

# **Protocol B7501001**

## **A PHASE 1 DOSE ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF PF-06650808 IN PATIENTS WITH ADVANCED SOLID TUMORS**

### **Statistical Analysis Plan (SAP)**

**Version:** 1.0

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## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable.

## 2. INTRODUCTION

This document describes the planned statistical analyses for Protocol B7501001. This analysis plan is meant to supplement the study protocol. In this document, any text taken directly from the protocol is italicized. Any deviations from this analysis plan will be described in the Clinical Study Report (CSR).

### 2.1. Study Design

*This is a Phase 1, open label, multi-center, single arm, non randomized, multiple dose, safety, pharmacokinetic (PK) and pharmacodynamic (PD) study of single agent PF-06650808 in sequential cohorts of adult patients with advanced solid tumors for whom no standard therapy is available. Successive cohorts of patients will receive escalating doses of PF-06650808 intravenously every 21 days starting at a dose of 0.2 mg/kg.*

*Approximately 55 patients are expected to be enrolled in the study at approximately 3-4 sites. The actual number of patients enrolled will depend upon tolerability of PF-06650808 and the number of dose levels required to identify the MTD.*

*The study will include two parts, a dose escalation phase (Part 1) followed by a dose expansion phase (Part 2). Part 1 will estimate the MTD in dose escalation cohorts in patients with advanced solid tumors for whom no standard therapy is available in order to establish the RP2D. Part 2 will include approximately 20 patients with TNBC enrolled at the MTD in order to explore benefit from treatment as suggested by preclinical findings, and will better define the safety profile at the RP2D. Additional safety information gathered in Part 2 may be used to modify the dose recommended for future Phase 2 studies.*

*The study is expected to be completed in approximately 24 months. The end of the study is the last visit of the last patient.*

### 2.2. Study Treatment

*A modified continual reassessment method (mCRM) targeting a DLT rate of 25% will be utilized for Part 1 (dose escalation phase). Patients will be enrolled in cohorts of 2 to 4, starting with 0.2 mg/kg for the first cohort. The possible doses explored will be from a fine grid of doses ranging from 0.2 mg/kg to 6.4 mg/kg. If a high DLT rate is observed at the starting dose of 0.2 mg/kg, a lower dose such as 0.14 mg/kg or lower will be considered. The study may be stopped if the drug is deemed not tolerable at the lowest reduced dose.*

*Patients will continue with study treatment every 21 days until disease progression, withdrawal of consent, unacceptable toxicity occurs, or the study is terminated. Patients experiencing a DLT may be managed with dose modification or discontinuation.*

*Part 2 will include patients enrolled at the MTD in order to explore benefit from treatment and will better define the safety profile at the RP2D.*

## 2.3. Study Objectives

### ***Dose Escalation (Part 1) Objectives***

*Primary Objective:*

- *To assess safety and tolerability at increasing dose levels of PF-06650808 in patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available in order to determine the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).*

*Secondary Objectives:*

- *To evaluate the overall safety profile.*
- *To characterize the single and multiple dose pharmacokinetics of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101).*
- *To evaluate the immunogenicity of PF-06650808.*
- *To document any preliminary evidence of anti-tumor activity.*

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### ***Dose Expansion (Part 2) Objectives***

*Primary Objective:*

- *To confirm safety and tolerability and explore preliminary evidence of anti-tumoractivity of PF-06650808 at the RP2D in patients with TNBC.*

*Secondary Objectives:*

- *To evaluate the overall safety profile at the R2PD.*
- *To characterize the single and multiple dose pharmacokinetics of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101).*
- *To evaluate the immunogenicity of PF-06650808.*

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### 3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis or blinding is planned for this study. The final analysis will be conducted after the last subject last visit (LSLV).

### 4. HYPOTHESES AND DECISION RULES

#### 4.1. Statistical Hypotheses

There are no statistical hypotheses. The emphasis of the final analyses will be on estimation of key summary statistics.

