Protocol C0591001

A PHASE 1 DOSE ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF PF-06840003 IN PATIENTS WITH MALIGNANT GLIOMAS

Statistical Analysis Plan
(SAP)

Version: **Amendment 1**

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[redacted]

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment 1	Section 2.1 and 4.3	Wording for sample size was updated to be consistent with the protocol amendment.
	Section 8.2.4.2	Shift table for ECG abnormality was deemed unnecessary in this study and was removed.
	Section 8.2.4.2	A brief paragraph about ECHO/MUGA data was added.
	Section 8.2.9.1	Further details about neurologic and cognitive assessment data (HVLT-R, TMT, COWA, NANO) were added.
		Other editorial updates to be consistent with the protocol amendment.

2. INTRODUCTION

This document presents the statistical analysis plan (SAP) for study C0591001. The SAP is based on the protocol amendment 1 for C0591001 dated December 19, 2016.

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

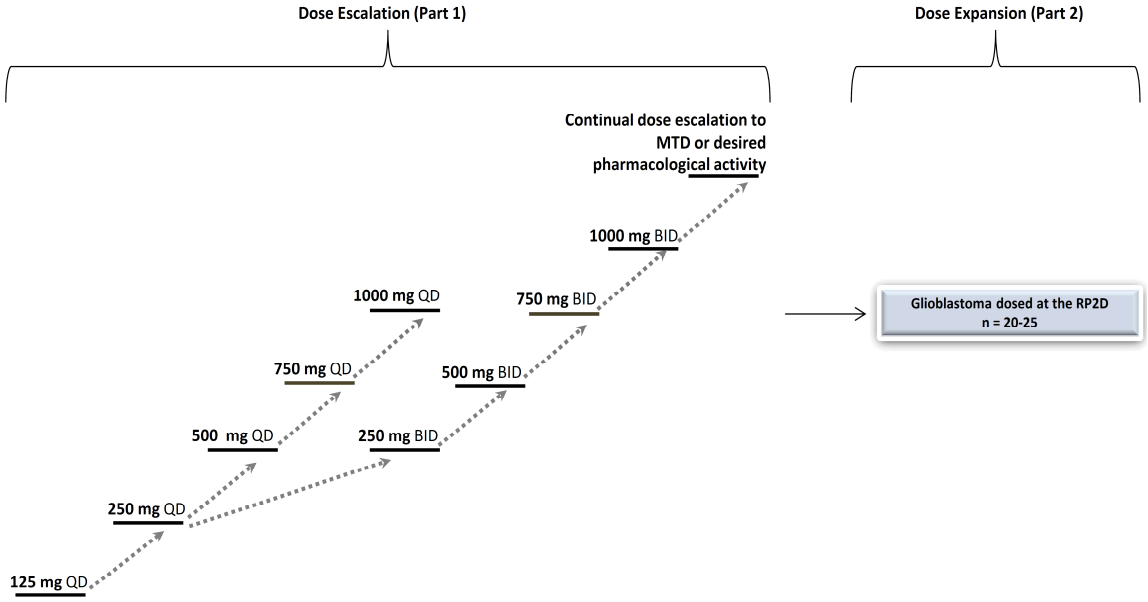
2.1. Study Design

This is a Phase 1, open-label, multi-center, multiple-dose, safety, PK and PD study of single agent PF-06840003. This study contains two parts, dose escalation (Part 1) followed by dose expansion (Part 2). In Part 1, sequential cohorts of patients with recurrent malignant gliomas (GBM and/or WHO grade III gliomas) will receive escalating doses of PF-06840003. Part 2 will evaluate safety as well as explore preliminary antitumor activity of the dose selected from Part 1 in additional patients with GBM.

The actual number of patients enrolled in the study will depend on the tolerability of PF-06840003 and the number of dose levels required to identify the MTD or Recommended Phase 2 Dose (RP2D) if the MTD is not reached. The target sample size for each cohort in Part 1 is 2-4 patients, but, the actual number of patients treated at each dose will vary from 2 to 12. It is estimated that the maximum sample size will be approximately 72 patients in Part 1 of the study, although this may be higher if more than 6 dose levels are required to be evaluated. Up to approximately 20 to 25 patients are anticipated to be enrolled in Part 2 of the study.

The overall study design is depicted in Figure 1.

