Protocol B7521001

A FIRST-IN-HUMAN PHASE 1, DOSE ESCALATION, SAFETY AND PHARMACOKINETIC STUDY OF PF-06647263 IN ADULT PATIENTS WITHADVANCED SOLID TUMORS

Statistical Analysis Plan (SAP)

Version: 1.0

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[redacted]

LIST OF TABLES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable.

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol B7521001. 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, two part, open label, multi-center, single arm, non-randomized, multiple dose, safety, pharmacokinetic and pharmacodynamic study of single agent ADC (PF-06647263) in sequential cohorts of adult patients with advanced solid tumors for whom no standard therapy is available. Successive cohorts of patients will receive doses of ADC (PF-06647263) intravenously on an outpatient basis every 21 days starting at a dose of 0.015 mg/kg.

The proposed doses, schedule(s) and PK timepoints may be reconsidered and amended during the study based on the emerging safety and pharmacokinetic data.

The actual number of patients enrolled will depend upon tolerability of ADC (PF-06647263) and the number of dose levels required to identify the MTD.

Patients will participate in the study for approximately 6 months. This assumes up to 4 weeks of screening, approximately 4 months of treatment, and a follow-up visit within 4 weeks after the last dose for adverse event (AE) and serious adverse event (SAE) collection. Treatment with study drug will continue until disease progression, patient refusal, unacceptable toxicity occurs, or the study is terminated.

This clinical study will include 2 parts. 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 30 patients 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. This expansion cohort will include approximately 15 patients with TNBC and 15 patients with OVCA. Additional safety information gathered in Part 2 may be used to modify the dose recommended for future Phase 2 trials.

2.2. MTD Determination (Part 1)

A modified toxicity probability interval method (mTPI) targeting a DLT rate of 25% with an equivalence interval (20%-30%) will be utilized in order to estimate MTD. Patients will be enrolled in cohorts of 2 to 4, starting with 0.015 mg/kg for the first cohort. Subsequent dose levels may include a maximum 100% escalation until either the dose is ≥0.060 mg/kg, a patient experiences a DLT or Grade 2 thrombocytopenia considered related to PF-06647263

after which, dose escalation in subsequent cohorts will follow a modified Fibonacci scheme with maximum dose increases of 67%, 50%, 33%, 33%. Table 1 illustrates the possible dose levels when the Modified Fibonacci scheme is initiated at the 3rd dose level. Intermediate dose levels to further evlatuate the safety and/or PK may be evaluated following discussion between Sponsor and Investigator.

	Modified Fibonacci^ scheme starts from dose level 3	**Modified Fibonacci^ scheme starts from dose level 2**	**Modified Fibonacci^ scheme starts from dose level 1**
Dose Level	Dose (mg/kg Q3W)	Dose (mg/kg Q3W)	Dose (mg/kg Q3W)
-1	0.01	0.01	0.01
1 (Starting dose)	0.015	0.015	0.015
2	0.030	0.030	0.025
3	0.060	0.050	0.038
4	0.100	0.075	0.050
5	0.150	0.100	0.067
6	0.200	0.134	0.089
7	0.267	0.178	0.119
8		0.238	0.158
9			0.211

The modified toxicity probability interval (mTPI) design uses a Bayesian decision-theoretic framework and a beta/binomial hierarchical model to tailor dose-escalation and de-escalation decisions. These rules are conceptually similar to those used by the 3+3 design and all the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table.

The decision rules to “dose escalate” (E), “no change in dose” (S), “dose de-escalate” (D) or “dose de-escalate, unacceptable toxicity” (U) are described below:

Table 1. Decision Rules

Number	Number of Patients treated at a Dose level										
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	D	S	S	S	E	E	E	E	E	E	E
2	U	D	D	S	S	S	S	S	S	S	S
3		U	U	D	D	S	S	S	S	S	S
4			U	U	U	D	D	D	D	D	S
5				U	U	U	U	U	D	D	D
6					U	U	U	U	U	U	D
7						U	U	U	U	U	U

Cohorts of patients could receive doses already tested but a dose that is associated with decision "Dose de-escalate, unacceptable toxicity" cannot be revisited and no more patients should be treated at this dose or higher doses for the remainder of the trial.