#### 4.2. Statistical Decision Rules

##### 4.2.1. Part 1

*A modified continual reassessment method (mCRM) targeting a DLT rate of 25% will be utilized for Part 1 (dose escalation phase) (Goodman et al, 1995; O'Quigley et al, 1990).<sup>3,7</sup> Patients will be enrolled in cohorts of 2 to 4, starting with 0.2 mg/kg for the first cohort. The possible doses explored will be from a fine grid of doses ranging from 0.2 mg/kg to 6.4 mg/kg. If a high DLT rate is observed at the starting dose of 0.2 mg/kg, a lower dose such as 0.14 mg/kg (a 30% reduction from starting dose) or lower will be considered. The study may be stopped if the drug is deemed not tolerable at the lowest reduced dose. The mCRM model will determine the next dose level based on the DLT rate using a 30%, 69% and 100% dose increment for 0, 1 or 2 dose skips respectively.*

*Starting with the second cohort, patients will be assigned to a dose that is closest to the current MTD prediction based on a model that mCRM utilized to learn about overall dose-toxicity relationship. This model is updated after DLT assessment of each cohort. At any given point in this phase, doses can be escalated, deescalated, unchanged or revisited, but always aiming towards the target MTD. To prevent overly aggressive dose-escalation, the maximum allowed dose increase will be limited to 2 increments at a time (ie, no more than 100% dose increase at a time). In addition, if two clinically significant Grade 2 toxicities of the same type are seen in a cohort, dose escalation will be limited to no greater than 69% for the next cohort. If there is one additional case of the same Grade 2 toxicity or two other cases of clinically significant Grade 2 toxicities of the same type, dose escalation will again be limited to no greater than 69% for the next cohort; otherwise dose escalation following the mCRM algorithm will resume. Grade 2 toxicities will not be considered clinically significant if a corresponding Grade 3 toxicity exists (by NCI CTCAE v 4.03);<sup>6</sup> Grade 2 toxicities without a corresponding Grade 3 toxicity will be considered clinically significant (eg, Grade 2 alopecia, dry skin, libido decrease). In addition, Grade 2 nausea, vomiting, and diarrhea will not be considered clinically significant unless it has been optimally medically managed.*

*The combination of a fine dose grid and the ability to skip doses allows rapid dose escalation if no DLTs are observed and small dose changes with exploration of adjacent doses once the observed DLT rate becomes noticeable. The algorithm will stop if any of the following criteria is met:*

1. *The maximum sample size has been achieved (approximately 35 patients total).*

2. *At least 6 patients have been accumulated on a dose that is predicted to be the MTD and there are at least 12 patients overall enrolled in the trial, or*
3. *All doses explored appear to be overly toxic and the MTD cannot be determined in the current trial setting.*

*Although dose levels are capped at 6.4 mg/kg, this mCRM will continue to operate subject to the constraints detailed above while allowing for doses higher than specified. Doses may continue to be skipped, visited more than once, or not visited at all. In addition, if necessary, doses beyond 6.4 mg/kg may be allowed in 30% increments.*

*All significant AEs and serious adverse events (SAEs) will be reviewed by the sponsor and investigators to determine if the dose allocation schedule requires modification. The cohort steering committee, comprised of the sponsor clinical team and the investigators, can override the dose escalation increment determined by the algorithm if a more conservative approach is mandated.*

*Patients will continue with study treatment every 21 days until disease progression, patient refusal or unacceptable toxicity occurs. Patients experiencing a DLT may be managed with dose modification or discontinuation.*

*Subsequent dose levels may not be opened until all patients entered at the current dose level have been treated and observed for at least one complete cycle (through Day 21) and the number of DLTs among those patients in their first cycle has been determined.*

#### **4.2.2. Part 2**

*Part 2 of this study is intended to confirm the safety and tolerability of the dose selected in Part 1 while assessing the antitumor activity of ADC (PF-06650808) in TNBC patients. Patients in the expansion cohort will be pre-selected according to their target tumor expression using archival tumor tissues. Only patients with relatively high target expression will be selected. The DLT rate and its 95% confidence interval at the selected dose may be estimated.*

