are provided in sections 8.1.1 and Appendix 9 in the protocol). 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. Censoring rules for time-to-event endpoints are detailed in Appendix 1.

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.

Further details are given in section 6.6.4.

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, as described in Section 6.1.5. 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)

Phase 1a:

6.1.1. Dose-Limiting Toxicities (DLTs) and MTD

- Analysis set: Per protocol analysis set. DLTs will be assessed during the first treatment cycle (ie, the first 21 days) to inform dose escalation and determine the MTD/RP2D.

- Analysis methodology:

  Statistical Methods:

  The dose escalation will be guided by a Bayesian analysis of DLT data for PF 07284890. Toxicity is modelled using two-parameter logistic regression (Neuenschwander et al., 2014) 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 07284890 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the true DLT rate lies within the following intervals:

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

The escalation with overdose control (EWOC) principle:
Dosing decisions are guided by the escalation with overdose control principal (Rogatko, 2007). A dose may only be used for newly enrolled participants if the risk of overdosing (DLT rate > 33%) at that dose is less than 25%.

Prior distributions:
Weakly informative prior distributions based on pre-clinical/expert opinion information will be chosen for the logistic parameters for prior distribution, see Appendix 11 (ie, section 10.11) of the protocol.

Starting dose:
The starting dose of PF 07284890 is 50 mg. For this dose the prior risk of overdosing

is 2.7%, which satisfies the EWOC criterion. A full assessment of the prior risk to participants is given in Appendix 11 of the protocol.

The trial will be stopped when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD/RP2D, d'. Where d' represents a given dose assessed during dose escalation.
- The dose d' satisfies one of the following conditions:
  - The probability (π) that the true DLT rate is within the target toxicity interval at dose d' exceeds 50%, ie, $Pr(0.16 \leqslant \pi_{d'} < 0.33) \geqslant 50\%$.
  - A minimum of 15 participants have been treated in the trial.

A table will be provided that summarizes the number of participants treated and the number of DLTs observed per dose level.

- Missing data: Missing values will not be imputed.

  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 (provided in Section 4.3.3 of the protocol) 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 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 6.6.1. The primary focus will be on TEAEs. TEAEs is defined as any AE that occurs during the on-treatment period, defined in Section 3.5. 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 6.6.1 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 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 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 Phase 1a and by expansion cohort for Phase 1b).

  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.

6.1.4. Incidence of dose interruptions, dose modifications and discontinuations due to AEs

The Safety Analysis Set will be used. Details of analyses are provided in Section 6.5.3.

Phase 1b:

6.1.5. Tumor Response

- Analysis set: Response Evaluable set
  - Analysis methodology:
    - For treatment response, 'start date' is defined as the first date that a participant received the study intervention.
- All tumor assessments are by Investigator
- Intracranial Response Rate
  - Intracranial response rate as assessed using mRECIST version 1.1. Intracranial response rate is defined as the proportion of patients with brain or CNS involvement who achieved a complete response (CR) or partial response (PR) per mRECIST version 1.1 (details are provided in sections 8.1.1 and Appendix 12 in

the protocol). Both confirmed intracranial response rate and unconfirmed intracranial response rate will be determined based on the confirmed and unconfirmed CR and PR, according to mRECIST (definitions provided below).

- RANO Response Rate
  - Response rate as assessed using Response Assessment in Neuro-Oncology (RANO). RANO response rate is defined as the proportion of glioblastoma patients who achieved a complete response (CR) or partial response (PR) per RANO (details are provided in sections 8.1.1 and Appendix 13 in the protocol).
- Extracranial Response Rate
  - Extracranial response rate is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR in extracranial lesions by Investigator assessment per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
- Global Overall Response Rate (ORR)
  - Global 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 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.
- Disease Control Rate (DCR)
  - A participant with a Best Overall Response (BOR) of CR, PR, non-CR/non-PD or stable disease (SD) is defined as having Disease Control (DC). The DC rate is defined as the percentage of participants with DC in the specified analysis set. The start date for treatment response is defined as the first study treatment date.
- 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". A figure for duration of exposure and BOR in brain metastasis (confirmed) per mRECIST v1.1 will be created.
A waterfall plot will be created to show the best percentage change from baseline in the sum of longest diameters of all target brain and extracranial metastases (separately and combined).

