Protocol B7831001

A PHASE 1 DOSE ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF PF-06671008 IN PATIENTS WITH ADVANCED SOLID TUMORS

Statistical Analysis Plan
(SAP)

Version: 2.0

Author: PPD (Early Oncology Development and Clinical Research Statistics, San Diego, CA, USA)

Date: 17-July-2018

[redacted]

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

APPENDICES

1. VERSION HISTORY

This is the second version of the statistical analysis plan, based on the protocol dated Jan 12, 2018.[1]

Texts taken directly from the protocol are made *Italicized.*

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7831001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Part 1 (Dose-Escalation) Primary Objective

- *To assess safety and tolerability of increasing dose levels of PF-06671008 administered in patients with advanced solid tumors for whom no standard therapy is available in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).*

Part 1 (Dose-Escalation) Secondary Objectives

- *To evaluate the overall safety profile;*
- *To characterize the single and multiple dose pharmacokinetics (PK) of PF-06671008;*
- *To evaluate the immunogenicity of PF-06671008;*
- *To document any anti-tumor activity.*

CCI

[redacted]

CCI

[redacted]

Part 2 (Dose-Expansion) Primary Objective

- *To confirm safety and tolerability and explore preliminary evidence of anti-tumor activity of PF-06671008 at the RP2D in patients with P-cadherin expressing advanced CRC, TNBC or NSCLC.*

Part 2 (Dose-Expansion) Secondary Objectives

- *To evaluate the overall safety profile at the RP2D;*
- *To characterize the single and multiple dose PK of PF-06671008;*
- *To evaluate the immunogenicity of PF-06671008;*
- *To evaluate preliminary anti-tumor activity through time to event endpoints.*

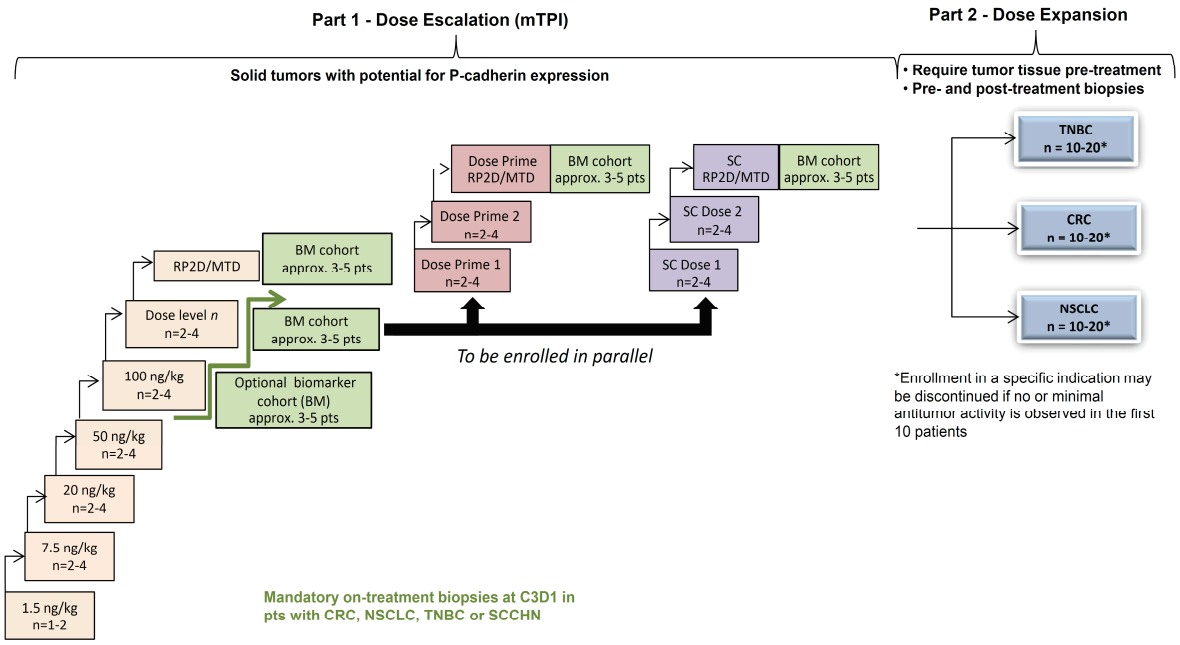
CCI

[redacted]

2.2. Study Design

This is a Phase 1, open-label, multi-center, multiple-dose, safety, PK [redacted] *study of single-agent PF-06671008. This study contains two parts, dose escalation (Part 1) followed by dose expansion (Part 2). Sequential cohorts of patients with tumor types with the potential to have P-cadherin expression, that is resistant to standard therapy or for whom no standard therapy is available will receive escalating doses of PF-06671008, in Part 1 of the study. Part 2 will evaluate the dose selected from Part 1 in patients with P-cadherin expressing TNBC, CRC or NSCLC. The overall study design is depicted in* Figure 1 *below.*

Figure 1. Overall Study Design



Upto approximately 152 patients are expected to be enrolled in the study overall. The actual number of patients enrolled will depend on the tolerability of PF-06671008 and the number of dose levels required to identify the MTD.