*Analyses may be performed on data from both Part 1 and Part 2 to explore the relationships between PK parameters, safety endpoints, and efficacy endpoints.*

### **5. SAMPLE SIZE DETERMINATION**

*Approximately 55 patients are expected to be enrolled in this study.*

*Similar to the conventional 3+3 design, the exact sample size of the CRM design in Part 1 cannot be pre-specified in advance due to the dynamic feature of the design. The minimum and maximum sample sizes after which the Part 1 can be stopped and MTD declared are approximately 12 and approximately 35 patients, respectively. Also, a minimum of 6 patients treated at the MTD dose in Part 1 is required to establish such dose as the RP2D. The actual sample size of Part 1 will depend on the underlying dose toxicity profile and variability in actual data realization.*

*As for the number of patients treated at each dose, it is expected that the typical number will be 2 to 4 patients for the doses actually studied. For the dose declared as MTD at the end of Part 1, this number will be 6 or more patients. However, since not every dose listed will be studied and variable cohort size is allowed, the actual number of patients treated at each dose will vary.*

*The sample size in Part 2 is based on clinical consideration, rather than statistical justification. Upon identification of the MTD by the mCRM method, approximately 20 patients with triple negative breast cancer will be enrolled in Part 2 to further evaluate safety and preliminary efficacy parameters.*

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## **6. ANALYSIS SETS**

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

### **6.1. Full Analysis Set**

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

### **6.2. ‘PER PROTOCOL’ Analysis Set**

*The per protocol analysis set includes all enrolled patients who receive at least one dose of study medication at the dose level of RP2D and who do not have major treatment deviations during first cycle. Patients with major treatment deviations in Cycle 1 are not evaluable for the RP2D assessment. Major 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. A baseline disease assessment and at least one post-baseline disease assessment are appropriate to allow efficacy analysis.*

### **6.3. Safety Analysis Set**

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

### **6.4. PK Analysis Set**

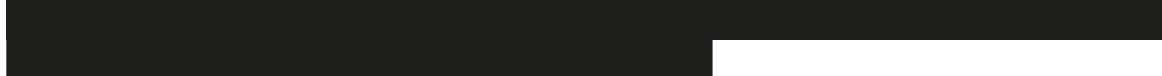
#### **6.4.1. PK Concentration Set**

The PK concentration population is defined as all treated patients who have at least 1 concentration measured.

## 6.4.2. PK Parameter 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.

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## 6.6. Other Analysis Sets

### 6.6.1. Modified Intent-to-Treat Set

*The modified intent-to-treat (mITT) is the analysis population that will follow the ITT principle and include subjects receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment or disease progression or death before the first tumor assessment. The mITT population may be used for occasions such as conference presentation when the study is still ongoing.*

## 6.7. Treatment Misallocations

Subjects who receive the wrong initial dose for whatever reason will be analyzed according to the initial dose actually received. Subjects who receive the wrong dose after the initial dose will be analyzed according to the initial dose received.

## 6.8. Protocol Deviations

All deviations will be listed in the CSR. Major treatment deviations include, but are not limited to, less than 80% of the planned Cycle 1 PF-06650808 dose provided the reduction/omission is not due to treatment-related toxicity. Subjects with major Cycle 1 treatment deviations are not evaluable for MTD.

## 7. ENDPOINTS AND COVARIATES

### 7.1. Efficacy Endpoint(s)

*Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 by calculating the Overall Response Rate (ORR), Progression Free Survival (PFS), and Overall Survival (OS).*

All efficacy endpoints are secondary in this study, which include objective tumor response, progression-free survival (PFS), and overall survival (OS) in the expansion cohort. The above efficacy endpoints are derived based on the disease response per investigator evaluation on the CRF pages, which is the primary method of documentation of disease.

- **Overall Response (OR)** – is defined as confirmed complete response (CR) or confirmed partial response (PR) according to RECIST 1.1 ([Appendix 2](#)). Confirmed responses are those that persist on repeat imaging study at least 4 weeks after the initial documentation of response. Patients who do not have on-study radiographic tumor re-evaluation, who receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will not

be counted as responders in the assessment of OR. Clinical benefit response (CBR) is defined as a CR, PR or SD  $\geq 6$  cycles.

