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

Investigational Product Number:	PF-06952229
Investigational Product Name:	Not Applicable (N/A)
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Protocol Number:	C3881001
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	07 May 2021	The overall rationale for the amendment is to revise inclusion and exclusion criteria in Part 1B (combination dose escalation) to enroll a patient population more reflective of the real world and to incorporate the administrative changes to ensure consistency throughout the protocol. • For Part 1B: the inclusion criteria was revised to remove the requirements regarding prior docetaxel and abiraterone therapy, and disease progression as measured by RECIST v1.1, the appearance of 2 or more new bone lesions per Prostrate Cancer Working Group 2 PCWG2 (PCWG2), or rising prostate specific antigen (PSA) per PCWG2. This allows safety, tolerability, and pharmacokinetic (PK) assessment in a broader study population. • Combination Dose Escalation Phase: histological or cytological diagnosis of metastatic castration-resistant prostate cancer (mCRPC). (Castration is defined as having a serum testosterone less than 50 ng/dL, due to medical or surgical castration), patients who are intolerant to standard treatment, resistant to standard therapy, or refuse standard therapy.

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		• For Part 1B: exclusion of patients treated with current or prior enzalutamide within 24 days prior to first dose. This allows adequate PK assessments of enzalutamide during the study. • CCI [redacted] • CCI [redacted] • SOA (Part 2B): Administration of PF-0695229 in clinic on Cycle 1 Day 2 and Cycle 1 Day 21 were added, as PK collections are performed during these visits. • SOA (Part 1B): Electrocardiogram (ECG) measurements were added on Cycle 1 Day 2 and Cycle 1 Day 15 to coincide with on-site PF-0695229 administration. • SOA (Part 2B): ECG measurements were added on

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		Cycle 1 Day 2 (predose) and Cycle 1 Day 21 (predose), and Cycle 1 D15 and Cycle 1 D21 (2 hours +/- 15 minutes postdose) to coincide with on-site PF-0695229 administration. • Due to emerging data, the use of proton pump inhibitors (PPIs) during the study was revised. Patients currently on PPIs should be switched to antacids or H2-Receptor antagonists 14 days prior to Cycle 1 Day 1 and should abstain from PPI use throughout the study. • SOA: Urine phosphate collections were removed, as serum phosphorus is collected. • Clarified the start of study entry is Cycle 1 Day 1. • Minor editorial changes were made throughout the document.
Amendment 2	24 August 2020	• The study design was amended to add a dose expansion for the monotherapy (Part 2A), and to further define the dose escalation and expansion for PF-06952229 in combination with enzalutamide in patients with mCRPC (Part 1B and Part 2B). • Based on clinical data from Part 1A, the study design was amended to focus on patients with mCRPC. The combination of PF-06952229 with palbociclib or the combination of

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		PF-06952229 with letrozole in patients with metastatic breast cancer was removed. • Pregnancy testing was removed from Part 1B – Combination Dose Escalation, Part 2A Monotherapy Dose Expansion, and Part 2B – Combination Dose Expansion since these parts of the study will only apply to male patients. • Based on the revised study design, the total study sample size of approximately 90 patients is planned: Part 1A – Monotherapy Dose Escalation N≈40, Part 1B Combination Dose Escalation N≈20, Part 2A – Monotherapy Dose Expansion N=10, and Part 2B – Combination Dose Expansion N=20. • An additional dose level of 750 mg BID was added to the protocol in relevant sections. • Due to the updated study design and study population, the objectives and endpoints are divided into Parts 1A, 1B, 2A, and 2B to reflect the updated study design. • Individual Schedule of Activities were updated for Part 1A, Part 1B, Part 2A, and Part 2B for clarity. • The inclusion and exclusion criteria for Part 1B, Part 2A, and

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		Part 2B were updated to enroll mCRPC patients who had failed prior docetaxel and abiraterone based on the CARD trial (doi: 10.1056/NEJMoa1911206). • It was clarified that enzalutamide is considered an Investigation Medicinal Product for this study. Additional information was added to Section 5.4.3 (Enzalutamide Administration), Section 5.4.5 (Dosing Interruptions), Section 5.4.6 (Dose Delays), and Section 5.4.7 (Dose Reductions). Reference to the SPC for enzalutamide was removed throughout the protocol. • Tumor assessments for mCRPC was changed from PCWG3 to PCWG2 based on the CARD trial. • Clinical PK and Clinical Safety data for PF-06952229 were added in Section 1.2.6 and Section 1.2.7, respectively. • Because alkaline phosphatase testing is not available in many centers, as it is not typically used to manage patients to differentiate liver disease vs bone metastasis. The schedule was reduced to C1D1 and as clinically indicated in order 1) to provide a baseline for each patient and 2) to provide sites with the ability to interpret such

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		assays as needed for clinical management. • Specified that serum phosphorus and urine phosphate should be collected during Blood Chemistry and Urinalysis, respectively. • Blood collection for RNA was removed from all parts of the study. • PK CCI collection timepoints were updated for Parts 1B, 2A, and 2B. • CCI [redacted] • Collection of the Gleason Score was added to the SoA for Part 2A and Part 2B. • In Section 3.1.2.1, it was clarified that the Accelerated Titration Design will only be used during the starting doses for Part 1A – Monotherapy Dose Escalation. Throughout the protocol it was clarified that Part 1B – Combination Dose Escalation will use the mTPI design. • Intra-patient dose escalation during the Accelerated Titration Design portion of the study was removed.

Document	Version Date	Summary of Changes and Rationale
		• It was clarified that during the 28-day cycle, PF-06952229 dosing is 7 days on followed by 7 days off in the Study Design. • Figure 1 was updated to include both canonical and non-canonical TGFβ signaling pathways. • General updates to the protocol template were incorporated. • Appendix 7 was updated to reflect Prostate Cancer Working Group 2. • Appendix 8 was added to provide alternative study measures during public emergencies. • Appendix 9 was added to list prohibited drugs having the potential for DDI. Lists of conmeds with potential DDI were removed from Section 5.7. • The Summary of Changes was reorganized to list the most recent amendment first. • General formatting and copy editing were performed throughout the protocol.
Amendment 1	30 October 2019	• Addition of MRI of brain at Screening and every 8 weeks. • Adjustment of tumor assessment schedule for all patients to every 8 weeks.

Document	Version Date	Summary of Changes and Rationale
		• Addition of timepoints for Blood Chemistry, Coagulation and Urinalysis in Schedule of Activities. • Edit to anticoagulation medication exclusion criteria. • Edit to Exclusion criteria regarding brain metastases. • Addition of exclusion criteria for patients with history of clinically significant bleeding. • Addition of exclusion criteria for tumors that compress or invade major blood vessels. • Addition of exclusion criteria for patients with a history of central nervous system metastases. • Edit to Patient Compliance Section 5.2. • Addition of text in Section 5.7 Concomitant Treatments. • Addition of discontinuation for patients who experience hemorrhages during trial participation. • Addition of 12-hour PK timepoint to Part 1, and Part 2 combination A and B; Schedule of Activities. • Addition of exclusion criteria for liver metastases at baseline that are likely to bleed; Section 4.2.

