Protocol C3881001

A PHASE 1 DOSE ESCALATION STUDY EVALUATING SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-06952229 IN ADULT PATIENTS WITH ADVANCED SOLID TUMORS

Statistical Analysis Plan
(SAP)

Version: Amendment 1

Author: PPD (PPD)

Date: 20-May-2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. VERSION HISTORY

Version	Section	Update
Amendment 1	All	Texts taken directly from the protocol are made *italicized* Updated per Protocol Amendment 3

2. INTRODUCTION

This analysis plan is meant to supplement the C3881001 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). This SAP is based on Protocol Amendment 3 dated May 7, 2021.

2.1. Study Objectives

Part 1A

Primary Objectives

- *To assess safety and tolerability at increasing dose levels of PF 06952229 in patients with advanced/metastatic tumors*
- *To determine MTD and RP2D of PF 06952229 as a single agent.*

Secondary Objectives

- *To evaluate the single and multiple dose PK of PF 06952229 when given as a single agent.*
- *To evaluate preliminary anti tumor activity of PF 06952229 when given as a single agent.*
- *To evaluate preliminary biochemical responses as a measure of anti tumor activity of PF 06952229.*

CCI

[redacted]

[redacted]

Part 1B

Primary Objectives

- *To assess safety and tolerability at increasing dose levels of PF 06952229 in combination with enzalutamide in patients with mCRPC.*
- *To determine MTD and RP2D of PF 06952229 in combination with enzalutamide in patients with mCRPC.*

Secondary Objectives

- *To evaluate the single and multiple dose PK of PF 06952229 when given in combination with enzalutamide.*
- *To evaluate preliminary anti tumor activity of PF 06952229 when given in combination with enzalutamide.*
- *To evaluate preliminary biochemical responses as a measure of anti tumor activity of PF 06952229 when given in combination with enzalutamide.*

CCI [redacted]

[redacted]

Part 2A

Primary Objectives

- *To confirm safety and tolerability of PF 06952229 at the estimated RP2D in patients with mCRPC.*
- *To estimate efficacy of PF 06952229 at the estimated RP2D in patients with mCRPC.*
- *To confirm the RP2D of PF 06952229 as a single agent.*

Secondary Objectives

- *To estimate additional efficacy of PF 06952229 at the estimated RP2D in patients with mCRPC.*
- *To further evaluate the single and multiple dose PK of PF 06952229 when given as a single agent.*
- *To evaluate immune cells in paired pre and post treatment tumor biopsies (where available).*

CCI

[redacted]

Part 2B

Primary Objectives

- *To confirm PF 06952229 safety profile in combination with enzalutamide at the estimated RP2D in patients with mCRPC.*
- *To estimate efficacy of PF 06952229 in combination with enzalutamide at the estimated RP2D in patients with mCRPC.*
- *To confirm the RP2D of PF 06952229 in combination with enzalutamide in patients with mCRPC.*

Secondary Objectives

- *To estimate additional efficacy of PF 06952229 at the estimated RP2D in patients with mCRPC.*
- *To further evaluate the PK of PF 06952229 when given in combination with enzalutamide.*
- *To evaluate immune cells in paired pre and post treatment tumor biopsies (where available).*

CCI [redacted]

2.2. Study Design

This is a Phase 1, open label, multi center, multiple dose, dose-escalation and expansion, safety, tolerability, PK, CCI *study of PF-06952229 in previously treated patients with advanced or metastatic cancers that may have high TGFβ signatures and EMT expression.*

The study includes Parts 1A and 1B, which are dose-escalation cohorts, and Parts 2A and 2B, which are dose expansion cohorts. The primary objectives for Part 1A are to assess the safety and tolerability of PF-06952229 administered as a single agent and to determine maximum tolerated dose (MTD). The primary objectives for Part 1B are to assess the safety and tolerability of PF-06952229 administered with enzalutamide and to determine MTD. The primary objectives for Part 2A are to confirm PF-06952229 safety and tolerability, estimate the single agent efficacy of PF-06952229 and determine a recommended Phase 2 dose (RP2D). The primary objectives of Part 2B are to confirm the safety profile of PF-06952229 combined with enzalutamide, estimate the efficacy of PF-06952229 combined with enzalutamide and determine a RP2D for the combination.

Part 1A is a sequential single-agent dose-escalation conducted in patients with advanced or metastatic solid tumors who have failed standard of care treatment or for whom no standard of care exists. Successive cohorts of patients are to receive escalating doses of PF-06952229 on an outpatient basis starting from 20 mg BID, which is based on non-clinical data. Nine candidate dose levels are planned using an Accelerated Titration Design (ATD) until reaching 250 mg BID, after which the design will revert to modified target probability interval (mTPI). The highest tested dose will not exceed 800 mg BID. If an MTD is not

observed during the 28 day safety window, additional dose levels may be considered based on PK, safety, tolerability, CCI [redacted] *assessments. Based on PK and safety, additional patients can be added to a dose lower than the MTD and also may be moved forward to monotherapy expansion.*