[Reference Source: Protocol Section 3.1]

2.2.1. Dose Escalation Phase (Part 1)

Increasing dose levels of PF-06671008 administered weekly will be evaluated using a modified toxicity probability interval (mTPI) method that targets a MTD associated with a 27.5% probability of DLT. Part 1 will follow a mTPI method initially with cohorts of 1-2 patients each and a primary DLT observation period of 21 days following the first dose (C1D1).

If a DLT or other toxicities occur (ie, those that have the potential to be DLTs if more severe) during Cycle 1 but prior to the observation of CTCAE Grade ≥2 cytokine release syndrome (as described below in Evaluation of a Priming Dose), dose escalation will continue to

follow a mTPI design but with cohorts of 2-4 patients each. The primary DLT observation period will continue to be 21 days following the first dose (C1D1).

Additional patients may be entered at any dose level in the IV and/or SC routes of administration at or below the MTD, after discussion with and permission by the sponsor, to obtain additional safety, PK CCI *and anti-tumor activity data.* CCI [redacted] *These additional patients will require paired biopsies. Because these additional patients will receive a dose lower than the concurrent dose escalation cohort or will be enrolled at dose following the DLT evaluation period in the first 2-4 patients enrolled, their potential DLT observations may not be strictly used in the mTPI algorithm for the ongoing dose finding. However, the safety profile from these additional patients will be used to establish the MTD or recommended Phase 2 dose (RP2D).*

2.2.2. Evaluation of a Priming Dose

Based on toxicity study results, the evaluation of a priming dose to allow subsequent higher level dose administration may be instituted in this study. In addition, blinatumomab, an approved bispecific agent for the treatment of ALL, has been able to overcome symptoms of cytokine release syndrome (CRS) with the implementation of a priming dose (Topp et al, 2014).[9] *Therefore, this study may implement the evaluation of a priming dose during the escalation phase.*

The initial priming dose will be defined to facilitate subsequent dose escalation towards establishing the MTD of a dosing regimen that includes a priming dose. The study aims to determine a MTD for an IV dose regimen that does not include a priming dose, and an independent MTD for an IV dose regimen that includes a priming dose. In addition, the study aims to similarly determine a MTD for PF-06671008 administered subcutaneously that may or may not include a priming dose.

The decision to evaluate a regimen that includes a priming dose may be made by the investigators and sponsor prior to reaching a MTD using the following criteria as guidance:

If a dose level induces symptoms consistent with Grade 3 CRS as defined in the protocol lasting for >24 hours considered not to be due to an infusion related reaction (IRR), allergic reaction, anaphylaxis or other causes in a cohort of 2-4 patients after the initial infusion, an additional 1-4 patients (up to approximately 6 patients overall) will be enrolled at that dose to confirm implementation of a priming dose (Dose Prime) for subsequent cohorts. If an additional confirmed CRS of Grade 3 lasting for >24 hours is observed at that dose, then a lower dose, which has been evaluated in at least 2-4 patients, will be chosen as a priming dose (Dose Prime) for subsequent cohorts. If a Dose Prime is selected, dose escalation will continue to determine the MTD of a dose regimen that includes a priming dose. The evaluation of a Dose Prime may be implemented for both the IV and/or SC routes of administration.

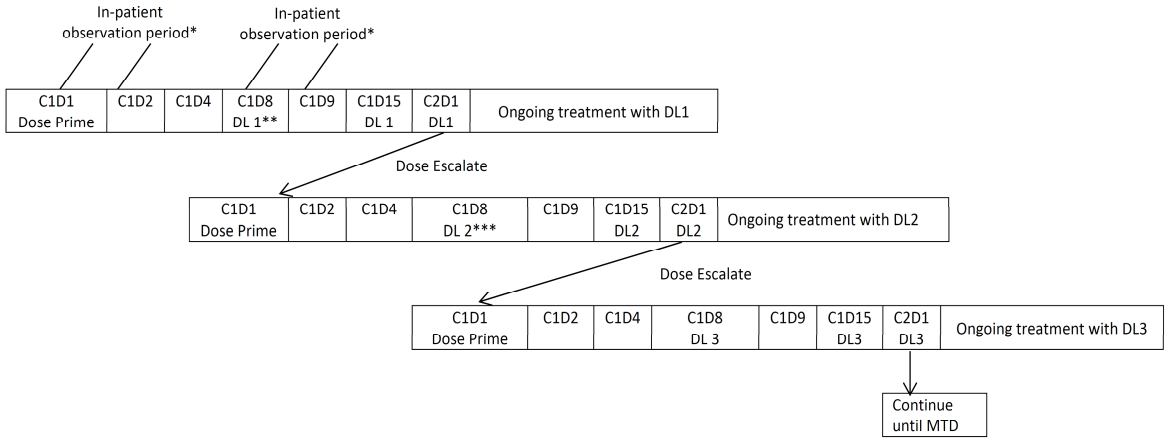
If a dose level induces confirmed CRS of Grade 4 considered not to be due to an IRR, allergic reaction, anaphylaxis or other causes, then a lower dose, which has been evaluated in at least 2-4 patients, will be chosen as a priming dose (Dose Prime) for subsequent cohorts.