- **Progression Free Survival (PFS)** - is defined as the time from Cycle 1 Day 1 (C1D1) to first documentation of disease progression or to death due to any cause, whichever occurs first. Subjects last known to be 1) alive 2) on treatment or within the post-treatment follow-up period and 3) progression-free, are censored at the date of the last disease assessment that verified lack of disease progression. Subjects who start new anti-cancer treatment prior to the end of post-treatment follow-up period and have adequate baseline and on-treatment objective disease assessments without evidence of progressive disease are censored at the date of the last objective disease assessment. Subjects with inadequate baseline or no on-study disease assessments are censored at C1D1 unless death occurred prior to the first planned assessment (in which case the death is an event). Subjects with at least one on-study disease assessment who discontinue treatment without disease progression and without death within 28 days of discontinuation are censored at the date of the last objective disease assessment that verified lack of disease progression (if progression or death is within 28 days of discontinuation the progression or death is an event). Subjects with documentation of progression or death after an unacceptably long interval ( $>16$  weeks) since the previous disease assessment will be censored at the time of the previous assessment.

PFS (days) = [progression/death date – C1D1 + 1].

- **Overall survival (OS)** is defined as the time from initial dose until death from any cause, and is measured in the intent-to-treat population.

More details of censoring are provided in [Appendix 3](#).

## 7.2. Safety Endpoints

### 7.2.1. DLT Definition

Dose limiting toxicity (DLT) is the primary endpoint of this study. Severity of adverse events will be graded according to CTCAE version 4.03. For the purpose of dose escalation, any of the following adverse events which are not considered related to disease progression occurring in the first cycle of treatment (21 days) will be classified as DLTs:

- *Hematologic:*
  - *Grade 4 neutropenia lasting  $>7$  days.*
  - *Febrile neutropenia (defined as neutropenia  $\geq$  Grade 3 and a single body temperature  $>38.3^{\circ}\text{C}$  or a sustained temperature of  $\geq 38^{\circ}\text{C}$  for more than one hour).*
  - *Grade  $\geq 3$  neutropenia with infection.*
  - *Thrombocytopenia (of any grade) associated with clinically significant or life-threatening bleeding.*

- *Grade 4 thrombocytopenia  $\geq 72$  hours or platelets  $\leq 10,000/mm^3$  regardless of duration.*
- *Non-hematologic:*
  - *Grade  $\geq 3$  toxicities, except those that have not been maximally treated (eg, nausea, vomiting, diarrhea).*
  - *Delay by more than 2 weeks in receiving the next scheduled cycle due to persisting toxicities not attributable to disease progression.*

*In addition, clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by the sponsor and the investigators.*

*Grade  $\geq 3$  cytokine release syndrome, infusion reaction, and allergic reaction will not be considered as DLTs but may be a reason for study discontinuation and should be reviewed with the sponsor.*

#### **7.2.2. Vitals**

See Schedule of Activities in the protocol for details.

#### **7.2.3. Laboratory Data**

The laboratory results will be graded according to the NCI CTCAE v4.03 severity grade. For labs for which an NCI CTCAE v4.03 scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized by dose. Baseline evaluations for laboratory data are those collected:

- Within 28 days prior to Cycle 1/Day 1.
- Closest but prior to Cycle 1/Day 1 if there is more than one baseline evaluation.

#### **7.2.4. Adverse Events**

*Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03) timing, seriousness, and relatedness.*

All AEs will be coded by system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA). The severity of all AEs will be graded by the investigator using NCI CTCAE version 4.03 whenever possible. For other AEs without specific CTC definitions, results are identified according to CTCAE “other” categories. Adverse events will be assigned to the appropriate cycle based on Day 1 of each cycle.

#### **Treatment Emergent Adverse Events**

- All deaths from start of treatment until 28 days after the final dose.