Part 1B is a dose-escalation of PF-06952229 in the combination of enzalutamide conducted in patients who were previously treated with metastatic castration-resistant prostate cancer (mCRPC). The starting dose of PF-06952229 will be the MTD or maximum administered dose (MAD) of Part 1A. Based on evolving PK, CCI *and safety profiles, assessed in Part 1A, Part 1B may commence before reaching the MTD, and will follow an mTPI design. The maximum PF-06952229 dose for the combination escalation may be higher than the monotherapy MTD due to the potential DDI between enzalutamide and PF-06952229, but not higher than 800 mg BID.*

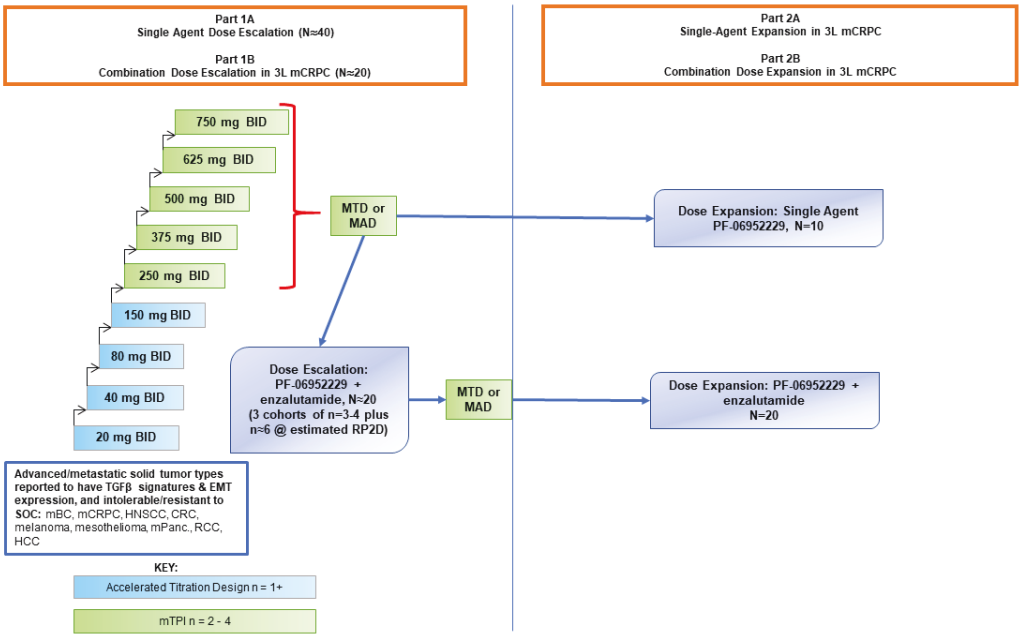
Part 2A and Part 2B are expansion cohorts for monotherapy and combination therapy, respectively, in patients with previously treated mCRPC.

To assess baseline TGFβ related biomarker signatures that may correlate with clinical efficacy, all patients enrolled in Part 1 will be required to provide a recent archival tumor sample or to undergo a fresh pre treatment biopsy if archival samples are unavailable prior to trial treatment.

Part 2 patients are required to provide either a recent archival tumor biopsy or, for all patients in Part 2A and from approximately 10 patients in Part 2B, mandatory de novo biopsies. Mandatory de novo pre-treatment and on-treatment tumor biopsies may not be required where it is determined that it is not medically feasible (such as constituting unacceptable medical risks). However, this would require agreement of Investigator and Sponsor.

See Figure 1 for the study schema.

Figure 1. Study Schema



CCI

All patients:

1. Will undergo up to 4 weeks of screening prior to study entry, ie, Cycle 1 Day 1.

2. Will receive doses of PF 06952229, administered orally on 28 day cycle, 7 days on, 7 days off, up to 2 years. Any additional treatment with PF 06952229 beyond 2 years shall be discussed and approved by the Sponsor.

3. Treatment with investigational product (IP) will continue until disease progression, patient refusal, or unacceptable toxicity occurs, whichever occurs first. However, patients who demonstrate clinical benefit (despite radiographic progression) with manageable toxicity and are willing to continue receiving the investigational product will be given the opportunity to continue treatment upon agreement between investigator and sponsor.

4. Will undergo a follow up visit approximately 4 weeks after the last dose for AE and serious adverse event (SAE) collection.

The proposed doses, schedule(s), and PK CCI *time points may be reconsidered and amended during the study based on the emerging safety and PK* CCI *data.*

3. ENDPOINTS AND COVARIATES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Part 1

- *First cycle Dose Limiting Toxicities (DLTs). The specific definition of DLT is provided in the study protocol.*
- *Adverse events (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0).*

Part 2

- *First cycle Dose Limiting Toxicities (DLTs) in combination with enzalutamide for CRPC and palbo/letrozole for HR+ BC.*
- *Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy.*
- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.*