In addition, observation of a confirmed CRS event that meets the above qualifications following later infusions (ie, after Cycle 1 Day 1) or CRS events that are approaching the limit of tolerablity may prompt the investigators and sponsor to include evaluation of a Dose Prime for subsequent cohorts.

After confirmation of the safety of Dose Prime, the treatment schedule will implement the inclusion of the fixed priming dose as the first dose (C1D1) followed by a second dose (C1D8) that will continue to be escalated in subsequent cohorts following an mTPI method in cohorts of 2-4 patients. After the MTD has been established, the priming dose may potentially be further verified in connection to the established MTD/RP2D, including consideration of more than one priming step, if indicated, using information from all patients who were included in the initial priming dose determination as well as those enrolled in subsequent dosing cohorts.

The primary DLT observation period for cohorts that include Dose Prime will be 21 days following the first dose (C1D1). The dose escalation should a Dose Prime be instituted is depicted in Figure 2.

Figure 2 Study Schematic Should Dose Prime Be Explored



DL = Dose Level
* In-patient observation applies to all cohorts
** Dose level 1 will be higher than Dose Prime
*** Dose level 2 will be higher than Dose Level 1

For cohorts instituting a Dose Prime, there will be a 72 hour observation period between the first dose administered to each of the initial patients enrolled (ie, patients contributing to initial DLT evaluation) at a new dose level. In addition to in-patient observation following the C1D1 dose, patients enrolled in cohorts instituting a Dose Prime must also undergo in-patient observation for at least 24 hours (for cohorts where PF-06671008 will be administered IV) or 48 hours (for cohorts where PF-06671008 will be administered SC) following the C1D8 dose.

2.2.3. Criteria for Dose Escalation

The study has been designed to establish the MTD defined as the dose that yields approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) 22.5% to 32.5%.

Typically patients will be enrolled in cohorts of 2 to 4, but patients could be initially enrolled in cohorts of 1-2 for the lower doses (see section Dose Escalation Phase (Part 1)). The initial 2-4 patients to be included in a cohort will be open to any of the tumor types outlined in the protocol. When required to expand a cohort for further evaluation of the MTD, enrollment of patients may be limited to those with NSCLC, SCCHN, CRC or TNBC.

For IV administration cohorts, initial dose levels are provided in Table 1 and will be followed if no DLTs are observed; intermediate doses may be evaluated based on clinical findings. Subsequent maximum dose increases will be a maximum of 2-fold (100%) if no DLTs are observed. For SC administration cohorts, during the initial dose escalation levels, maximum dose increases will be up to 3-fold if no DLTs or safety events that are approaching the limit of tolerability are observed. The initial dose to be evaluated for SC administration will be equal to the dose level selected as the IV Dose Prime. The evaluation of the IV and SC routes of administration will proceed through dose escalation independently according to the mTPI method. Once the first DLT is observed, the maximum increase would follow a modified Fibonacci series in case of dose escalation (ie, 67%, 50%, 33%, etc.). Patients will be assigned to a dose that is closest to the current MTD prediction based on the mTPI method. The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level to determine (Decision Rules) where future cohorts should involve dose escalation, no change in dose, or dose de-escalation as presented in Table 2.

Table 1. Dose Escalation Levels

Dose Level	Dose (ng/kg)
1 (Starting Dose)	1.5
2	7.5
3	20
4	50
5	100
6	200
7	300
8	400

Table 2. Decision Rules

	Number of Patient Treated at a Dose Level										
Number of Patients Having DLT	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	S	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

D: De-escalate the dose; E: Escalate the dose; S: Stay at the dose; U: Unacceptable toxicity
Note: If one patient has a DLT event observed in a dose cohort with 1 patient enrolled, additional patients (eg, 1 or 2) may be enrolled for dose escalation assessment.

Dose escalation will stop under any of the following conditions:

- *The maximum sample size has been achieved;*
- *6-12 patients have been enrolled at a dose that is predicted to be the MTD;*
- *All doses explored appear to be overly toxic and the MTD cannot be determined.*

Intrapatient dose escalation, other than the potential inclusion of a priming dose, will not be permitted in this study.