- All treatment related SAEs.
- All unrelated SAEs from treatment start until 28 days after final dose of treatment.
- All non-fatal AEs occurring after treatment start up until 28 days after final dose of treatment or until start of new anti-cancer treatment, whichever is first.
- Disease progression is not considered a treatment emergent adverse event unless the subject dies of disease prior to 28 days after discontinuation of treatment.
- Events that are continuations of baseline abnormalities are considered treatment emergent adverse events only if there is an increase in grade over baseline.

### **Treatment Related Adverse Events**

Treatment Related Adverse Events are treatment emergent adverse events with cause categorized by the investigator as related to study treatment. Events that are continuations of baseline abnormalities (signs and symptoms) are not considered treatment emergent, and hence are not considered treatment related, unless there is an increase in grade over baseline.

#### **7.2.5. ECG and QTc Interval**

ECG data will be collected. See Schedule of Activities in the protocol for details. 12 lead ECGs will be summarized. The baseline evaluation for ECGs is the pre-dose value on Cycle 1/Day 1. If the pre-dose value is not collected, the ECG closest but prior to Cycle 1/Day 1 will be used. If the closest ECGs are triplicate ECGs (or only 2), they will be averaged. If the closest ECG is a single, that will be used as baseline.

*QT intervals will be corrected for heart rate (QTc) using Fridericia's correction factors (QTcF). The adequacy of the correction method will be assessed graphically (plots of QT and QTcF versus RR) and supplementary transformations may be considered, as appropriate. Data will be summarized and listed for QT, HR, RR, PR, QRS and QTcF by treatment and dose. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTcF value and changes from baseline in QTcF after treatment by compound, dose and by time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Outlier analysis of the QTcF data will be conducted and summarized as follows:*

- *The number of patients with maximum change from baseline in QTcF (<30, 30-60, and ≥60 ms).*
- *The number of patients with maximum post-dose (post-baseline) QTcF (<450, 450-<480, and >=480 ms).*

*In addition, the number of patients with corrected and uncorrected QT values ≥500 msec will be summarized.*

*Shift tables will be provided for baseline vs. worst on study QTcF using Maximum CTCAE Grade. As well as tables of ECG abnormality at baseline (yes, no, not done: (n, %)). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).*

*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  $\geq 500$  msec, but the mean of the triplicates is not  $\geq 500$  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  $\geq 500$  msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are  $\geq 500$  msec will not be included in the categorical analysis unless the average from those triplicate measurements is also  $\geq 500$  msec. Changes from baseline will be defined as the change between QTcF post dose and the pre-dose values on Day 1.*

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

#### **7.2.6. Immunogenicity**

Anti-PF-06650808 antibody data will be collected at baseline and post-randomization according to the protocol.

### **7.3. PK Endpoints**

Blood samples for PK analysis of PF-06650808 (ADC), PF-06460005 (total antibody), and PF-06380101 (unconjugated payload) will be taken according to the Schedule of Activities given in the protocol.

- **Pharmacokinetic parameters of PF-06650808 (ADC):**

Cycle 1 -  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,  $AUC_{inf}$ ,  $AUC_{\tau}$ ,  $t_{1/2}$ ,  $CL$ , and  $V_{ss}$  as data permit.

Cycle 4 -  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,  $AUC_{\tau}$ ,  $t_{1/2}$ , and  $R_{ac}$  as data permit.

- **Pharmacokinetic parameters of PF-06460005 (total antibody) and PF-06380101 (unconjugated payload):**

Cycle 1 -  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,  $AUC_{inf}$ ,  $AUC_{\tau}$ , and  $t_{1/2}$  as data permit.

Cycle 4 -  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,  $AUC_{\tau}$ ,  $t_{1/2}$ , and  $R_{ac}$  as data permit.