Document	Version Date	Summary of Changes and Rationale
		• Update to statistical considerations, Section 3.1.2.2 Acceleration Phase with Intrapatient Escalation. • Addition of Study Stopping and Patient Discontinuation, Section 5.4.10.
Original protocol	13 July 2018	• Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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PROTOCOL SUMMARY

Background and Rationale

TGFβ

Elevated TGFβ expression by tumor and stromal cells in the tumor microenvironment, and activation of TGFβ receptor intracellular signaling is observed in many cancers. Activated TGFβR1 phosphorylates the signaling intermediate proteins termed mothers against decapentaplegic homolog 2 and 3 (SMAD2 and SMAD3), which assemble into complexes with SMAD4, and translocate to the nucleus, where they regulate the expression of TGFβ target genes. In addition, non-SMAD signaling may also be initiated downstream of TGFβ receptors, which can lead to the activation of various pathways such as phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), c-jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38), and extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAP).

The activation of the TGFβ pathway in cancer cells can induce epithelial to mesenchymal transition (EMT) in which epithelial cells lose their apico-basal polarity and cell-cell adhesion, to become highly migratory mesenchymal cells, leading to metastasis. In addition, EMT has been linked to tumor cell evasion of immune surveillance. TGFβ has been shown to be a potent immunosuppressive agent on both innate and adaptive immune cells, including dendritic cells, macrophages, natural killer (NK) cells, and CD4+ and CD8+ T cells. Conversely, TGFβ plays a key role stimulating the differentiation of immune-suppressive regulatory T (Treg) cells. Finally, inhibition of the TGFβR1 pathway in preclinical models has led to tumor growth inhibition.

Tumors and Combination Therapies

High TGFβ signatures and EMT expression are found in a variety of tumors, including metastatic breast cancer, metastatic castration-resistant prostate cancer (mCRPC), squamous cell cancer of the head and neck, melanoma, mesothelioma, metastatic pancreatic cancer, colorectal cancer, renal cell carcinoma, and hepatocellular cancer. These tumor types will be investigated in Part 1A of this protocol, a dose exploration of PF-06952229. Subsequent investigations in Part 1B, Part 2A, and Part 2B of the protocol will be undertaken in a more targeted subset of tumors, selected based on nonclinical data, preliminary Part 1A data, and unmet medical need. The monotherapy expansion (Part 2A) and combination portion of this clinical trial in Part 1B and Part 2B will focus on treatment of mCRPC.

STUDY OBJECTIVES AND ENDPOINTS

Part 1A - PF-06952229 Single Agent Dose Escalation Phase in Patients With Advanced/Metastatic Tumors.

Primary Objective(s):	Primary Endpoint(s):
• 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.	• First-cycle DLTs. • AEs as graded by NCI CTCAE version 5.0. • Laboratory abnormalities as graded by NCI CTCAE version 5.0.
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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	• Pharmacokinetic parameters of PF-06952229. o Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, and as data permit, AUC_{inf}, CL/F, V_z/F, and $t_{1/2}$. o 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}). • PSA50 Response Rate for prostate cancer patients. • Response assessment will be based on PCWG2 for prostate cancer and RECIST 1.1 for other tumor types.
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Part 1B - Dose Escalation of PF-06952229 in Combination With Enzalutamide in Patients with mCRPC

Primary Objective(s):	Primary Endpoint(s):
• 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.	• First cycle DLTs in combination with enzalutamide for mCRPC. • AEs as graded by NCI CTCAE version 5.0. • Laboratory abnormalities as graded by NCI CTCAE version 5.0.
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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.	• 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}). • PSA50 Response Rate • Response assessment will be based on PCWG2 and RECIST 1.1.
CCI [redacted]	[redacted]

Part 2A - PF-06952229 Single Agent Dose Expansion Phase in mCRPC

Primary Objective(s):	**Primary Endpoint(s):**
• 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.	• AEs as graded by NCI CTCAE version 5.0. • Laboratory abnormalities as graded by NCI CTCAE version 5.0. • PSA50 Response Rate. • Response assessment will be based on PCWG2 and RECIST 1.1.
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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).	• ORR based on PCWG2 and RECIST 1.1. and time to event endpoints (DoR, PFS, OS, TTP, TTR). • 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}). • Assessment of levels of intra-tumor T cells (eg, CD8 IHC);
CCI [redacted]	[redacted]
[redacted]	[redacted]

Part 2B - Dose Expansion of PF-06952229 in Combination With Enzalutamide in Patients With mCRPC

Primary Objective(s):	Primary Endpoint(s):
• 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.	• AEs as graded by NCI CTCAE version 5.0. • Laboratory abnormalities as graded by NCI CTCAE version 5.0. • PSA50 Response Rate. • Response assessment will be based on PCWG2 and RECIST 1.1.
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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).	• ORR based on PCWG2 and RECIST 1.1. and time to event endpoints (DoR, PFS, OS, TTP, TTR). • Pharmacokinetic parameters of PF-06952229 (in at least 8 subjects). ○ 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}). • Peak and trough concentrations at selected cycles. • Assessment of levels of intra-tumor T cells (eg, CD8 IHC);
CCI [redacted]	[redacted]

STUDY DESIGN

Study Overview

This is a Phase 1, open-label, multi-center, multiple-dose, dose-escalation and expansion, safety, tolerability, PK, and PD 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 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, PD, 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.

The biomarker studies will be used to help understand the in vivo mechanism of action of the agent(s) studied as well as potential mechanisms of resistance. The studies may help in the future development of PF-06952229 as a single agent, or in combination with other compounds, and may provide information on tumor sub-types that may respond to the Investigational Product.

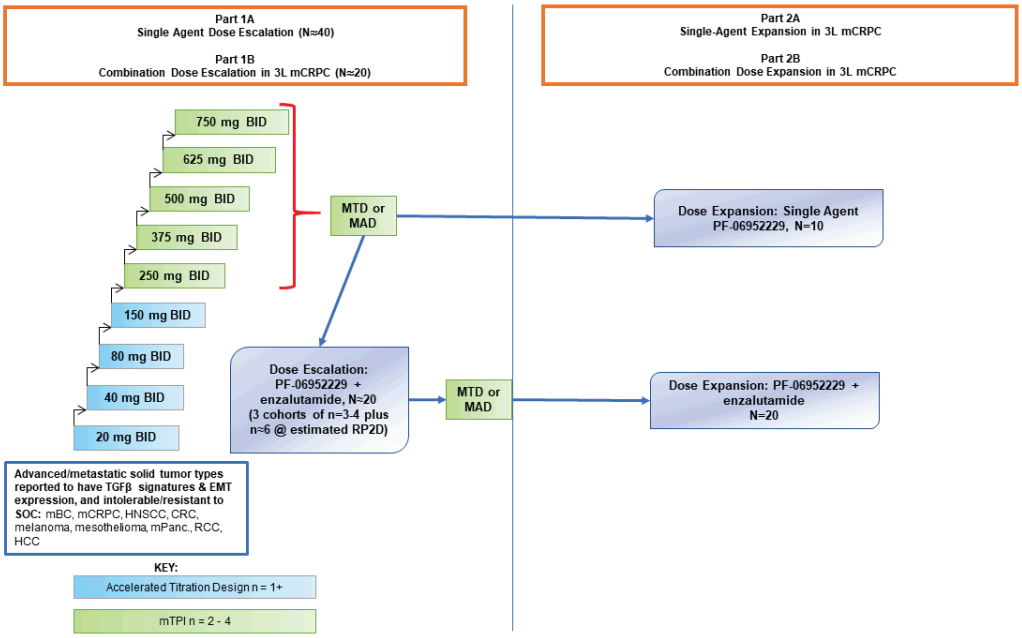
Approximately 90 patients are to be enrolled in this study. The total sample size may vary depending on the number of the dose levels with patients enrolled and the actual number of patients at each dose level. A maximum sample size of 40 patients may be needed to establish and confirm MTD in Part 1A, and approximately 20 patients may be needed for Part 1B. A maximum of 10 and 20 patients are planned for the expansion cohorts in Part 2A and Part 2B, respectively.