Figure 1. Overall Study Design



2.2. Study Objectives

Primary Objective – Part 1

- *To evaluate the safety and tolerability of increasing dose levels of daily oral PF-6840003 in patients with malignant gliomas.*
- *To characterize the dose limiting toxicities (DLTs) of escalated doses of PF-06840003.*
- *To determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).*

Primary Objective – Part 2

- *To further evaluate the safety and tolerability of PF-06840003 at the RP2D.*
- *To evaluate the efficacy of PF-06840003 in patients with glioblastoma.*

Secondary Objectives Parts 1 and 2

- *To evaluate the overall safety profile.*
- *To characterize the single and multiple dose plasma PK of active enantiomer PF-06840002, and inactive enantiomer PF-06840001 after administration of the racemic mixture, PF-06840003.*

- *To document any anti-tumor activity (Part 1 only).*
- *To evaluate dose and concentration response relationship for target engagement and PD biomarkers and to then correlate with PK, safety and efficacy to select dose with full or optimal target engagement.*
- *To assess the CSF PK exposure of active enantiomer PF-06840002, and inactive enantiomer PF-06840001 after administration of the racemic mixture, PF-06840003.*

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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

There is no formal interim analysis planned in this study. This is an open label study, the Pfizer study team will review safety, immunogenicity, pharmacodynamics, CCI [redacted] and other data throughout the study.

4. HYPOTHESES, SAMPLE SIZE AND DECISION RULES

4.1. Statistical Hypotheses

There are no statistical hypotheses in this study.

4.2. Statistical Decision Rules

In Part 1 of the study, dose escalation and de-escalation will follow a modified Toxicity Probability Interval (mTPI) method, targeting a DLT rate of 27.5% and an acceptable DLT interval 22.5 to 32.5%. The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in the current dose level to determine one of the

following dose-finding decisions: the subsequent dose should be escalated, maintained at the current dose, or de-escalated in the next cohort of 2 to 4 patients, or the trial should be terminated.

As an example, if the total number of patients treated at the current dose level is 4, the following dosing rules are applied:

- *0 DLT -> escalate;*
- *1 DLT -> remain at the same dose;*
- *2 DLTs -> de-escalate;*
- *3-4 DLTs -> de-escalate and consider current dose as intolerable.*

The general approach to dose-finding, using the mTPI method, involves the following:

- *The target cohort size is 2 to 4, depending on the number of potential patients identified at participating sites;*
- *The next cohort can be enrolled when all patients at the current dose cohort have been evaluated for 28 days of the first treatment cycle, or experience a dose-limiting toxicity (DLT), whichever comes first;*
- *If a patient withdraws from the study before receiving ≥80% of the planned first-cycle dose for reasons other than investigational product-related toxicity, another patient will be enrolled to replace that patient at the current dose combination;*
- *In the situation in which the safety of the starting dose does not allow for escalation to the next dose level, a lower dose will be considered.*

The dose escalation portion of the study is completed when at least 6 to 12 evaluable patients have been treated at the highest dose associated with DLT rate ≤32.5%.

Table 1. Decision Rules

Number of Patients having DLT	Number of Patients Treated at a Dose Level										
	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12
0	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E
2	U	D	S	S	S	S	S	S	S	E	E
3		U	U	D	D	S	S	S	S	S	S
4			U	U	U	U	D	D	D	S	S
5				U	U	U	U	U	D	D	D
6					U	U	U	U	U	U	U
7						U	U	U	U	U	U

Actions to be taken:
D = De-escalate the dose; E: Escalate the dose; S: Stay at the dose.
U = Unacceptable toxicity.

4.3. Sample Size Determination

Due to the dynamic nature of the Bayesian allocation procedure, the sample size using the mTPI approach cannot be determined in advance in the dose escalation phase of the study. The target sample size for each cohort is 2 to 4, the actual number of patients treated at each dose will vary from 2 to 12. It is estimated that the maximum sample size will be approximately 72 patients in Part 1 of the study, although this may be higher if more than 6 dose levels are required to be evaluated. Up to approximately 20 to 25 patients are anticipated to be enrolled in Part 2 of the study.

In Part 2, the expansion phase of the study, multiple efficacy endpoints will be investigated, namely: 1) disease control rate (DCR) at Week 9; 2) DCR at Week 25; 3) objective response rate (ORR) by MRI by or at Week 9; 4) ORR by F-18-FLT-PET scan by or at Week 9 (if collected). The sample size is driven by DCR at Week 9 and ORR by MRI.