PK parameters will be derived from the concentration-time data as follows:

Parameter	Definition	Method of Determination
$AUC_{last}$	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration	Linear/Log trapezoidal method
$AUC_{\tau}$	Area under the concentration-time profile from time zero to the time $\tau$ , the dosing interval	Linear/Log trapezoidal method
$AUC_{inf}$	Area under the concentration-time profile from time zero extrapolated to infinite time	$AUC_{(0-t[last])} + (C_{last}^* / kel)$ , where $C_{last}^*$ is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis.
$C_{max}$	Maximum observed concentration	Observed directly from data
$T_{max}$	Time for $C_{max}$	Observed directly from data as time of first occurrence
$T_{1/2}$	Terminal elimination half-life	$\log(2) / kel$ , 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	$Dose / AUC_{inf}$ for cycle 1; $Dose / AUC_{\tau}$ for cycle 4
$V_{ss}$	Volume of distribution at steady state	$CL \times MRT$
$R_{ac}$	Observed accumulation ratio	$AUC_{cycle\ 4,\ \tau} / AUC_{cycle\ 1,\ \tau}$

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## 7.5. Covariates

Not applicable.

## 8. HANDLING OF MISSING VALUES

### 8.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1<sup>st</sup> 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, and pharmacodynamic analyses, which will only use the actual date collected or if date not available deem the data missing.

### 8.2. Efficacy Analysis

Censoring rules for time-to-event endpoints are detailed in [Section 11.3 Appendix 3](#).

### 8.3. 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**

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.

### **Pharmacokinetic parameters**

Actual PK sampling times will be used in the derivation of PK parameters.

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

### **QTc**

For the QTc analyses, no values will be imputed for missing data.

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## **9. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES**

### **9.1. Statistical Methods**

No formal hypothesis testing will be performed in this exploratory study.

### **Analyses of Time-to-Event Endpoints**

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint (Brookmeyer and Crowley, 1982)<sup>1</sup> will be provided.

## **Analyses of Binary Endpoint**

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

## **Analyses of Continuous Data**

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

### **9.2. Statistical Analyses**

#### **9.2.1. Primary Analysis**

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 Safety 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 the DLT may be provided using the Per Protocol Analysis Set for patients in the MTD expansion portion of the study.

#### **9.2.2. Secondary Analyses**

##### **9.2.2.1. Efficacy Analysis**

In this Phase 1 study efficacy is a secondary objective. Note that the efficacy analysis is to be conducted for patients in the MTD expansion cohorts who are in the Safety Analysis Set and have baseline disease assessment and at least one post-baseline disease assessment. In the event that a large number of patients in the escalation portion of the study have the same malignancy, the efficacy analysis may be conducted.

Summary tables of best Overall Response Rate, Progression Free Survival, and Overall Survival will be provided overall and by malignancy if necessary. 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.

A response rate overall for Part 1 dose escalation and response rates by low, medium, and high dose groups may be presented.

The following table provides an overview of the efficacy analysis.

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata*	Missing Data	Interpretation
Overall response	Per Protocol, expansion cohorts, etc.	Exact CI	By dose range/ malignancy	Censored per <a href="#">Section 11.3</a>	Secondary Analysis
Progression Free Survival (PFS)	Per Protocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per <a href="#">Section 11.3</a>	Secondary Analysis
Time to Progression (TTP)	Per Protocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per <a href="#">Section 11.3</a>	Secondary Analysis
Duration of Response (DR)	Per Protocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per <a href="#">Section 11.3</a>	Secondary Analysis

\* If patients in dose escalation phase are included.

### 9.2.2.2. Pharmacokinetics Analyses

#### Pharmacokinetic Parameters

To assess the pharmacokinetics of PF-06650808 (ADC), PF-06460005 (total antibody) and PF-06380101 (unconjugated payload), the PK parameters detailed in [Section 7.3](#) will be listed and summarized for subjects in the PK analysis set (as defined in [Section 6.4](#)). Missing values will be handled as detailed in [Section 8](#). Each PK parameter will be summarized by dose and cycle and will include the set of summary statistics as specified in the table below:

Parameter	Summary statistics
AUC <sub>last</sub> , AUC <sub>inf</sub> , AUC <sub>τ</sub> , C <sub>max</sub> , CL, V <sub>ss</sub> , and R <sub>ac</sub>	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
t <sub>1/2</sub>	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum
T <sub>max</sub>	N, median, minimum, maximum

There will be 1 summary table presenting all PK parameters. This will include data from all cohorts and will be summarized by dose group and cycle.