3.2. Secondary Endpoint(s)

Parts 1 and 2

- *Pharmacokinetic parameters of PF-06952229.*
- *Single Dose (SD) C_{max}, T_{max}, AUC_{last}, and as data permit, AUC_{inf}, CL/F, V_z/F, and $t_{1/2}$.*
- *Multiple Dose (MD) $C_{ss,max}$, $T_{ss,max}$, AUC_{last}, $C_{ss,min}$, and as data permit CL_{ss}/F, V_{ss}/F, $t_{1/2}$, and R_{ac} (AUC_{last}/AUC_{last}).*
- *Objective Response Rate (ORR). PSA50 Response Rate for prostate cancer patients only.*
- *Time to event endpoints (Duration of Response (DOR), Progression Free Survival (PFS), Overall Survival (OS), Time to Progression (TTP), Time to Response (TTR).*
- *For prostate cancer patients, response assessment will be based on Prostate Cancer Response criteria (PCWG2). For other tumor types, response will be assessed using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).*

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

3.4. Covariates

Biomarker data may be considered as covariates in PK and anti-tumor efficacy exploratory analyses. Covariates may also be considered when exploring QTc and PK relationship.

4. ANALYSIS SETS

4.1. Full Analysis Set

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

4.2. Safety Analysis Set

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

4.3. 'PER PROTOCOL' Analysis Set (evaluable for MTD)

The per protocol analysis set includes all enrolled patients who receive at least one dose of study treatment and who do not have major treatment deviations during the first cycle. Patients with major treatment deviations during the first cycle of treatment are not evaluable for the MTD assessment and will be replaced as needed to permit the MTD estimation. Major treatment deviations include the 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 period and disease follow up phases other than as defined/allowed in this protocol. Major treatment deviations will also include:

- *Administration of less than 70% of the planned number of doses of PF-06952229 (provided that the reduction in doses is not due to toxicity attributable to PF-06952229).*

- *Administration of more than 110% of the planned number of doses of PF-06952229.*

4.4. Modified Intent to Treat (mITT) Population

The modified intent to treat (mITT) is the analysis population that will follow the ITT principle and include patients receiving at least 1 dose of investigational product with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population will be used for analyses and to support conference presentations when the study is still ongoing.

4.5. PK Analysis Set

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

CCI [redacted]

4.7. 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.

4.8. Protocol Deviations

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

5. GENERAL METHODOLOGY AND CONVENTIONS

This is an open-label dose escalation study and the data will be continuously monitored during the study. No formal interim analysis is planned for this study.

5.1. Statistical Hypotheses

There are no statistical hypotheses.

5.2. Statistical Decision Rules

5.2.1. Dose Escalation

The dose escalation in Part 1A will start with Accelerated Titration Design (ATD) as proposed by Simon et al [2]. Part 1 will have an initial accelerated phase followed by a standard (mTPI) escalation phase. During the accelerated phase, initial cohorts to contain a minimum of one patient until the first instance of first-cycle CTCAE grade ≥2 toxicity.

The traditional mTPI design[5] uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.275). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to target probability (pT), the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model. The proposed mTPI method for this protocol includes stopping rules and dose escalation criteria, which prevents the target DLT rate to reach ≥33% for determining the MTD. This proposed mTPI method is more conservative than the traditional TPI method.

Decision rules are based on calculating unit probability mass (UPM) of 3 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, 1), and the proper-dosing interval (pT- e1, pT+ e2), where e1 and e2 are small fractions. Therefore, the target interval for the DLT rate is (0.225, 0.325).

The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose-escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to remaining at the current dose (R). Given a dosing and a probability distribution, the unit probability mass (UPM) of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the under-dosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Ji et al. (2010)[5] have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

5.2.2. MTD Determination

This study contains dose escalation with single agent (Part 1A) in patients with advance or metastatic solid tumor, and a combination dose escalation with enzalutamide in previously treated patients with mCRPC (Part 1B). Part 1A and Part 1B will determine the MTD/RP2D in sequential dose escalation cohorts.

The dose finding process in the current study is designed to establish the MTD defined as the highest dose that yields a target of approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) of (22.5%, 32.5%). Note the DLT rate for cardiac toxicity should not exceed 10%. *The 27.5% target was chosen based on safety considerations. The prior distribution of DLT is set as a beta (0.5,0.5) and the threshold probability for early termination and dose exclusion is set to 0.95 as suggested in the original mTPI method (Ji et al., 2010).[5] Similarly, doses with an incidence of DLT, eg 4 out of 10, or apparently higher than 32.5% cannot be selected as MTD, even though it might be allowed by the mTPI method.*

Cohorts of patients could receive doses already tested but a dose that is associated with decision to "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.

The maximum sample size for Part 1A would be approximately N=40 for the monotherapy dose escalation and approximately N=20 for the combination dose escalation, but actual sample size will depend on the underlying dose toxicity profile and variability in actual data realization.

The study will continue accruing until one of the three stopping conditions below is triggered.

- *The maximum sample size has been achieved (approximately 40 patients in Part 1A monotherapy dose escalation, approximately 20 patients in Part 1B combination dose escalation, and 10 patients in Part 2A monotherapy dose expansion and 20 patients in Part 2B combination dose expansion);*

- *6 - 12 patients that have been enrolled at a dose level that is predicted to be the MTD per the mTPI method;*

- *All dose levels explored appear to be overly toxic, and the MTD cannot be determined.*

Due to binomial data variability in small samples, DLTs may be observed in a first cohort(s) by chance even when the true Probability (DLT) is fairly low. This could result in the estimated posterior DLT rate to exceed the targeted 27.5% very early in the trial.