The expansion phase of the study will be a single arm study, the recommended dose from Part 1 will be used in this phase. With 20 patients, the study will have an approximately 75% power to detect a 25% improvement in Disease Control Rate (DCR), aiming for a 65% DCR, from the null hypothesis of 40% DCR. The study will have an approximately 78% power to detect a 15% improvement in ORR, aiming for a 20% ORR, from the null hypothesis of 5% ORR. These sample size calculations use a one-sample test for a single

proportion with a one-sided alpha level of 0.05. The statistical power will be slightly higher than stated above if this phase of the study enrolls more than 20-25 patients.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set includes all enrolled patients who receive at least one dose of study treatment.

5.2. Full Analysis Set

The full analysis set includes all enrolled patients. All efficacy endpoints will be analysed with this population.

5.3. Per-Protocol Analysis Set

The per-protocol analysis set includes all enrolled patients who receive at least one dose of study treatment and who do not have major treatment deviations during the 28-day observation period. Patients with major treatment deviations in this cycle are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include:

- *Administration of less than 50% of the planned dose of PF-06840003, provided that it is not due to toxicity attributable to PF-06840003;*
- *Administration of more than 150% of the planned dose of PF-06840003.*

5.4. PK analysis sets

The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest.

The PK concentration population is defined as all enrolled patients who are treated and have at least 1 analyte concentration.

5.5. Biomarker analysis set(s)

The biomarker analysis set includes all enrolled patients with at least one of the PD/biomarker parameters evaluated at pre- and/or post-dose.

5.6. Treatment Misallocations

For patients with errors in treatment allocation the following approach will be followed:

If a patient was:

- Enrolled but not treated, then they will be reported under their enrolled treatment group for demographic analyses only. These patients will be excluded from the immunogenicity, efficacy and safety analyses as the actual treatment is missing;

- Enrolled but took incorrect treatment, then they will be reported under their enrolled treatment group for efficacy analyses, excluded from analyses based on PP, but will be reported under the treatment they actually received for all safety, PK, immune responses, and immunogenicity analyses.

5.7. Protocol Deviations

Protocol deviations will be determined on an ongoing basis per medical data review. Any major protocol deviation will prevent the patient from being included in the per-protocol population.

A full list of major protocol deviations will be compiled prior to database closure. Once the final list of major protocol deviations is determined the per-protocol population flag will be updated.

6. ENDPOINTS AND COVARIATES

6.1. Primary Endpoint – Part 1

- *Incidence and grade of treatment-emergent adverse events (TEAE) including Dose Limiting Toxicity (DLTs) as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.* The specific definition of DLT is provided in the study protocol.

6.2. Primary Endpoint – Part 2

- *Adverse Events (AE) as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy.*

- *Disease control rate (DCR) at 9 and 25 weeks by MRI using Macdonald criteria (Macdonald et al, 1990).* DCR is defined as the proportion of patients achieving CR, PR, or SD as assessed by MacDonald criteria.

6.3. Secondary Endpoint

- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;*

- *Vital Signs;*

- *PK parameters in the blood of PF-06840002 and PF-06840001 Single Dose (SD) – C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and V_z/F and $t_{1/2}$, AUC_{inf} as data permit. Multiple Dose (MD) (assuming steady state is achieved) – $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL/F, V_z/F, R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$) and R_{ss} ($AUC_{ss,\tau}/AUC_{sd,inf}$) as data permit;*

- *Objective tumor response based on Macdonald criteria.* Objective tumor response is defined as the proportion of patients achieving CR or PR as assessed by Macdonald criteria.

- *Disease Control Rate at 9 and 25 weeks by MRI based on Response Assessment for Neuro-Oncology (RANO) criteria.*
- *On-target activity of PF-06840003 by measurement of kynurenine, tryptophan and kyn/trp (ratio) levels in peripheral blood.*
- Steady-state trough level ratio between CSF and plasma samples for PF-06840002 and PF-06840001.

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6.5. Covariates

Not applicable.

7. HANDLING OF MISSING VALUES

7.1. Missing Values For Safety, Immune Responses, Pharmacodynamics, Immunogenicity, [redacted]

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All the safety, immune responses, pharmacokinetic, pharmacodynamics, immunogenicity analyses and summaries will be based on data as observed and no explicit imputation will be applied.