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 and PD time points may be reconsidered and amended during the study based on the emerging safety and PK and PD data.

Study Schema



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STUDY TREATMENTS

For this study, the Investigational Medicinal Products are PF-06952229 and enzalutamide.

Refer to the respective IBs for further information on PF-06952229 and enzalutamide.

DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

Statistical Methods and Properties

Statistical Methods for Dose Escalation

This study contains 2 parts, dose escalation with PF-06952229 alone in patients with advanced/metastatic solid tumors (Part 1A) and in combination with enzalutamide in patients with mCRPC (Part 1B), followed by a monotherapy dose expansion (Part 2A) and combination dose expansion of PF-06952229 with enzalutamide in patients with mCRPC (Part 2B).

Part 1A and 1B Dose Escalation

The dose escalation in Part 1A will start with Accelerated Titration Design (ATD) as proposed by Simon et al (Journal of the National Cancer Institute, Vol. 89, No. 15, August 6, 1997). Part 1A will have an initial accelerated phase followed by a standard (mTPI) escalation phase. Part 1 B will follow a standard mTPI design. During the accelerated phase in Part 1A, initial cohorts to contain a minimum of one patient until the first instance of first-cycle CTCAE grade ≥2 toxicity.

Statistical Methods for Determining the MTD

This study contains dose escalations with single agent and single agent in combination with enzalutamide (Part 1A and Part 1B, respectively) and dose expansions with single agent and single agent in combination with enzalutamide (Part 2A and Part 2B, respectively). Part 1B, Part 2A and Part 2B will include previously treated patients with mCRPC. Part 1A and Part 1B will determine the MTD in sequential dose escalation cohorts for monotherapy and combination therapy, respectively.

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%), provided the DLT rate for cardiac toxicity does 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.[4] 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 is approximately 40 patients for the monotherapy dose escalation, approximately 20 patients for the Part 1B combination escalation, approximately 10 patients for Part 2A monotherapy expansion, and approximately 20 patients for Part 2B combination expansion. Actual sample size will depend on the underlying dose toxicity profile and variability in actual data realization.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Assessments section of the protocol for detailed information on each assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities table in order to conduct evaluations or assessments required to protect the well-being of the patient.

SCHEDULE OF ACTIVITIES PART 1A- Monotherapy Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days					End of Treatment/ Withdrawal[24]	Post-Treatment Follow-Up[25]
		Cycles 1 & 2			Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**		
Informed consent[2]	X							
Medical/Oncological history[3]	X							
Physical examination[4]	X						X	
Abbreviated physical examination[4]		X	X	X	X	X		X
Baseline signs and symptoms[5]	X	X						
Height	X							
Weight	X	X			X		X	
Vital signs[6]	X	X[6]	X	X	X[6]	X	X	
ECOG Performance Status[7]	X	X			X		X	X
Laboratory								
Hematology[8]	X	X	X	X	X	X	X	
Blood Chemistry[9]	X	X	X	X	X	X	X	
Coagulation[10]	X	X	X	X	X		X	
Urinalysis[11]	X		X	X	X		X	
Pregnancy test[11]	X	X			X		X	
Viral disease screening[11]	X							
Contraception check[14]	X	X			X		X	X
12-lead ECG[15]	X	See Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 1A						
Echocardiogram[16]	X	Cycle 3 Day 1 and every other cycle						
Troponin I + BNP[17]	X	X	X	X	X		X	
Alk phos fractionation[18]		X						

SCHEDULE OF ACTIVITIES PART 1A- Monotherapy Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days					End of Treatment/ Withdrawal[24]	Post-Treatment Follow-Up[25]
		Cycles 1 & 2			Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**		
Registration and Treatment								
Registration[19]	X							
PF-06952229[20]		◄--► Orally twice daily (BID) on Days 1-7 and 15-21 of each Cycle						
Disease assessments								
CT/MRI Scans[21]	X	See footnote for frequency of scans					X	
99Tc Bone scan (for CRPC and symptomatic other patients)[21]	X				X		X	
Tumor markers (CA 15-3 and CEA for breast cancer; PSA for prostate cancer)[21]	X	X			X		X	
Other clinical assessments								
Serious and non-serious adverse event monitoring[22]	X	◄--►						
Concomitant treatment(s)[23]	X	◄--►						
Survival Follow-Up[26]								X

Abbreviations: ◄--►= ongoing/continuous event; BID = twice daily; C = cycle; CA 125 = cancer antigen 125; CA 15-3 = cancer antigen 15-3; carcinoembryonic antigen = CEA; Day = D; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; CT = computed tomography; LHRH = luteinizing hormone releasing hormone; MRI = magnetic resonance imaging; OS = overall survival; (X) = optional assessment.

- After Cycle 1, Day 1, tests and procedures should be done on schedule, but occasional changes by ±3 days (unless otherwise stated differently) are allowed for holidays, vacations and other administrative reasons.
- For Pharmacokinetics and additional sampling requirements, please see Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 1A below.

a. Patients must maintain their original dosing schedule (7 days on, 7 days off) regardless of dose reductions or holds. To accommodate the dosing schedule, visit windows are not allowed into the "drug off" periods due to safety concerns; however, 2 day windows are allowed during the "drug on" period.

†**Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their morning (or afternoon as applicable) dose, which will be administered by study staff onsite on clinic days. Acceptable time windows for performing

SCHEDULE OF ACTIVITIES PART 1A- Monotherapy Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days					End of Treatment/ Withdrawal[24]	Post-Treatment Follow-Up[25]
		Cycles 1 & 2			Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**		

each assessment are described in the column headers. One cycle consists of 28 days. **Day 1 of any cycle visit should coincide with the day the PF-06952229 treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit may be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving PF-06952229.

Study entry is Cycle 1 Day 1.

1. **Screening:** To be obtained within 28 days prior to study entry.
2. **Informed Consent**: Must be obtained prior to undergoing any study-specific procedures.
3. **Medical/Oncologic History**: Includes history of disease process (eg, staging) (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
4. **Physical Examination:** Physical examinations (PEs) may be performed within 48 hours prior to a scheduled visit. A full physical examination is required at Screening and abbreviated PEs should be performed as appropriate at each visit where complete physical examinations are not required. For both full and abbreviated exams, patient should be assessed for evidence of bleeding (eg, bruising, petechiae, or hematomas). No need to repeat PE if baseline assessment is within 96 hours on Cycle 1 Day 1.
5. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry.
6. **Vital Signs**: Includes temperature, sitting or semi-recumbent (same position must be used throughout the study and documented in source notes) blood pressure (BP), pulse rate (PR, to be recorded in the sitting position after 5 minutes of rest), and pulse oximetry (at rest and after exertion). On Day 1 of each cycle, vital signs should be measured prior to dosing (predose); BP, and PR will be repeated 1 hour after dosing. The time window for Vital Signs will match the allowable window for PK and ECGs.
7. **ECOG Performance Status**: Use Eastern Cooperative Oncology Group (ECOG) – see Appendices.
8. **Hematology**: No need to repeat on Cycle 1 Day 1 (C1D1) if baseline assessment performed within 72 hours prior to that date. Assessments performed on Cycle 2 Day 1 (C2D1) and each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments section for Laboratory Tests list.
9. **Blood Chemistry**: No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date (with the exception of serum creatinine which must be performed within 72 hours of C1D1). See Assessments section for Laboratory Tests list. (Testosterone to be performed at Screening for mCRPC patients only.) Note that chemistries performed require serum phosphorus measurements.
10. **Coagulation**: No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. See Assessments section for Laboratory Tests list.
11. **Urinalysis**: Dipstick is acceptable at Screening, during trial conduct, and at the End of Treatment visit. At Screening, if dipstick shows urine protein ++ or above, perform 24-hour urine protein test. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests list.
12. **Pregnancy Test**: described in the Pregnancy Testing section. From Cycle 3 onward, pregnancy testing will be performed every other cycle.
13. **Viral Disease Screening:** Hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti HBc), (HbcAb), hepatitis B surface antibody (anti HBs), hepatitis C virus antibodies (HCVAb), and human immunodeficiency virus testing (HIV) to be conducted by local laboratory where required by local regulations or if warranted by patient history.
14. **Contraceptive Check (frequency to match that of pregnancy tests)**: Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The Investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