2.2.4. MTD Definition

The estimated MTD is the dose level associated with approximately 27.5% of DLT-evaluable patients experiencing a DLT. The target interval for the DLT rate is (22.5%-32.5%). Due to the discreteness of the dose levels and in the interest of the safety of patients, the estimated MTD is the highest tested dose level with DLT rate ≤0.325 in at least 6-12 DLT evaluable patients for DLT. The study aims to determine a MTD for a dose regimen that does not include a priming dose administered IV, and an independent MTD for an IV dose regimen that includes a priming dose. In addition, the study aims to determine a MTD for PF-06671008 administered SC and may also determine an independent MTD for a SC dose regimen that includes a priming dose.

2.3. Dose Expansion Phase (Part 2)

The maximum sample size for each tumor indication (ie, TNBC, CRC and NSCLC) will be in the range of n=10 to 20 evaluable patients. Enrollment of patients in one indication may be discontinued if minimal or no anti-tumor activity (eg, 0 or 1 response) is observed in the first 10 evaluable patients for that indication.

2.3.1. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further study based on Phase 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD (eg, if in the expansion part >25% of patients require a dose reduction due to toxicity, then the sponsor and investigator determine if a lower RP2D needs to be determined).

3. ENDPOINTS AND COVARIATES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Primary Endpoint (Part 1)

- *First cycle Dose-Limiting Toxicities (DLTs).*

Primary Endpoint (Part 2)

- *Objective response (OR) as determined by the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 criteria (Appendix 3).*

3.2. Secondary Endpoint (s)

- *Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03) timing, seriousness, and relationship to study therapy;*
- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;*
- *Vital sign abnormalities;*
- Pharmacokinetic parameters of PF-06671008 Single Dose (SD) - C_{max}, T_{max}, $AUC_{sd,\tau}$, $t_{1/2}$, AUC_{inf}, and CL for intravenous (IV) administration or apparent clearance (CL/F) for subcutaneous (SC) administration as data permit. Multiple Dose (MD) (assuming steady state is achieved) - $C_{max,ss}$, $T_{max,ss}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{min,ss}$, CL for IV or CL/F for SC, volume of distribution (V_{ss}) for IV or apparent volume of distribution at steady state (V_{ss}/F) for SC, and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$) as data permit;
- Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies against PF-06671008;
- *Objective response, as assessed using the RECIST version 1.1 – Part 1 only;*
- *Progression Free Survival (PFS) and Overall Survival (OS) – Part 2 only.*

CCI

CCI

Covariates may also be considered when exploring QTc and PK relationship.

4. ANALYSIS SETS

Several analysis sets are defined and will be considered for this study.

4.1. Full Analysis Set

The full analysis set includes all enrolled patients. This is equivalent to the ITT (intent-to-treat) population.

4.2. Safety Analysis Set

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

4.3. 'PER PROTOCOL' Analysis Set (Part 1)

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 first cycle. Patients with major treatment deviations during the first cycle of treatment are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include failure to satisfy major entry criteria (eg, confirmation of the target disease; signed informed consent) or use of other anticancer treatments during the active treatment and disease follow-up phases other than as defined/allowed in this protocol.

4.4. PK Analysis Set

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 and who have no major protocol deviations influencing the PK assessment.

CCI [redacted]

[redacted].

4.6. Modified Intent-to-Treat Set

The modified intent-to-treat (mITT) population is defined as all the randomized subjects who have received at least 1 dose of study medication, have measurable disease baseline assessment (within 28 days prior to study entry) and at least 1 post baseline assessment or disease progression or death before the first tumor assessment. The mITT population may be used for interim analysis and conference presentations when the study is still ongoing.

4.7. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as patients who receive at least 1 dose of study treatment and have at least 1 ADA sample analyzed.

4.8. Protocol Deviations

The determination of protocol deviations (PDs) and important protocol deviations (IPDs) will follow Pfizer standard operating procedures. A full list of PDs, IPDs, and IPDs that exclude a patient from the Per-protocol analysis will be determined prior to the database release and be included in the CSR.

5. GENERAL METHODOLOGY AND CONVENTIONS

This is an open-label dose escalation study and no interim analysis or blinding is planned for this study. The final analysis will be conducted after the last subject last visit (LSLV).

5.1. Statistical Hypotheses

There are no statistical hypotheses. The emphasis of the final analyses will be on estimation of study endpoints.

5.2. Statistical Decision Rules

5.2.1. Part 1 (MTD Finding)

In Part 1, patients will participate in a dose escalation phase aimed at estimating the MTD. The sample size for this component of the study will vary depending on the number of DLTs observed. It is anticipated that the maximum sample size of approximately upto 92 patients are expected to be enrolled in Part 1 of the study at 3 - 6 sites. The actual number of patients enrolled will depend upon tolerability and the number of dose levels required to identify the MTD.