A minimum of 9 patients treated at the MTD dose is required to establish such dose as the RP2D. The maximum sample size would be N=70 but actual sample size will depend on the underlying dose toxicity profile and variability in actual data realization. The initial dosing regimen tested in Part 1 will be PF-06647263 administered once every 3 weeks (Q3W) consistent with the pre-clinical toxicity study. Evaluation of a weekly (QW) regimen will be initiated when the first patient treated with the Q3W regimen experiences a DLT or Grade 2 thrombocytopenia related to study treatment. The starting dose of the QW regimen will not exceed one-third of the highest Q3W dose evaluated. Once initiated, the 2 regimens will be evaluated in parallel and independently based on the same dose-escalation criteria as described above.

Dose escalation will stop under any of the following conditions:

1. The maximum sample size has been achieved;
2. At least 9 patients have been accumulated at a dose that is predicted to be the MTD;
3. All doses explored appear to be overly toxic and the MTD cannot be determined.

2.3. Part 2

Upon identification of the MTD, approximately 30 patients will be 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. This expansion component aims at evaluating ADC (PF-06647263) at the MTD in two cancer indications:

a. Previously treated metastatic TNBC which expresses EFNA-4 (15 patients).

b. Advanced epithelial ovarian cancer, primary peritoneal or fallopian tube cancer (OVCA) which expresses EFNA-4 and which has progressed or relapsed during or within 6 months post most recent therapy with a platinum agent (15 patients).

2.4. Study Objectives

Study Objectives and Endpoints

Part 1 (Dose escalation) Primary Objective

- To assess safety and tolerability at increasing dose levels of PF-06647263 administered as an intravenous (IV) infusion every 3 weeks (Q3W) and weekly (QW) in patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available, in order to estimate 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 (PK) of PF-06647263, total antibody, and unconjugated payload;
- To evaluate the immunogenicity of PF-06647263;
- To document preliminary evidence of anti-tumor activity based on response rate (RR).

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Part 2 (Expansion) Primary Objective

- To confirm safety and tolerability and explore preliminary evidence of anti-tumor activity of PF-06647263 based on response rate (RR) at the RP2D in patients with previously treated metastatic TNBC and advanced platinum-resistant OVCA which express EFNA4.

[redacted]

Secondary Objectives

- To evaluate the overall safety profile at the RP2D;
- To characterize the single and multiple dose PK of PF-06647263, total antibody, and unconjugated payload;
- To evaluate the immunogenicity of PF-06647263;
- To document preliminary evidence of anti-tumor activity based on progression free survival (PFS) and overall survival (OS).

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- [redacted]

Endpoints

Primary Endpoint (Part 1)

- First cycle Dose Limiting Toxicities (DLTs) in order to determine the MTD and RP2D.

Primary Endpoint (Part 2)

- Response rate (RR) as determined by the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 criteria.

Secondary Endpoints (Parts 1 and 2)

- Adverse Events as characterized by type, frequency, severity (as graded by 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;
- Systemic PK exposure of PF-06647263, total antibody, and unconjugated payload will be determined with validated methods. Standard noncompartmental PK parameters will be determined from the respective concentration-time data;

[redacted]

- Immunogenicity of PF-06647263; Human serum ADA (anti-PF-06647263 antibody) samples will be analyzed for the presence or absence of anti-PF-06647263 antibodies, following a tiered approach using screening, confirmation and titer/quantitation;

- Objective tumor response, as assessed using RECIST version 1.1 by calculating the Overall Response Rate (ORR), Clinical Benefit Response Rate (CBRR), Progression Free Survival (PFS), and Overall Survival (OS)-Part 2 only.

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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

Decision rules are based on calculating unit probability mass (UPM) of three dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as (0; pT-e1), the over-dosing interval (pT+e2), and the proper-dosing interval (pT-e1, pT+ e2), where e1 and e2 are small fractions. For a target DLT rate of 0.25, the target equivalence interval is (0.20, 0.30). The three dosing intervals are associated with three different dose-escalation decisions (Table 1). The under-dosing interval corresponds to a dose escalation (E), over-dosing corresponds to a dose de-escalation (D), and proper-dosing corresponds to remaining at the current dose (S). Given a dosing interval and a probability distribution, the unit probability mass (UPM) is defined as the ratio of the probability of the interval to the length of the interval. Once the safety assessment is complete for Cycle 1, the focus will be on allocation of new subjects to the dose most likely to be an MTD.