To assess the relationship between the PK parameters and dose, dose normalized AUC<sub>inf</sub>, AUC<sub>last</sub>, AUC<sub>τ</sub>, and C<sub>max</sub> will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg/kg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented are presented on the plot.

## **Pharmacokinetic Concentrations**

To assess the PK profile of PF-06650808 (ADC), PF-06460005 (total antibody) and PF-06380101 (unconjugated payload), PK concentrations will be listed, summarized and plotted for subjects in the PK analysis set (as defined in [Section 6.4](#)), where missing and BLQ values will be handled as detailed in [Section 8.3](#).

Presentations for PF-06650808 (ADC), PF-06460005 (total antibody) and PF-06380101 (unconjugated payload) will include:

- a listing of all concentrations sorted by dose, subject id, day and nominal time post dose. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.
- a summary of concentrations by dose, day and nominal time post dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv) and the number of concentrations above the lower limit of quantification.
- a plot of mean concentrations against nominal time postdose by dose (based on the summary of concentrations by dose and time postdose), preferably with all doses also on the same graph.
- a plot of median concentrations against nominal time postdose by dose (based on the summary of concentrations by dose and time postdose), preferably with all doses also on the same graph.
- a log-linear plot of mean concentrations against nominal time postdose by dose (on the same plot), preferably with all doses also on the same graph.
- a log-linear plot of median concentrations against nominal time postdose by dose (on the same plot), preferably with all doses also on the same graph.
- plots of individual concentrations against actual time postdose.

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PK concentration is quantifiable in the matrix.

In addition to the above, a median plot of the predose concentrations at each cycle against day will be provided for each dose, on the same plot, in order to assess the attainment of steady-state. Individual subject profiles will also be plotted.

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

## **Population Pharmacokinetic Analysis or PK/PD Modeling**

*Pharmacokinetic and pharmacodynamic data from this study may be analyzed using compartmental or mixed-effect modeling approaches and may also be pooled with other study results. PK/PD modeling may be attempted to investigate any causal relationship between PF-06650808 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.*

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **9.2.3. Safety Analyses**

#### **Adverse Events**

Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 4.03 and coded using the MedDRA. 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). The Safety Analysis Set will be used.

#### **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. The analyses will summarize laboratory tests both in the entire study period and by cycle (Cycle 1 and Cycles beyond 1). The Safety Analysis Set will be used.

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

#### **Other Variables: Anti-PF-06650808 antibody**

For anti-PF-06650808 antibody, a listing, sorted by subject and study day, of the result of anti-PF-06650808 antibody screening (positive/negative [<1:negative]), the specificity, and titer will be listed. Summary counts of the patients, who are positive for the anti-PF-06650808, will be derived by study treatment and visit for the safety population. No summary statistics other than those cited above, will be generated.

### **9.2.4. 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. The Safety Analysis Set will be used.

#### **Treatment Administration/Compliance**

Listings and tables by dose level will be provided. Cycle length is 21 days. Day 1 of a cycle is the first date of dose within that cycle. The safety analysis set will be used.

Dose modifications may occur in the following ways:

- Cycle delay—Day 1 of current cycle starts later than 21 days from Day 1 of the previous cycle (only applies to cycle 2 and above);
- Dose reduction—A decrease in the administered total daily dose (non-zero) compared to the planned total daily dose upon enrollment.

Intra-patient dose escalation is not allowed in this study. The following will be summarized by subject for each dose level:

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

The following will be summarized by cycle received for each dose level:

- Total number of cycles started.
- Number of cycles started per subject (median, range).
- Number of cycles before 1<sup>st</sup> delay (median, range).
- Number of cycles before 1<sup>st</sup> reduction (median, range).
- Number of cycles before 1<sup>st</sup> 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 subject (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0mg), administered total daily dose for each period, any missed doses with unknown dates (Y/N), number of missed doses with unknown dates, reason for any dosing changes.