7.2. Immune Responses Lower Limit Of Quantitation

Titers below the assay detection limit will be assigned a value of one-half that limit

7.3. Pharmacokinetic Concentrations And Parameters

Drug concentrations below the limit of quantification

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

Deviations, missing concentrations and anomalous values

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

In summary tables and plots of mean profiles of PK, 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 (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the PK analyst.

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

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

Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters. In the event that the actual sampling time is not available, the nominal time may be used if there is no evidence that the actual sampling time deviates substantially from the nominal time.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance, if applicable), PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter (due, for example, to an unexpected event such as vomiting before all the drug is absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

In general, all continuous endpoints will be summarized descriptively by dose level. If data are categorical then the standard contingency tables with counts and percent by dose level will be displayed.

8.1. Statistical Methodology

Part 1, the dose escalation phase of this study, employs an mTPI design to estimate the MTD. The mTPI design employs a simple beta binomial model with prior a conjugated prior beta (0.5, 0.5). Decision rules are based on calculating the unit probability mass (UPM) of 3 intervals corresponding to underdosing, proper dosing, and overdosing in terms of dose limiting toxicity. A proper dosing interval is centered at the target toxicity rate (pT) of 27.5% with 5% uncertainty (0.225 < pT <0.325). The under dosing interval is (0, 0.225), and the overdosing interval is (0.325, 1). The 3 dosing intervals are associated with 3 different dose escalation decisions. The underdosing interval corresponds to a dose escalation, overdosing corresponds to a dose de-escalation, and proper dosing corresponds to staying at the same current dose. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM implies the corresponding dose finding decision. That decision provides the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, decision E (to escalate) will be executed, and the next cohort of patients will be treated at the next higher dose level. Under the mTPI design, a trial is terminated when either the lowest dose is above the MTD or a pre-specified maximum sample size is reached. Doses with an incidence of DLT >33% (eg, 4 out of 10) will not be declared as MTD even though it is allowed by the mTPI method.

8.2. Statistical Analyses

There are 2 parts in the study. Generally analysis output is to be generated for Part 1 and Part 2 separately, unless where it specifies a combined analysis is to be conducted.

8.2.1. Subject Disposition

Subject disposition will be summarized by dose level and will include the number of patients enrolled, treated, treated and completed the study, treated but did not complete the study and reason for early discontinuation from the study. Subject disposition summary will be generated using the full analysis set.

8.2.2. Subject Demographics and Baseline Characteristics

Demographic, ECOG performance status (Karnofsky Performance Score, as detailed in Appendix 2 of the study protocol), childbearing potential and other baseline characteristics CCI and number of prior therapies) will be summarized by dose level using the full analysis set.

8.2.3. Study Treatment Exposure and Dose Intensity

Duration of treatment (number of days and number of cycles) will be summarized by dose level. Relative Dose Intensity (ratio of actually administered dose to scheduled/planned dose per unit time) will be summarized for each dose level and by cycle. Relative Dose will be summarized for each dose level across all cycles. Detailed algorithms for these calculations are provided in the appendix. (Appendix 1.1).

The number of patients with missed dose may be summarized by dose level.

Patient level study treatment administration data will be listed in chronological order by dose level.

These analyses will be performed with the safety analysis set.

8.2.4. Safety Analysis

Safety analysis will be based on the safety analysis set.

8.2.4.1. Analysis of Primary Safety Endpoint

In Part 1 of the study, dose limiting toxicity (DLT) is a primary endpoint. Adverse events constituting DLTs are detailed in the study protocol. Adverse events constituting DLTs will be listed by dose level. A binary variable will be created at the patient level to indicate whether or not a patient has experienced any of the adverse events that are considered DLT. If required, a summary table will be created by dose to present number and percentage of patients experiencing DLT.

Treatment-emergent adverse events (TEAE) are defined as those events that occur after the first dosing or any pre-existing adverse event that worsened after the first dosing. The lag time required for defining TEAE will be based on Pfizer Standard. TEAE will be listed by dose level where system organ class and preferred term as well as other collected variables about the AE will be displayed. If necessary, a summary table for TEAE by system organ class and preferred term for each dose level will be generated. Similarly serious adverse events (SAE), and treatment related SAEs will be listed. Summary tables may be generated if necessary.

In Part 2, TEAE, treatment related TEAE, SAE, and treatment related SAEs will be listed and summarized. TEAE will also be summarized by CTC AE (version 4.03) grade and by system organ class and preferred term.

8.2.4.2. Analysis of Secondary Safety Endpoint

These safety endpoints will be analyzed according to the Pfizer Data Standard.