SCHEDULE OF ACTIVITIES PART 1A- Monotherapy Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days					End of Treatment/ Withdrawal[24]	Post-Treatment Follow-Up[25]
		Cycles 1 & 2			Cycles 3+			
Visit Identifier (Visit Window)[a]		Day 1	Day 7	Day 15	Day 1	Day 7		

15. **Triplicate 12-Lead ECG:** The Screening ECG will be a single 12-lead ECG. ECGs will be collected at times specified in the Pharmacokinetic, ECG [redacted] Sampling Schedule of Activities for Part 1A.
16. **Echocardiogram:** Echo to be done once patient is confirmed to meet all other inclusion requirements, beginning Cycle 3 Day 1 pre-dose and every other cycle. A ±7 day window will be applied.
17. **Troponin I and BNP:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. Will be performed per the SOA and will be repeated if abnormal and clinically significant.
18. **Alk Phos Fractionation**: Obtain alkaline phosphatase (ALP) fractionation (bone, liver) per the SOA and as clinically indicated. With each ALP increase in AE grade level once at the grade level, fractionation will be obtained and appropriate clinical evaluation will be conducted to determine the suitability of the patient continuation in the trial.
19. **Registration**: Patient number and dose level allocation assigned by Pfizer Inc.
20. **Study Treatment**: PF-06952229 will be administered orally for 7 days on, 7 days off, during a 28 day cycle. Day 1 safety laboratory tests must be reviewed by the Investigator prior to dosing at the beginning of each cycle for dosing confirmation. Patients will self dose as described above, with the exception of doses that will be administered on site. Patients must maintain their original dosing schedule regardless of dose reductions or holds. Patients will be required to return all bottles of PF-06952229 as well as the completed patient diary for drug accountability. For a minimum of the first 2 cycles, patients will be contacted by site personnel on drug start and stop days to ensure compliance to the study drug schedule. On days of scheduled clinic visits, morning (AM) dosing should be undertaken in the clinic (ie, not at home).
21. **Tumor Assessments:** Tumor assessments will include CT or MRI of chest, abdomen and pelvis, and MRI of the brain. If a brain MRI is medically contraindicated, a CT scan with contrast (unless contrast is medically contraindicated) may be performed, however the same modality should be used on an individual patient throughout the study. Other disease sites may be imaged if disease is suspected. Tumor assessments will be performed at Screening and every 8 weeks (±7 days) for the first year, then every 12 weeks (±7 days) Bone scans will be performed as medically indicated. Patients who are found to have hemorrhage in other organs will discontinue treatment with PF-06952229 and enter the follow-up portion of the trial. Tc-99m bone scans (required for CRPC at baseline) will be performed at baseline if disease is suspected and on study as appropriate to follow disease. The frequency of CA-15-3 assessments should match the frequency of other tumor assessments. Tumor assessments with continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Given the exploratory nature of the study, confirmation of response (complete response (CR)/partial response (PR)) is preferred (see RECIST version 1.1). Tumor assessments should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation. Patients should have a confirmatory scan for PD and can remain on trial if they are receiving clinical benefit upon discussion with investigator and sponsor MD. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. FDG-PET will be performed per standard of care.

    Bone Scans for mCRPC: 99mTc-methylene diphosphonate radionuclide bone scintigraphy should be performed every 8 weeks for first 24 weeks, then every 12 weeks (up to 2 years), then every 16 to 24 weeks (± 14 days). Changes in lesions that are considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form (see Appendices). ***mCRPC Only:*** Prostate specific antigen (PSA) assessment to be performed on Screening (for historical progression per Prostate Working Group 2), C1D1 (-14 days) and Day 1 of Cycle 4, 7, 10 and every 2nd cycle thereafter as well as the End of Treatment visit. Please see Appendix for Prostate Cancer Working Group 2 (PCWG2) - Soft Tissue Response Criteria.

SCHEDULE OF ACTIVITIES PART 1A- Monotherapy Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days					End of Treatment/ Withdrawal[24]	Post-Treatment Follow-Up[25]
		Cycles 1 & 2			Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**		

22. **Adverse Event (AE) Assessments**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
23. **Concomitant Treatments**: All concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF including supportive care drugs, eg, anti-emetic treatment and prophylaxis, radiotherapy on study is permitted (eg, skeletal administration for CRPC, drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions [eg, infusions]).
24. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
25. **Post Treatment Follow-Up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, ECOG, abbreviated physical exam, and assessment for resolution of any treatment related toxicity and for confirmation of contraception use. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
26. **Survival Follow-Up:** Subsequent to the follow-up period, overall survival (OS) follow-up will be conducted by telephone every 8 weeks (± 7 days) until end of the entire study (2 years after last patient first treatment). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call.

Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 1A – Monotherapy Dose Escalation

Visit Identifier	Screen	Cycle 1			Cycle 2		Cycle ≥3	EOT
Study Day		**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**	**Day 7**	
Dose of PF-06952229 in clinic[1]		X	X	X	X	X	X	
Meal administration[2]					X			
Pharmacokinetics (PK)								
Predose (if dosing day)		X	X	X	X	X	X	X
0.5 hours (±5 min)		X	X		X			
1 hour (±10 min)		X	X		X			
2 hours (±15 min)		X	X		X			
4 hours (±25 min)		X	X		X			
6 hours (±40 min)		X	X		X			
12 hours (-180 min)		X	X		X			
12-Lead ECG[3]								
0	X	X	X	X		X	X	X
2 hours (±15 min)		X	X					
4 hours (±25 min)		X	X					
CCI [redacted]								

Visit Identifier	Screen	Cycle 1			Cycle 2		Cycle ≥3	EOT
Study Day		**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**	**Day 7**	
Dose of PF-06952229 in clinic[1]		X	X	X	X	X	X	
Meal administration[2]					X			
Pharmacokinetics (PK)								

Abbreviations: PK = pharmacokinetic; CCI ; EOT = End of Treatment; CCI

1. **Dose of PF-06952229 in Clinic:** On days of scheduled clinic visits, morning (AM) dosing should be undertaken in the clinic (ie, not at home).