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

Probability of Escalating Dose

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

5.2.3. Sample Size Determination

Part 1

In Part 1, patients will participate in a dose escalation phase aimed at estimating the MTD. The sample size for this component of the study will vary depending on the number of DLTs observed.

A maximum of 60 patients are expected to be enrolled in the dose escalation safety cohorts in Part 1, including approximately 40 patients for the monotherapy dose escalation and approximately 20 patients for the combination dose escalation. The actual number of patients enrolled will depend on the tolerability of PF 06952229 and the number of dose levels required to identify the MTD/RP2D. It is expected that the dose escalation process can be stopped and MTD declared with approximately 6 to 12 patients at the MTD dose. As for the number of patients treated at each dose, it is expected to be at 1 to 4 patients for the doses actually studied. However, since variable cohort size is allowed, the actual number of patients treated at each dose (including MTD) will vary from 1 to 12 patients.

Part 2

For PF 06952229 single agent expansion in patients with mCRPC, the planned sample size of the expansion cohort is 10 based on clinical consideration.

PF 06952229 single agent in combination with enzalutamide for patients with metastatic castration resistant prostate cancer (mCRPC), assuming a sample size of 20, and the observed PSA50 response is 60% (12/20), the Bayesian posterior probability to demonstrate that the "True PSA50 response" is greater than 37% is 98.15%. Assuming 80% of the 20 patients have measurable disease and are response evaluable (16 patients evaluable), and

the observed ORR is 43.75% (7/16), the Bayesian posterior probability to demonstrate that the "True ORR" is greater than 30% is 86.89%.

All the Bayesian calculations above assume a non informative Uniform (0,1) prior.

5.3. General Methods

Whilst every effort has been made to pre-specify all analyses in this statistical analysis plan, if any additional exploratory analyses are found to be necessary, the analyses and the reasons for them will be detailed in the clinical study report (CSR).

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

5.3.1. Analyses for Time to Event Data

Time to event endpoints in this study may include progression-free survival (PFS), duration of response (DOR), time to response (TTR), time to progression (TTP), and overall survival (OS). These endpoints will be summarized using the Kaplan-Meier method[6] and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for time-to-event endpoint (Brookmeyer and Crowley, 1982)[7] will be provided.

5.3.2. Analyses for Binary Data

Binary endpoints in this study include ORR, complete response (CR), and partial response (PR). Response assessment will be based on PCWG2 for prostate cancer patient, and will use RECIST 1.1 for other tumor types. If deemed necessary disease control rate (ie, DCR, which is defined as the proportion of patients that achieved CR, or PR, or stable disease) may also be calculated for Part 2. Descriptive statistics along with the corresponding 2-sided 95% confidence intervals using an exact method will be provided for these endpoints.

5.3.3. Analyses for Continuous Data

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

5.4. Methods to Manage Missing Data

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

5.4.2. Efficacy Analysis

For the time-to-event endpoints, the missing data handling method will be censoring. Censoring rules for time-to-event endpoints are detailed in Section 9.2.

5.4.3. Pharmacokinetics

Concentrations below the limit of quantification

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

Deviations, missing concentrations and anomalous values

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

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

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

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

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

Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters. 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, this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

CCI [redacted]

6. ANALYSES AND SUMMARIES

For efficacy related endpoints in this study, the following analysis plan may be implemented if the data is sufficient. For tumor response assessment, PCWG2 will be used for prostate cancer patient and RECIST 1.1 will be used for other tumor types.

Endpoint	CCI [redacted]	Part 2
ORR		Both
PFS		Unconfirmed*
DOR		Both
TTP		Unconfirmed*
TTR		Both

Note: "Both" in the above table represents both unconfirmed and confirmed tumor assessments.
*: Confirmation for progressed disease is not applicable in RECIST 1.1.

In the "unconfirmed" analyses (ie, tumor response or progression without confirmation required), all tumor assessments data will be included for analyses. Specifically, regardless if a patient's tumor response or progression is subsequently confirmed or not, the patient data will all be included in the "unconfirmed" analyses. This is a more comprehensive analysis where tumor confirmation is not required and not taken into account. For example in the ORR analysis, if a patient achieved CR or PR, regardless it is subsequently confirmed or not, the patient will be included in the numerator.

In the "confirmed" analyses (ie, tumor response with confirmation required), only those tumor assessments data that's subsequently confirmed by a consecutive tumor scan will be considered as a "success" or "event" and be included for analyses as appropriate. For example, in the ORR analysis, a patient will only be counted in the numerator (the "success") if the tumor response (CR or PR) is subsequently confirmed. If a patient's tumor response is not subsequently confirmed, the patient will still be included in the denominator (the population set) but will not be included in the numerator (the "success").