The study continues accruing until one of the three stopping conditions below is triggered. The algorithm will stop if any of the following criteria is met:

1. The maximum sample size has been achieved.

[redacted]

2. MTD has been identified with sufficient accuracy: at least 9 patients have been accumulated on a dose that is currently estimated to be the MTD, or

3. All doses explored appear to be overly toxic and the MTD cannot be determined.

Specifically the mTPI approach formalizes stopping rules as follow:

Rule 1 (early termination): if the first dose is too toxic → $\Pr(p_1 > p_T / data) > \xi \quad ; \quad \xi = 0.975$

Rule 2 (dose exclusion), if dose= i is too toxic → $\Pr(p_i > p_T / data) > \xi \quad ; \quad \xi = 0.975$
then exclude doses $\geq i$

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 PF-06647263 in patients with solid tumors. The DLT rate and analyses of concorcance and confidence interval 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

Similar to the conventional 3+3 design, the exact sample size of the mTPI design in Part 1 cannot be pre-specified in advance because it is a dynamic feature of the design. The minimum sample size after which the Part 1 can be stopped and MTD declared is 9. If two dose regimens are evaluated, the maximum sample size would be 70 patients.

As for the number of subjects treated at each dose, it is expected that the typical number will be 2-4 subjects for the doses actually studied. For the dose declared as MTD at the end of trial, this number will be at least 9. However, since variable cohort size is allowed, the actual number of subjects treated at each dose will vary from 2 to 12. For example, N=12 is achieved if 4 additional patients are enrolled in a cohort of n=8.

The sample size in Part 2 is based on clinical considerations, rather than statistical justification. It will include 30 subjects in two cohorts of tumor types of interest (ie, TNBC and OVCA) to confirm the safety and tolerability of the recommended dose based on Part 1 and to assess preliminary anti-tumor activity.

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

Part 2: the per protocol (PP) analysis sets includes all enrolled patients (for each indication) who receive at least one dose of study medication and who do not have major treatment deviations during first cycle.

> Specifically: Patients with major treatment deviations in Cycle 1 are not evaluable for the RP2D assessment and therefore will not be included in the PP analisys. 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. At least one baseline and one post-baseline disease assessment are required for the PP analysis.

Modified PP analysis sets may be considered for additional analyses and would include patients enrolled either in Part 1 or in Part 2.

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 interim analysis and conference presentations when the study is still ongoing.

[redacted]

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-06647263 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) for each tumor type in the expansion cohorts. 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) –** or Response Rate (RR) is defined as complete response (CR) or partial response (PR) according to RECIST 1.1 (Appendix 2). Overall response is the best response recorded from first dose until disease progression/recurrence.

- **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.

[redacted]

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 Definitions

Severity of adverse events will be graded according to NCI 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 (Q3W regimen: 21 days or until the patient receives the 2nd infusion if there are treatment delays, QW regimen: 21 days or until the patient receives the 4th infusion if there are treatment delays) will be classified as DLTs:

- Hematologic:
  - Grade 4 neutropenia lasting >7 days.
  - Febrile neutropenia (defined as neutropenia ≥ Grade 3 and a single body temperature >38.3°C or a sustained temperature of ≥38°C for more than one hour).
  - Grade ≥3 neutropenia with infection.
  - Any grade thrombocytopenia associated with clinically significant or life-threatening bleeding.
  - Grade 4 thrombocytopenia ≥72 hours or platelets ≤10,000/mm^3 regardless of duration.
- Non-hematologic:
  - Grade ≥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 attributable to PF-06647263.

Grade ≥3 cytokine release syndrome, infusion related reaction, allergic reaction, or anaphylaxis will not be considered as DLTs but may be a reason for study discontinuation and should be reviewed with Pfizer.

7.2.2. MTD Definition

The MTD would be any doses with true toxicity probabilities in the Equivalence Interval (EI) where the EI is defined as [20%-30%].

In practice, the MTD will be the highest dose associated with the occurrence of DLTs ≤33% (eg, 3/9 evaluable patients experience a DLT during the first treatment cycle).

7.2.3. Recommended Phase 2 Dose (RP2D) Definition

The Recommended Phase 2 Dose (RP2D) is the dose chosen for further study based on Part 1 results. If the MTD proves to be clinically feasible for long term administration in a reasonable number of patients, such dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

7.2.4. Vitals Signs

Vital signs, See Schedule of Activities in the protocol for details.

7.2.5. 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.

7.2.6. 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 4.0) timing, seriousness, and relatedness.

All AEs will be coded by system organ class (SOC) and preferred term using Medical Dictionary for Regualtory 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.

7.2.7. ECG and QTc Interval

The analysis of ECG results will be based on Safety Population patients with baseline and on-treatment ECG data.