- 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.

6.2. Secondary Endpoints

Phase 1a:

6.2.1. Pharmacokinetic Analysis

- Analysis set: PK analysis set

Plasma concentrations of PF-07284890 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. This summarization will also be reported for PF-07284890 administered alone and coadministered with binimetinib. Plasma concentrations of binimetinib will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose of PF-07284890, cycle, day and nominal time, and again by cycle, day and nominal time.

Individual participant plasma concentration-time data of PF-07284890 within a dose interval after Cycle 1 Day 1 and Cycle 1 Day 14 will be analyzed using noncompartmental methods to determine single- and multiple- dose PK parameters.
Single-dose PK parameters of PF 07284890, where appropriate, to be estimated will include the maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and area under the plasma concentration versus time curve (AUC) from time 0 to the last sampling time point within the dose interval (AUClast), AUC within the first dose interval (AUCtau), and if data permit, AUC from time 0 extrapolated to infinity (AUCinf), terminal elimination half life (t1/2), apparent oral plasma clearance (CL/F), and apparent volume of distribution (Vz/F).

Multiple-dose PK parameters of PF 07284890, where appropriate, to be estimated will include steady state Cmax (Cmax,ss), time to maximum plasma concentration at steady state (Tmax,ss), AUC within one dose interval at steady state (AUCtau,ss), area under the plasma concentration versus time curve (AUC) from time 0 to the last sampling time point within the dose interval at steady state (AUClast,ss) minimum plasma concentration (Cmin,ss), steady-state CL/F (CLss/F), and if data permit, apparent volume of distribution (Vss/F), t1/2, and accumulation ratio (Rac) for AUCtau and Cmax.

Dose normalized parameters including AUCinf, AUCtau,ss, AUClast, Cmax and Cmax,ss will be generated by dividing the parameter value by the nominal dose level.

The single dose and steady state (ie, multiple dose) PK parameters described above will be listed and summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose level, analyte, cycle, CYP2D6 genotype and day.

Dose normalized AUCinf, AUCtau,ss, AUClast, Cmax and Cmax,ss 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. PK parameters of AUCinf, AUCtau,ss Cmax, and Cmax,ss and will be used for an informal dose proportionality analysis using the power model. All PK parameters and dose levels will be analyzed on the log scale. A linear mixed model will be used with ln(dose) as the fixed effect and patient as random effect. The 90% confidence interval of the slope will be computed from this model.

For Phase 1b Cohort 6, plasma concentrations of midazolam will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by day and nominal time.
Individual participant plasma concentration-time data for midazolam on Day -7, Cycle 1 Day 1 and Cycle 1 Day 15 will be analyzed using noncompartmental methods to determine single-dose PK parameters. PK parameters to be estimated will include the plasma Cmax, Tmax, and AUClast, and if data permit, AUCinf, t½, CL/F, and Vz/F. Midazolam 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 day.
If appropriate, a mixed effects model will then be used to analyze natural log-transformed midazolam AUClast. This model will have a fixed effect term for treatment, with participants considered random. Compound symmetry will be assumed and estimation will use REML. The difference in treatment means will be determined along with their associated 90% CI. If appropriate, midazolam Cmax and AUClast will also be analyzed using a mixed effects model with a fixed effect of treatment and participant as random. There will be no such statistical analyses of other parameters (eg, Tmax, CL/F, and t½).

6.2.2. Tumor Response

Tumor response will be analyzed and reported as decribed in section 6.1.5.

Phase 1b:

6.2.3. Adverse Events

Adverese events will be analyzed and reported as decribed in section 6.1.2.

6.2.4. Laboratory abnormalities

Laboratory abnormalities will be analyzed and reported as decribed in section 6.1.3.

6.2.5. Incidence of dose interruptions, dose modifications and discontinuations due to AEs

The Safety Analysis Set will be used. Details of analyses are provided in Section 6.5.3

6.2.6. Pharmacokinetic Analysis

Pharmacokinetics data will be analyzed and reported as decribed insection 6.2.1.