6.1. Standard Analyses

Study Conduct and Patient Disposition

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

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

Baseline Characteristics

Baseline characteristics such as demographics, prior medication, medical history, ECOG performance status, and primary diagnosis will be tabulated and listed. For ECOG

performance status a shift table (worst post-baseline vs baseline may be produced). The Safety Analysis Set will be used.

Treatment Administration/Compliance

Listings and tables by dose level will be provided. Cycle length is 28 days (±2 days) for oral administration. 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 28 (+2) days from Day 1 of the previous cycle (only applies to cycle 2 and above), will be used in determining cycle delay. For example, after cycle 1 ended for a patient in Part 1, a new cycle didn't start until 28 (+2) days after (but before 56 days after) cycle 1 day 1, the newly started cycle will be considered as cycle 2, and cycle 2 is considered delayed.

- Cycle skip – Day 1 of current cycle starts later than 56 (+4) days from Day 1 of the previous cycle (only applies to cycle 2 and above). For example, After cycle 1 ended for a patient in Part 2, a new cycle didn't start until 56 (+4) days after cycle 1 day 1, the newly started cycle will be considered as cycle 3, and cycle 2 is considered skipped for this patient.

- 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. Intrapatient dose reductions are not permitted during the study unless, in discussion with the sponsor, a dose level is deemed beyond the determined MTD.

- Dose interruption – a skip in the planned administered daily dose upon enrollment. It includes missed dose and the dose with 0 administered collected on the CRF.

The following will be summarized for each dose level:

- Number of subjects;

- Number of cycles per subject

- Number (%) of subjects with cycle delays and cycle skips;

- Number (%) of subjects with dose interruptions;

- Number (%) of subjects with dose reductions;

- Number (%) of each reason (drug related AE vs AE vs. Other) for cycle delays, dose interruptions and dose reductions;

- Time on treatment (median, range).

- 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.

6.2. Analysis of Primary Endpoint

6.2.1. DLT (Part 1 and Part 2)

Dose Limiting Toxicity is the primary endpoint of the dose escalation phase 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.

6.2.2. Safety Endpoints (Part 1 and Part 2)

Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 5.0 and coded using the MedDRA.[8] The focus of AE summaries will be on Treatment Emergent Adverse Events (TEAE), which is defined as any adverse event that occurs after the beginning of the study treatment (on or after Study Day 1) or any pre-existing adverse event that worsens after the beginning of the study treatment and at least 28 days after final dose of study treatment or start of new anticancer therapy (whichever comes first). 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 Safety Analysis Set will be used. Part 1 and Part 2 data will be

summarized separately and may also be pooled together for analysis. Pfizer standard on safety data reporting will be followed.

Laboratory Tests Abnormalities

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

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

6.3. Analysis for Secondary Endpoints

6.3.1. Efficacy Endpoints Analysis

ORR, as assessed using PCWG2 for prostate cancer and RECIST version 1.1 for other tumor types,is a key efficacy endpoint. The following analyses will be performed in the mITT population by tumor type and pooled:

The ORR, along with other efficacy analyses will be performed in the mITT population. Part 1 and Part 2 data will be summarized separately, and may also be pooled together for analysis if deemed necessary. Specifically, the key tables in Part 2 include:

1. ORR by visit: investigator provided tumor response CR, PR, and CR+PR will be presented by descriptive statistics (frequency and percentage) and 95% confidence interval.

2. Best overall response of CR, PR, and CR+PR. This will include best overall response derivation without confirmation and with confirmation. Descriptive statistics (frequency and percentage) and 95% confidence interval will be provided.

Tumor response data in Part 1, Part 2 and across the two Parts may be summarized with descriptive statistics (frequency and percentage) in the following groups by visit and then best overall response across all visits:

- Overall summary for all doses and all tumor types;
- By tumor type regardless of dose;
- By dose regardless of tumor type;
- By dose and tumor type if data permit.

Summary tables of best overall response rate, PFS, OS, DOSD, and DOR may be provided by the groups aforementioned when deemed necessary (eg, if there are ≥5 patients in a specific group).

In addition, PSA50 Response Rate defined as ≥50% PSA reduction from baseline assessed by PCWG2 for prostate cancer patients will be summarized similarly as ORR. See Section 9.5 for more details on PSA measurement.

Efficacy listings (tumor measurements listings and tumor response listings) will be provided that include the investigator provided tumor measurement data, tumor response, best overall response, first CR/PR date, last date with CR or PR, most recent date without progression, progression date, death date, and last tumor assessment date, etc.

Endpoint	Analysis Set	Statistical Method	Model/Covariates/Strata	Missing Data
Overall response	mITT	Exact CI	See aforementioned summary descriptions on data pooling across dose and tumor type	Observed case
Overall Survival	ITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored at last visit
Progression Free Survival (PFS)	mITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling 3721 across dose and tumor type	Censored per Section 9.2
Time to Progression (TTP) and Time to Response (TTR)	mITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored per Section 9.2
Duration of Response (DOR)	mITT	Kaplan-Meier	See aformentioned summary descriptions on data pooling across dose and tumor type	Censored per Section 9.2

Swimmer plot for individual clinical response and time on treatment, waterfall plot for individual tumor size percent change from baseline, and spider plot for individual tumor size percent change from baseline over time may be presented if needed. The following table provides an overview of the efficacy analysis if the data is sufficient.