The minimum and maximum sample sizes after which Part 1 can be stopped and MTD declared are approximately 6-12 and approximately 92 patients, respectively. As for the number of patients treated at each dose, it is expected that the typical number will be 1 to 4 patients for the doses actually studied. However, since variable cohort size is allowed, the actual number of patients treated at each dose will vary from 1 to 12.

The following table shows the probability of escalating to the next dose level for a range of underlying true DLT rates. For example, for a cohort size of n=3 and for a DLT that occurs in 10% of patients, there is a greater than 90% probability of escalating. Conversely, for a DLT that occurs with a rate of 70%, the probability of escalating is 3%. It is assumed that dose escalation occurs with either 0/3 or 1/6 patients with DLTs.

Probability of Escalating Dose									
True underlying DLT rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalating	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.009	0.001

5.2.2. Part 2 (Dose Expansion)

In **Part 2** the maximum sample sizes for each tumor indication (ie, TNBC, CRC and NSCLC) will be of n=10 to 20 evaluable patients. Enrollment of patients in one indication may be discontinued if minimal or no anti-tumor activity (eg 0 or 1 response) is observed in the first 10 evaluable patients for that indication.

5.2.3. Sample Size Determination

The exact sample size for the dose escalation design in Part 1 cannot be specified in advance due to the dynamic features of mTPI.

Assuming a non-informative prior (ie, Jeffrey's prior) if 1 out of 10 patients have tumor response, this would predict a posterior probability (Beta-Binomial) equal to 0.93 that the true response is inferior to 30%. On the other hand, if 7 out of 20 patients have tumor response, this would predict a posterior probability equal to 0.70 that the true response is not inferior to 30% and a posterior probability equal to 0.05 (5%) that the true response is inferior to 20%. In addition, posterior probabilities may be calculated by using informative priors based on the antitumor activity that may be observed during Part 1 (eg 2 out of 3 TNBC patients experience tumor response in Part 1). These posterior probabilities will be assessed for each indication during Part 2 when at least the first 10 Pts are enrolled in that indication. Posterior Probabilities >0.75 of an ORR <20% (eg, 0,1 out of 10; 0,1,2 out of 16) may provide evidence of no substantial anti-tumor activity for that indication.

[Reference Source: Protocol Section 9.3]

CCI [redacted]

[redacted]

[redacted]

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration in the first cycle (in general C1D1). All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

5.3.1. Analyses for Time to Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method[2] and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint (Brookmeyer and Crowley, 1982[3]) will be provided.

5.3.2. Analyses for Binary Data

The rates of binary endpoints will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method.

5.3.3. Analyses for Continuous Data

Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints.

5.3.4. Analyses for Pharmacokinetic Data

Blood samples for PK analysis of PF-06671008 will be taken according to the Schedule of Activities given in the protocol. PK parameters listed in Section 3.2 will be derived from the concentration-time data using non compartmental analysis as follows:

Parameter	Definition	Method of Determination
$AUC_{sd,\tau}$	Area under the concentration-time profile from time zero to the time τ, the dosing interval	Linear/Log trapezoidal method
$AUC_{ss,\tau}$	Area under the concentration-time profile during one dosing interval, τ, at steady state	Linear/Log trapezoidal method
AUC_{inf}	Area under the concentration-time profile from time zero extrapolated to infinite time	$AUC_{(0\text{-}t[last])}$ + (Clast*/kel), where Clast* is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum observed oncentration	Observed directly from data
$C_{max,ss}$	Maximum observed oncentration at steady state	Observed directly from data
$C_{min,ss}$	Minimum observed oncentration at steady state	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data
$T_{max,ss}$	Time for C_{max} at steady state	Observed directly from data
$t_{½}$	Terminal elimination half-life	Loge(2)/kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL	Clearance for IV administration	Dose/ AUC_{inf} for dose 1; Dose/ AUC_{τ} for dose 4
CL/F	Apparent clearance for SC administration	Dose/ AUC_{inf} for dose 1; Dose/ AUC_{τ} for dose 4
V_{ss}	Volume of distribution at steady state for IV administration	CL×MRT
V_{ss}/F	Apparent volume of distribution at steady state for SC administration	CL/F×MRT
R_{ac}	Observed accumulation ratio	$AUC_{dose\ 4,\ \tau}$/ $AUC_{dose\ 1,\ \tau}$

5.3.5. Analyses for Immunogenicity Data

Anti-PF-06671008 antibody data will be collected at baseline and post treatment according to the protocol.

5.4. Methods

5.4.1. Missing Data

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, ECG, CCI [redacted] which will only use the actual date collected or if date not available deem the data missing.

5.4.2. Efficacy Analysis

In this First In Patient study anti-tumor activity is a primary objective for Part 2 of the study.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor response at each visit, and best overall response. In addition, progression date, death date, date of first response and last tumor assessment date, and date of last contact will be listed.