Laboratory Tests Abnormalities

Laboratory tests will be listed by dose level and cycle and day. Upon reviewing the lab data listing, if study team deems necessary, summary tables and tables presenting the change and percent change from baseline may be generated by dose level and cycle and day. Shift tables may be provided to examine the distribution of laboratory toxicities. Shift tables will be created for each laboratory test for baseline relative to each post-baseline measurement by maximum CTCAE grade, cycle, and dose. The most recent measurement prior to dosing is considered as baseline.

On-target activity of PF-06840003 by measurement of kynurenine, tryptophan and kyn/trp (ratio) levels in peripheral blood will be listed by dose and cycle and day.

Vitals signs

Vital signs, (ie, body temperature and blood pressure), will be listed by dose level and cycle and day. Upon reviewing the vital signs data listing, if study team deems necessary, summary tables and tables presenting change and percent change from baseline may be generated by dose level and cycle and day. The most recent measurement prior to dosing is considered as baseline.

ECG

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as the latest assessment prior to receipt of the first dose (ie, Cycle 1 Day 1), ie, the average of the latest pre-dose triplicate ECG on Cycle 1 Day 1. If the Cycle 1 Day 1 timepoint is not available, the screening assessment will be used as the baseline.

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 (QTc) using standard correction factors (ie, Fridericia's). Data will be summarized and listed for QT, HR, response rate (RR), PR, QRS, QTcF, and dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive

statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT using maximum CTCAE Grade. Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

Physical Examination

Physical examination results will be listed by dose level and cycle. Upon reviewing the subject level data listing, if study team deems necessary, summary table may be generated by dose level and cycle.

ECHO/MUGA

LVEF (left ventricle ejection fraction) results from the cardiac function evaluation by ECHO or MUGA will be listed by dose level and cycle in a subject data listing. Upon reviewing the subject data listing, if study team deems necessary, summary table of LVEF over time and/or change from baseline in LVEF may be generated by dose level and cycle.

8.2.5. Efficacy Analysis

Efficacy will be investigated in both Part 1 and Part 2 of the study.

8.2.5.1. Primary Efficacy Analysis

Tumor assessments including MRI will be performed every 8 weeks (with an allowable window per study protocol) after the first dose. Disease control rate (DCR), defined as the proportion of patients achieving CR, PR, or SD as assessed by Macdonald criteria, will be summarized and listed by dose level and week. A cycle is 4 weeks long. Number of weeks will be derived based on cycle numbers. This will be performed for Part 1 and Part 2 separately. If deemed necessary and data permits, a combined analysis may be performed where Part 2 and the same dose level in Part 1 as that in Part 2 will be combined. These analyses will be based on investigator provided overall disease assessment.

As data accumulates, a Bayesian approach with a non-informative Jeffery's prior beta (0.5, 0.5) will be used to calculate the posterior probability of observing certain DCR (eg, 40%, 50%, 60% etc.). The purpose of it is to monitor data on an ongoing basis and to provide more analytical data for the study team. No official analysis output needs to be generated for this. This is only applicable to Part 2.

8.2.5.2. Secondary Efficacy Analysis

ORR with Macdonald Criteria

Objective tumor response (ORR), defined as the proportion of patients achieving CR or PR as assessed by Macdonald criteria, will be summarized and listed by dose level week. This will be performed for Part 1 and Part 2 separately. If deemed necessary and data permits, a combined analysis may be performed where Part 2 and the same dose level in Part 1 as that in Part 2 will be combined.

As data accumulates, a Bayesian approach with a non-informative Jeffery's prior beta (0.5, 0.5) will be used to calculate the posterior probability of observing certain ORR (eg, 5%, 10%, 15%, or 20% etc.). The purpose of it is to monitor data on an ongoing basis and to provide more analytical data for the study team. No official analysis output needs to be generated for this. This is only applicable to Part 2.

For example, if 2 responders were observed in the first 10 patients enrolled, the posterior probability of observing 20% ORR is about 53.3%; if 2 responders were observed in the first 12 patients enrolled, the posterior probability of observing 20% ORR is about 41.5%; if only 1 responder was observed in the first 15 patients enrolled, the posterior probability of observing 20% ORR is about 8.7%. If a posterior probability is less than 15% for both of the 2 efficacy endpoints, the study team may choose to stop the expansion phase for futility. The safety data will also be reviewed in that decision-making process.