6.3.2. Pharmacokinetics Analyses

The concentration-time data of PF-06952229 will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) according to dosing cohort and time for each part of the study. In addition, the concentration-time data from Part 2 dose expansion will also be summarized by descriptive statistics according to tumor type.

The actual time of sample collection will be used in PK parameter calculation. In the event that the actual sampling time is not available, the nominal time may be used if there is no evidence that the actual sampling time deviates substantially from the nominal time.

Presentation of PF- PF-06952229 concentration-time data

The concentration-time data of PF-06952229 will be presented as below:

- a listing of all concentrations by cohort, subject ID and nominal time. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- a summary of concentrations by cohort and nominal time, where the summary statistics will include n, mean, standard deviation, median, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- for the concentration-time data after the 1st (C1D1) and 7th dose (C1D7), median concentration-time plots (on both linear and semi-log scales) against nominal time postdose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time postdose).

For drug concentration summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used; for individual subject plots by time, the actual PK sampling time will be used, with the pre-dose time set to zero.

Calculation of PF-06952229 PK parameters

For patients enrolled in the dose escalation stage of the study, the individual concentration-time data of PF-06952229 during Cycle 1 and Cycle 2 will be analyzed separately by non-compartmental methods to estimate the PK parameters. The PK parameters estimated will include C_{max}, T_{max}, and AUC_{last} (AUC_{tau} at steady state). If data permit or if considered appropriate, $t_{1/2}$, CL/F, V_d/F (orV_{ss}/F at steady state), and accumulation ratio (R_{ac}) will also be estimated. The PK parameters will be summarized descriptively by dose level and cycle.

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

For patients enrolled in Part 2 of the study, trough concentrations of PF-06952229 will be summarized descriptively by cycle and by tumor type.

PK parameters will be calculated using standard non-compartmental methods:

Parameter	*State*	*Method of Determination*
AUC_{tau}	sd, ss	Linear/Log trapezoidal method
AUC_{last}	sd,ss	Linear/Log trapezoidal method
AUC_{inf}[a]	sd	AUClast + (C_{last}*/k_el), where C_{last}* is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	sd, ss	Observed directly from data
T_{max}	sd, ss	Observed directly from data as time of first occurrence
CL/F	sd, ss	Dose/AUC_{inf} for sd[a] Dose/AUC_{tau} for ss
Vd/F	sd, ss	Dose/(AUC_{inf} *k_el) for sd Dose/(AUC_{τ} * k_el) for ss
V_{ss}/F[a]	sd, ss	CL * MRT, where MRT is the mean residence time adjusted for the duration of infusion
$t_{½}$[a]	sd	$Log_e(2)/k_e$l, where k_el is the terminal phase rate constant calculated by a linear regression of the log-linear concentration timecurve.

a if data permit; sd: single dose; ss: steady-state

CCI [redacted]

[redacted]

[redacted]

[redacted]

6.6. ECHO, ECG and Vital Sign Data Analysis

The analysis of Echocardiogram (Echo) will be based on the Safety Analysis Set. A clinically significant asymptomatic cardiac event or the LVEF abnormality is defined as an absolute decline in LVEF from baseline of more than 15 points and to a value that is below the institution's lower limit of normal. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the LVEF change from baseline. Shift tables will also be provided for LVEF abnormality at baseline vs. on treatment (yes, no, not done: (n, %).

The analysis of ECG results will be based on patients in the Safety Analysis Set with baseline and on-treatment ECG data, and will follow the ICH E14 guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.[9]

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

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

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

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

Data will be summarized and listed for QT, HR, response rate (RR), PR, QRS, QTcF (and/or QTcB if deemed appropriate by overall, and by dose group. Individual QT (all evaluated corrections) intervals will be listed by study arm time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by study arm dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post- baseline QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction methods will be used) using maximum CTCAE version 4.03 Grade. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %).

Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

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

Changes from baseline for the ECG parameters QT interval, heart rate (HR), QTc interval, PR interval and QRS interval will be summarized by treatment and visit. Categorical data analysis will follow Section 9.3.

If more than one ECG is collected at a nominal time post dose (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also ≥500 msec. Changes from baseline will be defined as the change between QTc post dose from the time-matched average of the pre-dose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of subject factors (covariates) on the relationship will be examined.

7. INTERIM ANALYSES

There is no formal interim analysis planned in this study.

A final analysis will be performed when all the patients are enrolled and have completed their scheduled tumor assessments.

This is an open label study. The Pfizer study team will review safety, immunogenicity, CCI and other data throughout the study.

8. REFERENCES

1. C3881001 Protocol Amendment 3, May 7, 2021.

2. Simon R, Freidlin B, Rubinstein L, et al. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst 1997; 89(15):1138-47.

3. Palbociclib Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/4449/smpc accessed 30 April 2018.

4. Letrozole Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/4686/smpc/history accessed 30 April 2018.

5. Y Ji, P Liu, Y Li, and BN Bekele. A modified toxicity probability interval method for dose-finding trials. Clinical Trials, 7:653 663, 2010.