CCI [redacted]

3. **Triplicate 12-Lead ECG:** The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) will be performed approximately 2 minutes apart to determine mean QTcF interval. All 12-lead ECGs should be confirmed by a qualified person at the institution. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥45 msec from the baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

CCI [redacted]

SCHEDULE OF ACTIVITIES PART 1B – Combination Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 21[c]**	**Day 1**	**Day 7**		
Informed consent[2]	X										
Medical/Oncological history[3]	X										
Physical examination[4]	X									X	
Abbreviated physical examination[4]		X		X		X		X	X		X
Baseline signs and symptoms[5]		X									
Height	X										
Weight	X	X						X		X	
Vital signs[6]	X	X[6]		X		X		X[6]	X	X	
ECOG Performance status[7]	X	X						X		X	X
Laboratory											
Hematology[8]	X	X		X		X		X	X	X	
Blood Chemistry[9]	X	X		X		X		X	X	X	
Coagulation[10]	X	X		X		X		X		X	
Urinalysis[11]	X			X		X		X		X	
Viral disease screening[12]	X										
Contraception check[13]	X	X						X		X	X
12-lead ECG[14]	X	See Pharmacokinetic, ECG [redacted] Sampling Schedule for Part 1B									
Echocardiogram[15]	X							X		X	
Troponin I + BNP[16]	X	X		X		X		X		X	
Alk Phos fractionation[17]		X									
Registration and Treatment											
Registration[18]	X										
PF-06952229[19]		◄--► Orally twice daily (BID) on Days 1-7 and 15-21 of each Cycle									
Enzalutamide[19]		◄--► Orally QD as continuous daily dosing									
Tumor assessments											
CT/MRI Scans[20]	X	See footnote for frequency of scans								X	

SCHEDULE OF ACTIVITIES PART 1B – Combination Dose Escalation

Protocol Activity	**Screening (≤28 days prior to enrollment)** [1]	**Active Treatment Phase†- One Cycle = 28 days**								**End of Treatment/ Withdrawal**[23]	**Post-Treatment Follow-Up**[24]
		Cycles 1 & 2						**Cycles 3+**			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2**	**Day 7**	**Day 10**[b]	**Day 15**	**Day 21**[c]	**Day 1**	**Day 7**		
Tumor markers PSA for prostate cancer[20]	X	X						X		X	
CCI [redacted]		[redacted]						[redacted]			
Other clinical assessments											
Serious and non-serious adverse event monitoring[21]	X	◄--►									
Concomitant treatment(s)[22]	X	◄--►									
Survival Follow-Up[25]											X

Abbreviations: ◄--►= ongoing/continuous event; BID = twice daily; C = cycle; Day = D; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; CT = computed tomography; MRI = magnetic resonance imaging; OS = overall survival; (X) = optional assessment.

- After Cycle 1, Day 1, tests and procedures should be done on schedule, but occasional changes by ±3 days (unless otherwise stated differently) are allowed for holidays, vacations and other administrative reasons.
- For Pharmacokinetics and additional sampling requirements, please see Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 1B Table below.

a. Patients must maintain their original dosing schedule (7 days on, 7 days off) regardless of dose reductions or holds. To accommodate the dosing schedule, visit windows are not allowed into the "drug off" periods due to safety concerns; however, 2 day windows are allowed during the "drug on" period.
b. Day 10 assessments are only performed in Cycle 2.
c. Day 21 assessments are only performed in Cycle 1.

†**Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their morning (or afternoon as applicable) dose, which will be administered by study staff onsite on clinic days. Acceptable time windows for performing each assessment are described in the column headers. One cycle consists of 28 days. **Day 1 of any cycle visit should coincide with the day the PF-06952229 treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit may be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving PF-06952229.

Study entry is Cycle 1 Day 1.

1. **Screening:** To be obtained within 28 days prior to study entry.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
3. **Medical/Oncologic History:** Includes history of disease process (eg, staging) (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.

SCHEDULE OF ACTIVITIES PART 1B – Combination Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment) [1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2**	**Day 7**	**Day 10**[b]	**Day 15**	**Day 21**[c]	**Day 1**	**Day 7**		

4. **Physical Examination:** Physical examinations (PEs) may be performed within 48 hours prior to a scheduled visit. A full physical examination is required at Screening and abbreviated PEs should be performed as appropriate at each visit where complete physical examinations are not required. For both full and abbreviated exams, patient should be assessed for evidence of bleeding (eg, bruising, petechiae, or hematomas). No need to repeat PE if baseline assessment is within 96 hours on Cycle 1 Day 1.
5. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry.
6. **Vital Signs:** Includes temperature, sitting or semi-recumbent (same position must be used throughout the study and documented in source notes) blood pressure (BP), pulse rate (PR, to be recorded in the sitting position after 5 minutes of rest), and pulse oximetry (at rest and after exertion). On Day 1 of each cycle, vital signs should be measured prior to dosing (predose), BP, and PR will be repeated 1 hour after dosing. The time window for Vital Signs will match the allowable window for PK and ECGs.
7. **ECOG Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendices.
8. **Hematology**: No need to repeat on Cycle 1 Day 1 (C1D1) if baseline assessment performed within 72 hours prior to that date. Assessments performed on Cycle 2 Day 1 (C2D1) and each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments section for Laboratory Tests list.
9. **Blood Chemistry**: No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date (with the exception of serum creatinine which must be performed within 72 hours of C1D1). See Assessments section for Laboratory Tests list. Note that chemistries performed require serum phosphorus measurements.
10. **Coagulation**: No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. See Assessments section for Laboratory Tests list.
11. **Urinalysis**: Dipstick is acceptable at Screening, during trial conduct, and the End of Treatment visit. At Screening, if dipstick shows urine protein ++ or above, perform 24-hour urine protein test. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests list.
.
12. **Viral Disease Screening:** Hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti HBc), (HbcAb), hepatitis B surface antibody (anti HBs), hepatitis C virus antibodies (HCVAb), and human immunodeficiency virus testing (HIV) to be conducted by local laboratory where required by local regulations or if warranted by patient history.
13. **Contraceptive Check**: Male patients who are able to father children need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The Investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient's partner.
14. **Triplicate 12-Lead ECG:** The Screening ECG will be a single 12-lead ECG. ECGs will be collected at times specified in Pharmacokinetic, ECG, CCI Sampling Schedule for Part 1B.
15. **Echocardiogram:** Echo to be done once patient is confirmed to meet all other inclusion requirements, beginning Cycle 3 Day 1 predose and every 2 cycles for 6 months, then every 3 cycles. A ±7 day window will be applied.
16. **Troponin I and BNP:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. Will be performed per the SOA and will be repeated if abnormal and clinically significant.
17. **Alk Phos Fractionation**: Obtain alkaline phosphatase (ALP) fractionation (bone, liver) per the SOA and as clinically indicated. With each ALP increase in AE grade level once at the grade level, fractionation will be obtained and an appropriate clinical evaluation will be conducted to determine the suitability of the patient continuation in the trial.
18. **Registration**: patient number and dose level allocation assigned by Pfizer Inc.