ECG 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 values. Interval measurements from repeated ECGs will be included in the outlier analysis as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Bazett's, Fridericia's and possibly a study specific factor). The adequacy of the correction method will be assessed graphically (plots of QT and QTc versus RR) and supplementary transformations may be considered, as appropriate. Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF and QTcB by treatment and dose. Individual QTc (all evaluated corrections) intervals will be listed by compound, 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 QTc value and changes from baseline in QTc 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 QTc data will be conducted and summarized as follows:

- The number of patients with maximum change from baseline in QTc (<30, 30-60, and ≥60 ms).

- The number of patients with maximum post-dose (post-baseline) QTc (<450, 450-<480, 480-<500, and >=500 ms).

[redacted]

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 QTc (one or more correction method will be used) using Maximum CTC AE 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 ≥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 those triplicate measurements is also ≥500 msec. Changes from baseline will be defined as the change between QTc post dose from Day 0, or the pre-dose values on Day 1.

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

7.2.8. Immunogenicity

Anti-PF-06647263antibody data will be collected at baseline and post randomization according to the protocol.

7.3. PK Endpoints

Blood samples for PK analysis of PF-06647263 (ADC), total antibody, and unconjugated payload will be taken according to the Schedule of Activities given in the protocol.

- **Pharmacokinetic parameters of PF-06647263 (ADC) and total antibody:**

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

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

- **Pharmacokinetic parameters of Payload (unconjugated payload)**:

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

Cycle 4 - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, $t_{1/2}$, 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_{τ}	Area under the concentration-time profile from time zero to the time τ, the dosing interval	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 cobserved oncentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$T_{½}$	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	Dose/ AUC_{inf} for cycle 1; Dose/ AUC_{τ} for cycle 4
V_{ss}	Volume of distribution at steady state	CL×MRT
R_{ac}	Observed accumulation ratio	$AUC_{cycle\ 4,\ \tau}$/ $AUC_{cycle\ 1,\ \tau}$

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[redacted]

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 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, 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.

[redacted]

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.

Pharmacodynamic parameters

Missing data for the pharmacodynamic parameters will be treated as such and no imputed values will be derived.

[redacted]

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) 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 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 the DLT by malignancy 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 by malignancy 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. 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 Section 11.3	Secondary Analysis
Progression Free Survival (PFS)	Per Protocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per Section 11.3	Secondary Analysis
Time to Progression (TTP)	Per Protocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per Section 11.3	Secondary Analysis
Duration of Response (DR)	Per Prtocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per Section 11.3	Secondary Analysis

9.2.2.2. Pharmacokinetics Analyses

Pharmacokinetic Parameters

To assess the pharmacokinetics of PF-06647263 (ADC), total antibody and 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_{last}, AUC_{∞}, AUC_{τ}, C_{max}, CL, V_{ss}, 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}	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.

[redacted]

To assess the relationship between the PK parameters and dose, dose normalized AUC_{∞}, AUC_{last}, AUC_{τ}, and C_{max} 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-06647263 (ADC), total antibody and 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-06647263 (ADC), total antibody and 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 (linear and log scale) 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 (linear and log scale) 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-06647263 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

CCI [redacted]

[redacted]

9.2.3. Safety Analyses

Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 4.0 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). 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.

[redacted]

Other Variables: Anti-PF-06647263 antibody

For anti-PF-06647263 antibody, a listing, sorted by subject and study day, of the result of anti-PF-06647263 antibody screening (positive/negative [<1:negative]), the specificity, and titer will be listed. Summary counts of the patients, who are positive for the antibody, 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. 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. 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. If in the CRF the prescribed dose unit is mg/kg, but the actual dose is in mg the actual dose mg/kg should be calculated considering the body weight of the patient at that visit.

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 1st delay (median, range)
- Number of cycles before 1st reduction (median, range)
- Number of cycles 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 subject (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0 mg), 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.

[redacted]

[redacted]

10. REFERENCES

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

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

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

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

NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE). http://evs.nci.nih.gov/ftp1/CTCAE/Documentation/CTCAE_Governance_2010-03-11.pdf

11. APPENDICES

11.1. APPENDIX 1: 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.

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

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 ≥ 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.

[redacted]

- 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 ≥ 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/non-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[a]
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.

[a] 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[1]	Outcome
Inadequate baseline assessment	Start date (C1D1)	Censored
No on-study assessments	Start date (C1D1)	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	Start date (C1D1)	Censored
No on-study assessments	Start date (C1D1)	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.