6.2.7. Disease Control Rate

- Analysis set: Response Evaluable

Disease control rate (DCR) is defined as the proportion of patients with a BOR of CR, PR or SD by Investigator assessment. DCR will be calculated for intracranial and global assessment (brain metastasis and extracranial lesions).

6.2.8. Progression-free Survival

- 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 for brain metastasis per mRECIST v1.1 and global assessment (brainmetastasis and extracranial lesions) as follows:

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

The algorithm to derive the outcome, event dates and reasons for censoring for PFS will be the same as that to derive those for the analysis of DOR (Section 6.2.11). The censoring and event date options to be considered for PFS analysis are presented in Table 2.

PFS time will be estimated using the same Kaplan-Meier method as described for DOR in Section 6.2.11. 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, or	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

6.2.9. Overall Survival

- 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.

6.2.10. Duration of Response

- Analysis set: Response Evaluable

Duration of response (DOR) is defined as the time from date of the first radiographic response (CR or PR) to the earliest documented disease progression or death due to any cause. DOR will be calculated for intracranial and global assessment (brain metastasis and extracranial lesions). Table 2 shows the censoring and event options.

6.2.11. Time to Response

- Analysis set: Response Evaluable

For patients with an objective response, time to response is the time from treatment start to date of first documentation of objective response (PR or CR).

TTR (days) = [first date of OR – date of first dose +1]

Only descriptive statistics will be provided for this endpoint. TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max, Q1, Q3).

TTR will be calculated for intracranial and global assessment (brain metastasis and extracranial lesions).

6.2.12. PK parameters of CYP3A4 probe substrate midazolam

For Cohort 6, C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F will be calculated and reported.

6.3. Tertiary/Exploratory Endpoints

Phase 1a:

CCI [redacted]

6.3.2. CSF concentrations

The concentration of PF-07284890 in CSF, as well as time-matched PK samples, will be listed for individual subjects. As CSF samples are only obtained when they are needed as part of standard of care, these data may only be obtained for a small number of patients. Additionally, the time of the CSF samples relative to drug administration will be inconsistent. Given the challenges, these data will not be summarized.

6.3.3. Biomarker Analyses

- Analysis set: Biomarker analysis set and PK analysis set

PK and biomarker (CCI [redacted]), safety endpoint or efficacy data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF 07284890 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately and are detailed in the bSAP.

6.3.4. PK- QTcF relationship

- Analysis set: PK analysis set

Matched PK and ECG data from Phase 1a may be used to investigate any possible relationship between PF-07284890 exposure (as measured by PK assessments of PF-07284890 plasma concentration) and QT prolongation. To investigate the possible relationship between PF-07284890 concentration and change from baseline in QTcF, hereafter denoted ΔQTcF, a linear mixed effect model will be used to quantify the relationship between ΔQTcF and time-matched plasma concentrations of PF-07284890. Time-matched PK and triplicate ECG data will be used in the analysis. The model will be of the form:

$$\Delta QTcF = a + b \times \text{Baseline QTcF} + c \times Cp$$

where Cp is the logarithm of time-matched plasma concentration of PF-07284890, a is the intercept, b and c are the slope for Baseline QTcF and Cp, respectively. 90% CI around b and c will be determined. Coadministration of binimetinib will be tested as a covariate. Additional model structures may be tested as appropriate. The ΔQTcF at Cmax of the RP2D will be calculated.

Phase 1b:

CCI [redacted]

6.3.6. CSF concentrations

CSF concentrations will be analyzed and reported as decribed in section 6.3.2.

6.3.7. BiomarkerAnalyses

Biomarkers will be analyzed and reported as decribed in section 6.3.3.

6.4. Subset Analyses

There are no planned subset analyses.

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 $\leq$ 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.

6.6.2. 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.

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 1. 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. 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 will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and biomarker measurements.

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

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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
ath 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
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
CCI	[redacted]
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

Abbreviation	Term
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
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}
TTR	time to response
WHO	world health organization