The definition of each response category is provided in Appendix 3 (RECIST v1.1) CCI [redacted]

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.

5.4.3. Pharmacokinetics

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).

Deviations, missing concentrations and anomalous values

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

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

1. A concentration has been reported 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 pharmacokineticist.

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

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

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). (Note that NC values will not be generated beyond the day that a subject discontinues).

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

If an individual subject has a known biased estimate of a PK parameter (due for example to 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.

6. ANALYSES AND SUMMARIES

6.1. Standard Analyses

Study Conduct and Patient Disposition

An accounting of the study patients will be tabulated. The subject evaluation groups will be listed. The Full Analysis Set will be used.

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

Baseline Characteristics

Baseline characteristics such as demographics, prior medication, medical history, ECOG performance status, and primary diagnosis will be tabulated and listed. For ECOG performance status a shift table (worst post-baseline vs baseline may be produced). The Safety Analysis Set will be used.

Treatment Administration/Compliance

Listings and tables by dose level will be provided. The safety analysis set will be used.

Dose modifications may occur in the following ways:

- Cycle delay;
- Dose delay within a Cycle;
- Dose reduction—A decrease in the administered total daily dose (non-zero) compared to the planned total daily dose upon enrollment. If in the CRF the prescribed dose unit is mg/kg, but the actual dose is in ng the actual dose ng/kg should be calculated considering the body weight of the patient at that visit.

The following will be summarized by patient for overall and each dose level:

- Number of subjects per dose level (Prime and non-Prime);
- Median and range of number of cycles started per subject;
- Number (%) of subjects starting a cycle (1, 2, 3…);
- Number (%) of patients with cycle delays;
- Number (%) of dose interruptions (include both known and unknown dates);
- Number (%) of patients with dose reductions;
- Number (%) of each reason (drug related AE vs AE vs. Other) for cycle delays, dose interruptions and dose reductions;
- Time on treatment (median, range).

The following will be summarized by cycle:

- For ongoing subjects, the last cycle end date is the cycle start date + number of days per cycle - 1 day;
- For completers and discontinued subjects, if the Systemic Therapy dataset exists , the end date would be the earliest date of the start date of the new anticancer treatment or last active treatment + 27 days. If the Systemic Therapy SCRF data does not exist then the last cycle end date will be set to last active treatment + 20 days;
- Total number of cycles started;
- Total number of doses;
- Number of cycles and doses started per patient (median, range);
- Number of cycles and doses before 1st delay (median, range);
- Number of cycles and doses before 1st reduction (median, range);
- Number of cycles and doses before 1st interruption (median, range).

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

- Summary statistics (mean, median, standard deviation and range) of cumulative dose and percent of starting dose (compared to Day 1 dose of each cycle).

Listings by patient (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0 ng), administered total daily dose for each period, any missed doses, number of missed doses, reason for any dosing changes.

Listings by patient and each cycle (ordered by dose level): cycle length, total planned dose, administered total dose, percentage of planned dose, dose delay (yes/no), dose reduction (yes/no), dose interruption (yes/no), and infusion rate and reason for infusion rate changes.

Prior, Concomitant, and Further Therapies

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.

6.2. Analysis of Primary Endpoint

6.2.1. DLT(Part 1)

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study, which will be summarized by dose level using the Per Protocol Analysis Set for patients in the dose escalation portion of the study. A listing of the DLTs will also be provided. If necessary, a summary and listing of AEs meeting the criteria for DLT by malignancy may be provided using the Per Protocol Analysis Set for patients in the MTD expansion portion of the study.

6.2.2. Safety Endpoints (Part 1 and Part 2)

Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 4.03 and coded using the MedDRA.[4] The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1) for overall and each dose. The Safety Analysis Set will be used. Part 1 and Part 2 data will be summarized separately and will also be pooled together for analysis. Pfizer standard on safety data reporting will be followed.

Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test for overall and each dose. The analyses will summarize laboratory tests both in the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory abnormalities. The Safety Analysis Set will be used.

For laboratory tests without CTC grade definitions, results will be categorized as normal, abnormal high/low or not done.

Vital signs

The number and percentage of patients who experienced vital signs abnormalities will be summarized (See Schedule of Activities in the protocol for details and Appendix 2).

6.3. Analysis for Secondary Endpoints

6.3.1. Efficacy Endpoints Analysis

In this Phase 1 study efficacy is a secondary objective for Part 1. The efficacy analysis will be performed in the mITT population. Part 1 and Part 2 data will be summarized separately and will also be pooled together for analysis. Efficacy will be analyzed separately from those assessed by RECIST CCI [redacted] criteria for solid tumor.

Efficacy data in Part 1, Part 2 and across the two Parts may be summarized in the following groups:

- Overall summary for all doses and all tumor types assessed by RECIST CCI [redacted] criteria;
- Same tumor type regardless of dose;
- Same dose regardless of tumor type;
- Same dose and same tumor type if data permit.