DCR with RANO Criteria

Overall DCR based on Response Assessment for Neuro-Oncology (RANO) criteria will be summarized by week. The analysis will be based on investigator provided overall response in the Response Assessment in Neuro-Oncology. This will be performed for Part 1 and Part 2 separately. If deemed necessary and data permits, a combined analysis may be performed where Part 2 and the same dose level in Part 1 as that in Part 2 will be combined.

CCI [redacted] On the basis of RANO, the key component of iRANO is specific additional guidance for the determination of PD among neuro-oncology patients undergoing immunotherapy. Specifically, iRANO advocates the confirmation of radiographic progression in appropriate patients defined by clinical status and time from initiation of immunotherapy. Other details related to the PD confirmation will be documented in the Programming Plan.

PFS

Progress-free survival (PFS) is defined as the time from date of enrollment to first PD or death due to any cause in the absence of documented PD. PFS will be analyzed in an exploratory manner. Kaplan-Meier analysis may be performed. If it is performed, the median PFS and 2-sided 95% confidence interval will be reported by dose level. Kaplan-Meier plot may also be generated by dose level.

This will be performed for Part 1 and Part 2 separately. If deemed necessary and data permits, a combined analysis may be performed where Part 2 and the same dose level in Part 1 as that in Part 2 will be combined.

Tumor measurement and assessment data

Tumor measurement data (target lesions, new measurable lesions, non-target lesions, and new non-measurable lesions), as collected, will be listed at patient level by dose and cycle.

Tumor assessment data for both Macdonald criteria and RANO criteria will be listed at patient level by dose and cycle.

Summary table for this data may be generated, if deemed necessary.

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CCI [redacted]	
[redacted]	
[redacted]	

8.2.7. Analysis of Biomarker Endpoints

For biomarker samples, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and post-treatment. For each pair of specimens, the percent change from baseline of these same parameters will also be calculated.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA). The statistical approach will examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

8.2.8. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

Pharmacokinetic and PD 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-06840002 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

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Appendix 1. Appendices

Appendix 1.1. Summarizing Relative Dose (RD) and Relative Dose Intensity (RDI)

Conventions:

- The Intended Dose Intensity is the same for all cycles: the daily dose is fixed at the start of treatment rather than start of a cycle and the intended treatment duration is the same for the entire dosing period;
- Actual Dose Intensity is calculated based on actual cycle length in all but last cycle where it is fixed at the intended length (eg, 3 weeks for a 2/1 dosing schedule).

Table 1.

Treatment / Summary	Calculation of RD	Example
Overall	$RD = \frac{Actual\ Total\ Dose}{Intended\ Total\ Dose} * 100\ \%$ *Actual Total Dose* = sum of Total daily dose across all cycles (as recorded on CRF) *Intended Total Dose* = (Planned Daily Dose) * (Actual Dose Duration in days) Actual Dose Duration (days) = (date of last dose – date of first dose +1)	• IDO is to be dosed at 125 mg QD. • 1st IDO: January 1, last IDO: December 31 (same year) • Actual dosing: 125 mg for 250 days and 100 mg for 115 days Actual Total Dose = 125*250 + 100*115=42,750 mg Actual Dose Duration (days) = 365 Intended Total Dose = 125*365=45,625 mg RD=(42,750 / 45,625)*100%=93.7%

Table 2.

Treatment / Summary Type (#)	Calculation of RDI	Example
By Cycle	$RDI = \frac{Actual\ Dose\ Intensity}{Intended\ Dose\ Intensity} * 100\%$ *Actual Dose Intensity (per week)* = (Actual Total Dose per cycle) / (Actual number of weeks in cycle) *Actual Number of Weeks in Cycle* = (Start date of next cycle – Start date of current cycle) / 7. *Intended Dose Intensity (per week)* = (Intended Total Dose per cycle) / (Intended number of weeks in cycle)	• IDO is to be dosed at 125 mg QD for a cycle of 28 days (4 weeks) Intended Dose Intensity = (125*7*4) / 4 = 875 mg/wk <u>Cycle 1:</u> Actual Dose Intensity = (125*7*4) / 4 = 875 mg/wk RDI = (875/875) * 100% = 100% <u>Cycle 2 (only took 3-week worth of dose overall a 4-week duration):</u> Actual Dose Intensity = (125*7*3) / 4 = 656.25 mg/wk RDI = (656.25/875) * 100% = 75%