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

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

8. NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

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

10. 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.

9. APPENDICES

9.1. Details of Definitions of Endpoints

DLT Definition

Severity of adverse events (AEs) will be graded according to CTCAE version 5.0. For the purposes of dose escalation, any of the following AEs occurring in the first cycle of treatment (within 28 days of first dose or until the patient completes the first cycle of therapy if there are treatment delays) which are clinically significant will be classified as DLTs, unless there is a clear alternative explanation and agreed upon by investigator and sponsor (eg, clearly and incontrovertibly due to underlying disease/progression or extraneous cause) where there has been a clinically significant change from baseline:

- Clinically important or persistent toxicities that are not included in the criteria below may be considered a DLT following review by Pfizer and the Investigators. All DLTs need to represent a clinically significant shift from baseline.

Note: Labs must be repeated for confirmation. Only the lab result requiring confirmation must be repeated, not the entire panel.

Hematologic:

Any treatment-related hematologic laboratory abnormality specifically defined as:

- Thrombocytopenia Grade 4 for ≥7 days, or Grade 3 or 4 associated with ≥ Grade 2 clinically significant bleeding or requiring platelet transfusion (for bleeding events with no grading available clinically significant bleeding is defined as required hospitalization or urgent medical intervention);

- Neutropenia Grade 4 for ≥7 days; Grade ≥3 neutropenia with infection;

- Anemia Grade 4, or Grade 3 or 4 requiring blood transfusion.

Nonhematologic:

- Grade ≥3 toxicities that are considered clinically significant;

- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3x the upper limit of normal (ULN) with bilirubin >2x the ULN without another explanation (eg, cholestasis) will be considered a DLT, ie, confirmed drug induced liver injury (DILI) meeting Hy's law criteria;

- Grade 3 nausea, vomiting or diarrhea that does not resolve within 4 days despite maximal supportive therapy.

Nonhematologic and Non-Hepatic:

- Any toxicity causing greater than 2 weeks of dose delay is a DLT. Note: Patients deriving clinical benefit from study treatment who experience a DLT may continue on study at a reduced dose following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and sponsor;

- Any toxicity preventing patients from receiving 75% of study drug during the DLT evaluation period is a DLT.

The following AEs will not be adjudicated as DLTs:

- Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement;

- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor);

- Any Grade 5 event clearly due to underlying disease or extraneous causes;

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset at data cut off will not be taken into account for MTD determination including but not limited to:

    - Grade ≥3 electrolyte abnormality lasting <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions;

    - Grade ≥3 amylase or lipase that is not associated with symptoms or clinical manifestations or pancreatitis.

- A patient is classified as DLT-evaluable if he/she experiences a DLT or if he/she otherwise in the absence of a DLT receives at least 75% of the planned doses of each investigational product and has received all scheduled safety assessments during the DLT window. If a patient fails to meet these criteria, he/she may be replaced.

MTD Definition

A DLT rate of 27.5% with an equivalence interval of (22.5%, 32.5%) (note: provided the DLT rate for cardiac toxicity does not exceed 10%) will be utilized to estimate the MTD; patients will be enrolled in dose cohorts of 2-4 patients, and each patient will receive 2 courses of PF-06952229 (7 days on, 7 days off) in a 28 day cycle. Due to the discreteness of the dose levels and in the interest of the safety of patients, the estimated MTD is the highest tested dose level with DLT rate ≤ approximately 32.5%. The dose finding decision will be based on a 1-cycle (28 day) DLT observation period.

At least 6 patients have been accumulated on a dose that can be predicted to be the MTD.

Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further investigation based on Phase 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

9.2. Time to Event Data Analysis Censoring Rules

Table 1. Progression Free Survival and Duration of Response

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

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

Table 2. Time to Progression

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	First dosing date in Cycle 1	Censored
No on-study assessments	First dosing date in Cycle 1	Censored
Alive, on treatment[2] and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation[2]	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation[2]	Censored

Table 2. Time to Progression

Situation	Date of Progression/Censoring[1]	Outcome
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.

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

9.3. 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

9.4. 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.[10]

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.

- 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 the following table.

Response Evaluation Criteria in Solid Tumors by RECIST 1.1

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 the following table.

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.

9.5. Prostate Cancer Working Group 2 (PCWG2) – Soft Tissue Response Criteria

Adapted from Scher H.I., et al: Design and End Points of Clinical Trials for Patients with Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 26 (2008) 1148-1159.