Listings by subject 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), and dose interruption (yes/no).

### **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.

#### **9.2.5. Additional Analysis**

Not applicable

**10. REFERENCES**

1. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. *Biometrics* 1982; 38:29-41.
2. 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.
3. Goodman SN, Zahurak ML, Piantadosi S. Some Practical Improvements in the Continual Reassessment Method for Phase 1 Studies. *STAT MED*. 1995;4:1149-1161.
4. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.
5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-481.
6. NCI Common Terminology Criteria for Adverse Events v4.03 (CTCAE). <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>
7. O'Quigley J, Pepe M, Fisher L. Continual Reassessment Method. A practical design for phase 1 clinical trials in cancer. *Biometrics*. 1990;46:33-48.

## 11. APPENDICES

### 11.1. APPENDIX 1: CATEGORICAL CLASSES FOR ECG AND VITAL SIGNS

#### Categories for QTcB and QTcF

QTcB/QTcF (ms)	max. $\leq$ 450	450 $<$ max. $\leq$ 480	480 $<$ max. $\leq$ 500	max. $>$ 500
QTcB/QTcF (ms) increase from baseline	max. $<$ 30	30 $\leq$ max. $<$ 60	max. $\geq$ 60	

#### Categories for PR and QRS

PR (ms)	max $\geq$ 300	
PR (ms) increase from baseline	Baseline $>$ 200 and max. $\geq$ 50% $\geq$ 25% increase	Baseline $\leq$ 200 and max. $\geq$ 50% increase
QRS (ms)	max $\geq$ 200	
QRS (ms) increase from baseline	Baseline $>$ 100 and max. $\geq$ 50% $\geq$ 25% increase	Baseline $\leq$ 100 and max. $\geq$ 50% increase

#### Categories for Vital Signs

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

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

## 11.2. APPENDIX 2: RECIST 1.1 TUMOR ASSESSMENT CRITERIA

*Adapted from 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.<sup>2</sup>*

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below:

### **Measurable Lesions**

Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

### **Non-measurable Lesions**

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a  $\geq 10$  but  $<15$  mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

### **Special Considerations Regarding Specific Lesions**

#### **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.

#### **Cystic lesions:**

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

#### **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.

#### **Solitary lesions:**

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

#### **Recording Tumor Measurements**

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of  $\geq 15$  mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

### **Definition of Tumor Response**

#### **Target Lesions**

**Response in target lesions is defined as follows:**

- **Complete Response (CR):** disappearance of all target lesions.
- **Partial Response (PR):** at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.
- **Stable Disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to ‘normal’ size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of ‘zero’ on the CRF.

#### **Non-Target Lesions**

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

**Response in non-target lesions is defined as follows:**

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

**Cytology, Histology**

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.

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.

**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.

### **Determination of Overall Response by the RECIST 1.1 Criteria**

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 1.

**Table 1. Response Evaluation Criteria in Solid Tumors**

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/no n-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease,			
PD = progressive disease, and NE = inevaluable.			

### **Best overall response**

The best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in [Table 2](#).

**Table 2. Best Overall Response when Confirmation of CR and PR Required**

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR <sup>a</sup>
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.		
<sup>a</sup> If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.		

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

### 11.3. APPENDIX 3: CENSORING DETAILS

**Table 3. Progression Free Survival and Duration of Response**

Situation	Date of Progression/Censoring <sup>1</sup>	Outcome
Inadequate baseline assessment	Start date (C1D1)	Censored
No on-study assessments	Start date (C1D1)	Censored
Alive, on treatment <sup>2</sup> and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation <sup>2</sup>	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 <sup>2</sup>	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation <sup>2</sup>	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation <sup>2</sup>	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 <sup>1</sup>	Outcome
Inadequate baseline assessment	Start date (C1D1)	Censored
No on-study assessments	Start date (C1D1)	Censored
Alive, on treatment <sup>2</sup> and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation <sup>2</sup>	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 <sup>2</sup>	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation <sup>2</sup>	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 <sup>2</sup>	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.