SCHEDULE OF ACTIVITIES PART 1B – Combination Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2**	**Day 7**	**Day 10**[b]	**Day 15**	**Day 21**[c]	**Day 1**	**Day 7**		

19. **Study Treatment**: PF-06952229 will be administered orally for 7 days on, 7 days off, during a 28 day cycle. Day 1 safety laboratory tests must be reviewed by the Investigator prior to dosing at the beginning of each cycle for dosing confirmation. For Part 1B mCRPC patients will receive PF-06952229 in combination with enzalutamide. Patients will self dose as described above, with the exception of doses that will be administered on site. Patients must maintain their original dosing schedule regardless of dose reductions or holds. Patients will be required to return all bottles of PF-06952229 as well as the completed patient diary for drug accountability. On days of scheduled clinic visits, morning (AM) dosing should be undertaken in the clinic (ie, not at home).
20. **Tumor Assessments**: Tumor assessments will include CT or MRI of chest, abdomen and pelvis, and MRI of the brain. If a brain MRI is medically contraindicated, a CT scan with contrast (unless contrast is medically contraindicated) may be performed, however the same modality should be used on an individual patient throughout the study. Other disease sites may be imaged if disease is suspected. Tumor assessments will be performed at Screening and every 8 weeks (±7 days) for the first year, then every 12 weeks (±7 days). Bone scans will be performed as medically indicated. Tc-99m bone scans (required for CRPC at baseline) will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Patients who are found to have hemorrhage in other organs will discontinue treatment with PF-06952229 and enter the follow-up portion of the trial. Tumor assessments with continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Given the exploratory nature of the study, confirmation of response (complete response (CR)/partial response (PR)) is preferred (see RECIST version 1.1). Tumor assessments should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation. Patients should have a confirmatory scan for PD and can remain on trial if they are receiving clinical benefit upon discussion with investigator and sponsor MD. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. FDG-PET will be performed per standard of care.

    Bone Scans for mCRPC: 99mTc-methylene diphosphonate radionuclide bone scintigraphy should be performed every 8 weeks for first 24 weeks, then every 12 weeks (up to 2 years), then every 16 to 24 weeks (±14 days). Changes in lesions that are considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form (see Appendices).

    Prostate specific antigen (PSA) assessment to be performed on Screening (for historical progression per Prostate working Group 2), C1D1 (-14 days) and Day 1 of Cycle 4, 7, 10 and every 3rd cycle thereafter as well as the End of Treatment visit. Please see Appendix for Prostate Cancer Working Group 2 (PCWG2)- Soft Tissue Response Criteria.

    CCI [redacted]

21. **Adverse Event (AE) Assessments**: AEs should be documented and recorded at each visit using the NCI CTCAE version 5.0. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.

SCHEDULE OF ACTIVITIES PART 1B – Combination Dose Escalation

Protocol Activity	Screening (≤28 days prior to enrollment) [1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 21[c]**	**Day 1**	**Day 7**		

22. **Concomitant Treatments**: All concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF including supportive care drugs, eg, anti-emetic treatment and prophylaxis, radiotherapy on study is permitted (eg, skeletal administration for CRPC), drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, infusions).
23. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks as applicable for disease assessments).
24. **Post Treatment Follow-Up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, ECOG, abbreviated physical exam, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
25. **Survival Follow-Up:** Subsequent to the follow-up period, overall survival (OS) follow-up will be conducted by telephone every 8 weeks (±7 days) until end of the entire study (2 years after last patient first treatment). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call.

Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 1B - Combination Dose Escalation with Enzalutamide

Visit Identifier	Screen	Cycle 1					Cycle 2				Cycle ≥3	EOT
Study Day		**Day 1**	**Day 2**	**Day 7**	**Day 15**	**Day 21**	**Day 1**	**Day 2**	**Day 7**	**Day 10 (-24hrs)**	**Day 7**	
Dose of PF-06952229 in clinic[1]		X*	X	X	X	X	X*	X	X		X	
Pharmacokinetics (PK)												
Predose (if dosing day)		N, E	N	N, E	N	N, E	N, E	N	N	N	N	N
0.5 hours (±5 min)		N				N	N					
1 hour (±10 min)		N				N	N					
2 hours (±15 min)		N				N	N					
4 hours (±25 min)		N				N	N					
6 hours (±40 min)		N				N	N					
12 hours (-180 min)		N				N	N					
12-Lead ECG[2]												
0	X	X	X	X	X	X			X		X	X
2 hours (±15 min)		X				X						
4 hours (±25 min)		X				X						
CCI [redacted]												
[redacted]												
[redacted]												
[redacted]												
[redacted]												
[redacted]												
[redacted]												

Visit Identifier	Screen	Cycle 1					Cycle 2				Cycle ≥3	EOT
Study Day		Day 1	Day 2	Day 7	Day 15	Day 21	Day 1	Day 2	Day 7	Day 10 (-24hrs)	Day 7	
CCI [redacted]												
[redacted]												
[redacted]												

Abbreviation: PK = pharmacokinetic; CCI [redacted]; EOT = End of Treatment; N=PF-06952229; E=Enzalutamide; CCI [redacted]

*** On Day 1 of Cycle 1 and Cycle 2 only a single dose of PF-06952229 to be given to evaluate PF-06952229 PK sampling up to 24 hr time point (ie, pre-dose on Day 2 of Cycle 1 and Cycle 2)**

1. **Dose of PF-06952229 in Clinic:** On days of scheduled clinic visits, morning (AM) dosing should be undertaken in the clinic (ie, not at home).
2. **Triplicate 12-Lead ECG:** The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) will be performed approximately 2 minutes apart to determine mean QTcF interval. All 12-lead ECGs should be confirmed by a qualified person at the institution. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥45 msec from the baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

CCI [redacted]

SCHEDULE OF ACTIVITIES PART 2A – Monotherapy Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment) [1]	Active Treatment Phase†- One Cycle = 28 days						End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2				Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 1**	**Day 7**		
Informed consent[2]	X								
Medical/Oncological history[3]	X								
Physical examination[4]	X							X	
Abbreviated physical examination[4]		X	X		X	X	X		X
Baseline signs and symptoms[5]		X							
Height	X								
Weight	X	X				X		X	
Vital signs[6]	X	X[6]	X		X	X[6]	X	X	
ECOG Performance status[7]	X	X				X		X	X
Laboratory									
Hematology[8]	X	X	X		X	X	X	X	
Blood Chemistry[9]	X	X	X		X	X	X	X	
Coagulation[10]	X	X	X		X	X		X	
Urinalysis[11]	X		X		X	X		X	
Viral disease screening[12]	X								
Contraception check[13]	X	X				X		X	X
12-lead ECG[14]	X	See Pharmacokinetic, ECG [redacted] Sampling Schedule for Part 2A							
Echocardiogram[15]	X					X		X	
Troponin I + BNP[16]	X	X	X		X	X		X	
Alk Phos fractionation[17]		X							
Registration and Treatment									
Registration[18]	X								
PF-06952229[19]		◄--► Orally twice daily (BID) on Days 1-7 and 15-21 of each Cycle							
Tumor assessments									
CT/MRI Scans[20]	X	See footnote for frequency of scans						X	
Tumor markers	X	X				X		X	

SCHEDULE OF ACTIVITIES PART 2A – Monotherapy Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days						End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2				Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 10**[b]	**Day 15**	**Day 1**	**Day 7**		
(PSA and Gleason Score for prostate cancer)[20]									
CCI [redacted]		[redacted]				[redacted]			
Other clinical assessments									
Serious and non-serious adverse event monitoring[21]	X	◄--►							
Concomitant treatment(s)[22]	X	◄--►							
Survival Follow-Up[25]									X

Abbreviations: ◄--► = ongoing/continuous event; BID = twice daily; C = cycle; Day = D; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; CT = computed tomography; MRI = magnetic resonance imaging; OS = overall survival; (X) = optional assessment.

- After Cycle 1, Day 1, tests administrative reasons.
- For and procedures should be done on schedule, but occasional changes by ±3 days (unless otherwise stated differently) are allowed for holidays, vacations and other Pharmacokinetics and additional sampling requirements, please see Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 2A Table below.

a. Patients must maintain their original dosing schedule (7 days on, 7 days off) regardless of dose reductions or holds. To accommodate the dosing schedule, visit windows are not allowed into the "drug off" periods due to safety concerns; however, 2 day windows are allowed during the "drug on" period.

b. Day 10 assessments are only performed in Cycle 2

†**Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their morning (or afternoon as applicable) dose, which will be administered by study staff onsite on clinic days. Acceptable time windows for performing each assessment are described in the column headers. One cycle consists of 28 days. **Day 1 of any cycle visit should coincide with the day the PF-06952229 treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit may be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving PF-06952229.
Study entry is Cycle 1 Day 1.