Summary tables of best Overall Response Rate, Progression Free Survival, and Overall Survival (for Part 2), duration of stable disease (DOSD), and duration of response (DOR) will be provided by the groups aforementioned. Efficacy listings will be provided that include best response, first CR/PR date, last date with CR or PR, most recent date without progression, progression date, death date, date of first response and last tumor assessment date, etc. Swimmer plot for individual clinical response and time on treatment, waterfall plot for individual tumor size percent change from baseline, and spider plot for individual tumor size percent change from baseline over time will be presented.

The following table provides an overview of the efficacy analysis.

Endpoint	**Analysis Set**	**Statistical Method**	**Model/ Covariates/ Strata**	**Missing Data**
Overall response	mITT	Exact CI	See aforementioned summary descriptions on data pooling across dose and tumor type	Observed case
Overall Survival	ITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored at last visit
Progression Free Survival (PFS)	mITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 1
Time to Progression (TTP)	mITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 1
Duration of Response (DOR)	mITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 1
Duration of Stable Disease (DOSD)	mITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 1

6.3.2. Pharmacokinetics Analyses

Pharmacokinetic Concentrations

The concentration-time data will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by treatment/dose, cycle, day and nominal time. In addition, the concentration-time data from Part 2 may also be summarized by descriptive statistics according to tumor type if data permit.

The concentration-time data will be presented as below:

- A listing of all concentrations by treatment/dose, subject ID, cycle, day, and nominal time post dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by treatment/dose, cycle, day, and nominal time post dose, where the set of statistics will include n, mean, standard deviation, median, coefficient of variation (CV), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentration-time plots (on both linear and semi-log scales) against nominal time postdose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time postdose).

- Mean concentration-time plots (on both linear and semi-log scales) against nominal time postdose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time postdose).

- Individual concentration time plots by subject (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each subject per scale].

For drug concentration summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used; for individual subject plots by time, the actual PK sampling time will be used.

In addition to the above, predose concentrations will be plotted for each dose using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady state.

Pharmacokinetic Parameters

To assess the pharmacokinetics of PF-06671008, the PK parameters detailed in Section 3.2 will be listed and summarized for subjects in the PK analysis set (as defined in Section 4.4). Missing values will be handled as detailed in Section 5.4.3. Each PK parameter will be summarized by dose, cycle, and day and will include the set of summary statistics as specified in the table below:

Parameter	Summary statistics
C_{max}, AUC_{inf}, $AUC_{sd,\tau}$, CL (for IV), CL/F (for SC), $C_{max,ss}$, $C_{min,ss}$, $AUC_{ss,\tau}$, V_{ss} (for IV), V_{ss}/F (for SC) and R_{ac}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum
T_{max}, $T_{max,ss}$	N, median, minimum, maximum

For Part 1, dose normalized AUC_{inf} (AUC_{τ} at steady state), and C_{max} will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual patient values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

6.3.3. Immunogenicity Assessment

For the immunogenicity data, the percentage of patients with positive ADAs and neutralizing antibodies will be summarized by overall, by treatment/dose and by tumor type, as data permit. For patients with positive ADAs, titer, time of onset, and duration of ADA response will also be described, if data permit. In addition, efforts will be made if data permit, as appropriate, to examine possible correlations of the ADA response with clinical data on the PK, safety and/or efficacy.

CCI [redacted]

[redacted]

[redacted]

6.5. Population PK and PK CCI Modeling

Pharmacokinetic CCI 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-06671008 exposure CCI [redacted] or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

6.6. ECG Analysis

The analysis of ECG results will be based on patients in the Safety Analysis Set with baseline and on-treatment ECG data, and will follow the ICH E14 guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.[5]

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for HR (QTc) using standard correction factors [ie, Fridericia's (default correction), , and possibly a study specific factor, as appropriate]. QTcF interval will be calculated using the Friderica formula, as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF (and/or QTcB if deemed appropriate by overall, and dose. Individual QT (all evaluated corrections) intervals will be listed by cohort, 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 study arm 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 (one or more correction methods will be used) using maximum CTCAE version 4.03 Grade. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %).

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[CCI] models.

Changes from baseline for the ECG parameters QT interval, heart rate (HR), QTc interval, PR interval and QRS interval will be summarized by treatment and visit. Categorical data analysis will follow Appendix 2.

If more than one ECG is collected at a nominal time post dose (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 three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report 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 QTc post dose from the time-matched average of the pre-dose 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[CCI] modeling approach, if data warranted. If a PK[CCI] relationship is found, the impact of subject factors (covariates) on the relationship will be examined.

7. INTERIM ANALYSES

No formal interim analysis is planned in this study. However, since this is an pen-label study, safety data [CCI] data will be monitored.