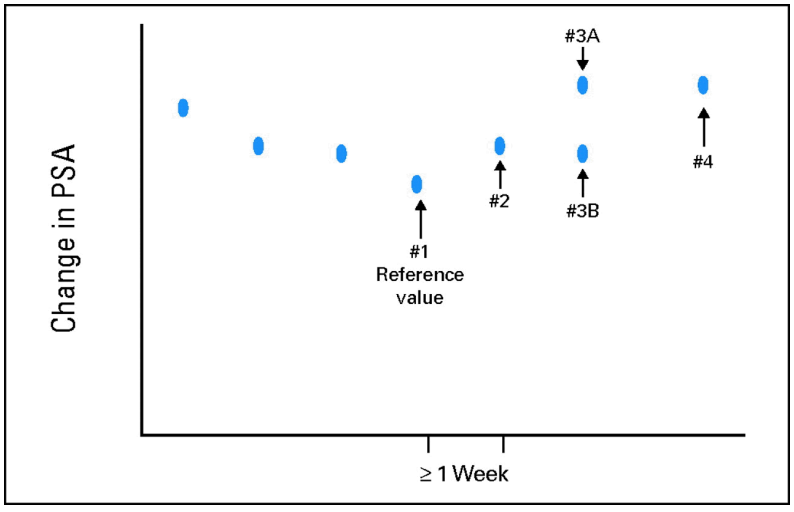
And Eisenhauer E.A., et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

Evidence of PD to Determine CRPC Eligibility

Patients being considered for trial entry should have evidence of disease progression by either PSA, RECIST, or bone scan to be eligible.

PSA: PSA evidence of disease progression based on the prostate cancer working group (PCWG) 2 criteria consist of a minimum PSA level 2.0 ng/ml that has risen on at least 2 successive occasions, at least 1 week apart. The reference value #1 is the last value before the rise in PSA was observed. If the confirmatory PSA value (Figure 2, #3A) is greater than the screening value then progression by PSA is met and the patient is eligible for trial enrollment on the basis of PSA alone. If the confirmatory PSA (Figure 2, #3B) value is less than the screening PSA (Figure 2, #2) value, then an additional test for rising PSA (#4) will be required to document progression before the patient can be enrolled.

Figure 2. Change in PSA



Target lesion/measurable disease: Patients are not required to have evidence of disease progression by measurable disease if they meet the criteria for disease progression on the basis of PSA or bone scan. Evidence of nodal or visceral disease RECIST 1.1 progression however is sufficient for trial entry independent of PSA readings. Because lymph nodes may be enlarged due to benign pathology, only lymph nodes that are ≥2.0 cm should be used for disease evaluation.

Bone scan: Evidence of disease progression based on bone scan appearance is sufficient for trial entry independent of PSA readings. If the appearance of the bone scan is the only indicator of progression, then there must be ≥2 new bone lesions compared with the prior bone scans. If there is ambiguity about the appearance of the bony lesions such as traumatic in nature or secondary to a flare reaction, then it is recommended that an alternative imaging modality such as MRI or fine-cut CT be used to evaluate these lesions further.

CRITERIA FOR OUTCOME MEASURES:

Soft-tissue lesions: Use RECIST with caveats,

- Only report changes in lymph nodes that were ≥2.0 cm in diameter at baseline;
- Record changes in nodal and visceral soft tissue sites separately;
- Record complete elimination of disease at any site separately;
- Confirm favorable change with second scan.

Bone:

- Record outcome as new lesion or no new lesions

Criteria for Evidence of Radiographic Progression

Bone disease will be assessed for progressive disease only by PCWG2. The documentation required for the determination of radiographic progression is shown in the table below.

Date Progression Detected[1]	**Criteria for Progression**	**Criteria to Confirm Progression**	**Criteria to Document Disease Progression on Confirmatory Scan**
Week 9	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG2	Timing: At least 6 weeks after progression identified or at Week 16 visit[2]	2 or more new bone lesions on bone scan compared to Week 8 scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression
Week 18 or later	Bone lesions: 2 or more new lesions on bone scan compared to Week 8 bone scan	Timing: At least 6 weeks after progression identified or at next imaging time point[2]	Persistent or increase in number of bone lesions on bone scan compared to prior scan[3]

Date Progression Detected[1]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression

[1] Progression detected by bone scan at an unscheduled visit either before Week 8 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
[2] Confirmation must occur at the next available scan.
[3] For confirmation, at least 2 of the lesions first identified as new must be present at the next available scan (confirmation scan).

Disease progression in bone must be confirmed at least 6 weeks later, as per PCWG2. See table below for the timing of confirmatory imaging requirements.

Confirmatory Imaging Requirements for Patients With CRPC Based on RECIST v1.1 and PCWG2

Disease Site	Response	Progression[1]
Soft tissue	Must be confirmed at least 4 weeks later	No confirmation required
Bone	Not applicable	Must be confirmed at least 6 weeks later

[1] To inform permanent treatment discontinuation.

Objective Response Status at Each Evaluation

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

If there is a protocol deviation and a patient has been enrolled allows enrollment of patients with only non-target disease, the following table will be used:

Objective Response Status at Each Evaluation for Patients With Non-Target Disease Only

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

Procedures for Assessing PSA Response/Progression Post Study Treatment

PSA measurements will be performed on C1D1 (±14 days) and Day 1 of Cycle 4, 7, 10 and every third cycle thereafter, as well as at the End of Treatment visit. Increases and decreases will be tracked in order to assess disease response. The PSA readings on its own will not be used to define progression in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG2:

- PSA partial response is defined as a ≥50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value. This PSA decline much be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.

- PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 4 or more weeks later. The first PSA reading will be obtained at week 12.