8. REFERENCES

1. B783 Protocol Amendment 5, Jan. 12, 2018.

2. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.

3. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics 1982; 38:29-41.

4. NCI Common Terminology Criteria for Adverse Events v4.03 (CTCAE). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

5. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.

6. E.A. Eisenhauer, P. Therasseb, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228-247.

7. Nishino M, Gargano M, Suda M, Ramaiya NH, Hodi FS. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Cancer 2014;2:17.

8. Guha M:The new era of immune checkpoint inhibitors; Pharm J Volume 293, 18 NOV 2014, No 7837/8 online URL 200671127.

9. Topp MS, Gokbuget N, Zugmaier G, et al. A phase II trial of the anti-CD19 BiTE blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblactic leukemia. J Clin Onco 2014; published online Nov 10. DOI:10.1200/JCO.2014.56.3247.

9. APPENDICES

Appendix 1. Time to Event Data Analysis Censoring Rules

Table 3. Progression Free Survival and Duration of Response

Situation	**Date of Progression/Censoring**[1]	**Outcome**
Inadequate baseline assessment	First dosing date in Cycle 1	Censored
No on-study assessments	First dosing date in Cycle 1	Censored
Alive, on treatment[2] and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation[2]	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation[2]	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation[2]	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation[2]	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1: For date of censorship, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.
2: or within 28 days of discontinuation of treatment.

Table 4. Time to Progression

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	First dosing date in Cycle 1	Censored
No on-study assessments	First dosing date in Cycle 1	Censored
Alive, on treatment[2] and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation[2]	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation[2]	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation[2]	Censored
New anticancer treatment <28 days after discontinuation of treatment without progression	Date of last objective tumor assessment prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Start date (C1D1)	Censored
Death without objective progression prior to treatment discontinuation[2]	Date of last objective tumor assessment prior to death	Censored
Progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1: For censoring date, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.
2: or within 28 days of discontinuation of treatment.

DOSD and DOR

Censoring rules for DOSD and DOR will be the same as for PFS.

Appendix 2. Categorical Classes for ECG and Vital Signs

Categories for QTcB and QTcF

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

Categories for PR and QRS

PR (ms)	max ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max ≥200	
QRS (ms) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
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. RECIST 1.1 Tumor Assessment Criteria

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

a. Categorizing Lesions at Baseline

1. Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

1. Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).

2. Lesions with longest diameter at least 20 mm when assessed by chest X-ray.

3. Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.

4. Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

2. Non-measurable Disease

1. Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

2. Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

3. Previous local treatment: A previously irradiated lesion (or lesion patientive to other local treatment) is non-measurable unless it has progressed since completion of treatment.

3. Normal Sites

1. Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

2. Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non measurable.

3. Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

4. Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

5. Solitary lesions: If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

4. Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Note: For the patient population being evaluated in this protocol, the baseline assessment may be completed within 6 weeks prior to randomization.

5. Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

1. If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

2. Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

6. Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

b. Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

7. Target Disease

1. **Complete Response (CR)**: Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

2. **Partial Response (PR)**: Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

3. **Stable Disease (SD)**: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

4. **Objective Progression (PD):** 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

5. **Indeterminate**. Progression has not been documented, and

    - one or more target measurable lesions have not been assessed;

    - or assessment methods used were inconsistent with those used at baseline;

    - or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

- or one or more target lesions were excised or irradiated and have not reappeared or increased.

8. Non-target Disease

1. **Complete Response (CR)**: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

2. **Non-CR/Non-PD**: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

3. **Progressive Disease (PD)**: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

4. **Indeterminate**: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

5. **Cytology, histology.**

6. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

7. For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non malignant should not be recorded on the CRF.

9. New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible 'new' disease). New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:

- Negative FDG PET at baseline, with a positive FDG PET at follow up
- No FDG PET at baseline and a positive FDG PET at follow up: if the positive FDG PET at follow up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG PET at follow up is not confirmed as a new site of disease on CT, additional follow up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG PET scan).

If the positive FDG PET at follow up corresponds to a pre existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

10. Supplemental Investigations

1. If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
2. If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

11. Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 5. Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 6. Objective Response Status at each Evaluation for Patients with Non Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Appendix 4. Immune-related RECIST (irRECIST) Tumor Assessment Criteria

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

This is particularly true for immunotherapeutic agents such as anti-cytotoxic T lymphocyte-associated protein 4 (CTLA4) and anti PD-1/anti-PD-L1 antibodies which exert the antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects. Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.

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

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare type responses into the RECIST v1.1 (irRECIST) [7].

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

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

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

irRECIST is defined as follows:

- Overall immune related complete response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.

- Overall immune-related partial response (irPR): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%. Overall immune related stable disease (irSD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions is neither irCR, irPR, (compared to baseline) or immune related progressive disease (irPD, compared to nadir).

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

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

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