1. **Screening:** To be obtained within 28 days prior to study entry.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
3. **Medical/Oncologic History:** Includes history of disease process (eg, staging) (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
4. **Physical Examination:** Physical examinations (PEs) may be performed within 48 hours prior to a scheduled visit. A full physical examination is required at Screening and abbreviated PEs should be performed as appropriate at each visit where complete physical examinations are not required. For both full and abbreviated exams, patient should be assessed for evidence of bleeding (eg, bruising, petechiae, or hematomas). No need to repeat PE if baseline assessment is within 96 hours on Cycle 1 Day 1.
5. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry.

SCHEDULE OF ACTIVITIES PART 2A – Monotherapy Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment) [1]	Active Treatment Phase†- One Cycle = 28 days						End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2				Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 1**	**Day 7**		

6. **Vital Signs:** Includes temperature, sitting or semi-recumbent (same position must be used throughout the study and documented in source notes) blood pressure (BP), pulse rate (PR, to be recorded in the sitting position after 5 minutes of rest), and pulse oximetry (at rest and after exertion). On Day 1 of each cycle, vital signs should be measured prior to dosing (predose), BP, and PR will be repeated 1 hour after dosing. The time window for Vital Signs will match the allowable window for PK and ECGs.
7. **ECOG Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendices.
8. **Hematology**: No need to repeat on Cycle 1 Day 1 (C1D1) if baseline assessment performed within 72 hours prior to that date. Assessments performed on Cycle 2 Day 1 (C2D1) and each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments section for Laboratory Tests list.
9. **Blood Chemistry**: No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date (with the exception of serum creatinine which must be performed within 72 hours of C1D1). See Assessments section for Laboratory Tests list. Note that chemistries performed require serum phosphorus measurements.
10. **Coagulation**: No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. See Assessments section for Laboratory Tests list.
11. **Urinalysis**: Dipstick is acceptable at Screening, during trial conduct, and the End of Treatment visit. At Screening, if dipstick shows urine protein ++ or above, perform 24-hour urine protein test. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests list.
12. **Viral Disease Screening:** Hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti HBc), (HbcAb), hepatitis B surface antibody (anti HBs), hepatitis C virus antibodies (HCVAb), and human immunodeficiency virus testing (HIV) to be conducted by local laboratory where required by local regulations or if warranted by patient history.
13. **Contraceptive Check**: Male patients who are able to father children need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The Investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient's partner.
14. **Triplicate 12-Lead ECG:** The Screening ECG will be a single 12-lead ECG. ECGs will be collected at times specified in Pharmacokinetic, ECG, CCI Sampling Schedule for Part 2A.
15. **Echocardiogram:** Echo to be done once patient is confirmed to meet all other inclusion requirements, beginning Cycle 3 Day 1 predose and every 2 cycles for 6 months, then every 3 cycles. A ±7 day window will be applied.
16. **Troponin I and BNP:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. Will be performed per the SOA and will be repeated if abnormal and clinically significant.
17. **Alk Phos Fractionation**: Obtain alkaline phosphatase (ALP) fractionation (bone, liver) per the SOA and as clinically indicated. With each ALP increase in AE grade level once at the grade level, fractionation will be obtained and an appropriate clinical evaluation will be conducted to determine the suitability of the patient continuation in the trial.
18. **Registration**: patient number and dose level allocation assigned by Pfizer Inc.
19. **Study Treatment**: PF-06952229 will be administered orally for 7 days on, 7 days off, during a 28 day cycle. Day 1 safety laboratory tests must be reviewed by the Investigator prior to dosing at the beginning of each cycle for dosing confirmation. Patients will self dose as described above, with the exception of doses that will be administered on site. Patients must maintain their original dosing schedule regardless of dose reductions or holds. Patients will be required to return all bottles of PF-06952229 as well as the completed patient diary for drug accountability. On days of scheduled clinic visits, morning (AM) dosing should be undertaken in the clinic (ie, not at home).

SCHEDULE OF ACTIVITIES PART 2A – Monotherapy Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment) [1]	Active Treatment Phase†- One Cycle = 28 days						End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2				Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 1**	**Day 7**		

20. **Tumor Assessments**: Tumor assessments will include CT or MRI of chest, abdomen and pelvis, and MRI of the brain. If a brain MRI is medically contraindicated, a CT scan with contrast (unless contrast is medically contraindicated) may be performed, however the same modality should be used on an individual patient throughout the study. Other disease sites may be imaged if disease is suspected. Tumor assessments will be performed at Screening and every 8 weeks (±7 days) for the first year, then every 12 weeks (±7 days). Bone scans will be performed as medically indicated. Tc-99m bone scans (required for CRPC at baseline) will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Patients who are found to have hemorrhage in other organs will discontinue treatment with PF-06952229 and enter the follow-up portion of the trial. Tumor assessments with continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Given the exploratory nature of the study, confirmation of response (complete response (CR)/partial response (PR)) is preferred (see RECIST version 1.1). Tumor assessments should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation. Patients should have a confirmatory scan for PD and can remain on trial if they are receiving clinical benefit upon discussion with investigator and sponsor MD. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. FDG-PET will be performed per standard of care.

    Bone Scans for mCRPC: 99mTc-methylene diphosphonate radionuclide bone scintigraphy should be performed every 8 weeks for first 24 weeks, then every 12 weeks (up to 2 years), then every 16 to 24 weeks (±14 days). Changes in lesions that are considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form (see Appendices).

    Prostate specific antigen (PSA) assessment to be performed on Screening (for historical progression per Prostate Cancer Working Group 2), C1D1 (-14 days) and Day 1 of Cycle 4, 7, 10 and every 3rd cycle thereafter as well as the End of Treatment visit. Please see Appendix for Prostate Cancer Working Group 2 (PCWG2)- Soft Tissue Response Criteria.

    CCI [redacted]

    Gleason Score should be collected at diagnosis.

21. **Adverse Event (AE) Assessments**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
22. **Concomitant Treatments**: All concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF including supportive care drugs, eg, anti-emetic treatment and prophylaxis, radiotherapy on study is permitted (eg, skeletal administration for CRPC), drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, infusions).
23. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks as applicable for disease assessments).

SCHEDULE OF ACTIVITIES PART 2A – Monotherapy Dose Expansion

Protocol Activity	**Screening (≤28 days prior to enrollment)** [1]	**Active Treatment Phase†- One Cycle = 28 days**						**End of Treatment/ Withdrawal**[23]	**Post-Treatment Follow-Up**[24]
		Cycles 1 & 2				**Cycles 3+**			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 7**	**Day 10**[b]	**Day 15**	**Day 1**	**Day 7**		

24. **Post Treatment Follow-Up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, ECOG, abbreviated physical exam, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
25. **Survival Follow-Up:** Subsequent to the follow-up period, overall survival (OS) follow-up will be conducted by telephone every 8 weeks (±7 days) until end of the entire study (2 years after last patient first treatment). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call.

Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 2A – Monotherapy Dose Expansion

Visit Identifier	Screen	Cycle 1			Cycle 2			Cycle ≥3	EOT
Study Day		**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**	**Day 10** (-24hrs)	**Day 7**	
Dose of PF-06952229 in clinic[1]		X	X	X	X	X		X	
Pharmacokinetics (PK)									
Predose (if dosing day)		X	X	X	X	X	X	X	X
0.5 hours (±5 min)		X	X						
1 hour (±10 min)		X	X						
2 hours (±15 min)		X	X						
4 hours (±25 min)		X	X						
6 hours (±40 min)		X	X						
12 hours (-180 min)		X	X						
Urine for PF-06952229 PK[2]			X						
12-Lead ECG[3]									
0	X	X	X	X		X		X	X
2 hours (±15 min)		X	X						
4 hours (±25 min)		X	X						
CCI [redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

Visit Identifier	Screen	Cycle 1			Cycle 2			Cycle ≥3	EOT
Study Day		**Day 1**	**Day 7**	**Day 15**	**Day 1**	**Day 7**	**Day 10** (-24hrs)	**Day 7**	
Dose of PF-06952229 in clinic[1]		X	X	X	X	X		X	
Pharmacokinetics (PK)									

Abbreviation: PK = pharmacokinetic; CCI ; EOT = End of Treatment; CCI

1. **Dose of PF-06952229 in Clinic:** On days of scheduled clinic visits, morning (AM) dosing should be undertaken in the clinic (ie, not at home).
2. **Urine for PF-06952229 PK:** Optional – See Section 7.3.2.
3. **Triplicate 12-Lead ECG:** The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) will be performed approximately 2 minutes apart to determine mean QTcF interval. All 12-lead ECGs should be confirmed by a qualified person at the institution. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥45 msec from the baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

CCI [redacted]

SCHEDULE OF ACTIVITIES PART 2B – Combination Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2[c]**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 21[c]**	**Day 1**	**Day 7**		
Informed consent[2]	X										
Medical/Oncological history[3]	X										
Physical examination[4]	X									X	
Abbreviated physical examination[4]		X		X		X		X	X		X
Baseline signs and symptoms[5]		X									
Height	X										
Weight	X	X						X		X	
Vital signs[6]	X	X[6]		X		X		X[6]	X	X	
ECOG Performance status[7]	X	X						X		X	X
Laboratory											
Hematology[8]	X	X		X		X		X	X	X	
Blood Chemistry[9]	X	X		X		X		X	X	X	
Coagulation[10]	X	X		X		X		X		X	
Urinalysis[11]	X			X		X		X		X	
Viral disease screening[12]	X										
Contraception check[13]	X	X						X		X	X
12-lead ECG[14]	X	See Pharmacokinetic, ECG [redacted] Sampling Schedule for Part 2B									
Echocardiogram[15]	X							X		X	
Troponin I + BNP[16]	X	X		X		X		X		X	
Alk Phos fractionation[17]		X									
Registration and Treatment											
Registration[18]	X										
PF-06952229[19]		◄--► Orally twice daily (BID) on Days 1-7 and 15-21 of each Cycle									
Enzalutamide[19]		◄--► Orally QD as continuous daily dosing									
Tumor assessments											

SCHEDULE OF ACTIVITIES PART 2B – Combination Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment)[1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2[c]**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 21[c]**	**Day 1**	**Day 7**		
CT/MRI Scans[20]	X	See footnote for frequency of scans								X	
Tumor markers (PSA and Gleason Score for prostate cancer)[20]	X	X						X		X	
CCI [redacted]		[redacted]						[redacted]			
Other clinical assessments											
Serious and non-serious adverse event monitoring[21]	X	◄--►									
Concomitant treatment(s)[22]	X	◄--►									
Survival Follow-Up[25]											X

Abbreviations: ◄--► = ongoing/continuous event; BID = twice daily; C = cycle; Day = D; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; CT = computed tomography; MRI = magnetic resonance imaging; OS = overall survival; (X) = optional assessment.

- After Cycle 1, Day 1, tests and procedures should be done on schedule, but occasional changes by ±3 days (unless otherwise stated differently) are allowed for holidays, vacations and other administrative reasons.
- For Pharmacokinetics and additional sampling requirements, please see Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 2B Table below.

a. Patients must maintain their original dosing schedule (7 days on, 7 days off) regardless of dose reductions or holds. To accommodate the dosing schedule, visit windows are not allowed into the "drug off" periods due to safety concerns; however, 2 day windows are allowed during the "drug on" period.

b. Day 10 assessments are only performed in Cycle 2.

c. Day 2 and Day 21 visit for first 8 subjects (min).

†**Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their morning (or afternoon as applicable) dose, which will be administered by study staff onsite on clinic days. Acceptable time windows for performing each assessment are described in the column headers. One cycle consists of 28 days. **Day 1 of any cycle visit should coincide with the day the PF-06952229 treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit may be delayed until the patient has recovered and can begin study treatment again. The active treatment phase is ongoing as long as the patient is receiving PF-06952229.
Study entry is Cycle 1 Day 1.

SCHEDULE OF ACTIVITIES PART 2B – Combination Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment) [1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2[c]**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 21[c]**	**Day 1**	**Day 7**		

1. **Screening:** To be obtained within 28 days prior to study entry.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
3. **Medical/Oncologic History:** Includes history of disease process (eg, staging) (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
4. **Physical Examination:** Physical examinations (PEs) may be performed within 48 hours prior to a scheduled visit. A full physical examination is required at Screening and abbreviated PEs should be performed as appropriate at each visit where complete physical examinations are not required. For both full and abbreviated exams, patient should be assessed for evidence of bleeding (eg, bruising, petechiae, or hematomas). No need to repeat PE if baseline assessment is within 96 hours on Cycle 1 Day 1.
5. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry.
6. **Vital Signs:** Includes temperature, sitting or semi-recumbent (same position must be used throughout the study and documented in source notes) blood pressure (BP), pulse rate (PR, to be recorded in the sitting position after 5 minutes of rest), and pulse oximetry (at rest and after exertion). On Day 1 of each cycle, vital signs should be measured prior to dosing (predose), BP, and PR will be repeated 1 hour after dosing. The time window for Vital Signs will match the allowable window for PK and ECGs.
7. **ECOG Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendices.
8. **Hematology**: No need to repeat on Cycle 1 Day 1 (C1D1) if baseline assessment performed within 72 hours prior to that date. Assessments performed on Cycle 2 Day 1 (C2D1) and each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments section for Laboratory Tests list.
9. **Blood Chemistry**: No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date (with the exception of serum creatinine which must be performed within 72 hours of C1D1). See Assessments section for Laboratory Tests list. Note that chemistries performed require serum phosphorus measurements.
10. **Coagulation**: No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. See Assessments section for Laboratory Tests list.
11. **Urinalysis**: Dipstick is acceptable at Screening, during trial conduct, and the End of Treatment visit. At Screening, if dipstick shows urine protein ++ or above, perform 24-hour urine protein test. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests list.
12. **Viral Disease Screening:** Hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti HBc), (HbcAb), hepatitis B surface antibody (anti HBs), hepatitis C virus antibodies (HCVAb), and human immunodeficiency virus testing (HIV) to be conducted by local laboratory where required by local regulations or if warranted by patient history.
13. **Contraceptive Check (frequency to match that of pregnancy tests)**: Male patients who are able to father children need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The Investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient's partner.
14. **Triplicate 12-Lead ECG:** The Screening ECG will be a single 12-lead ECG. ECGs will be collected at times specified in Pharmacokinetic, ECG, CCI Sampling Schedule for Part 2B.
15. **Echocardiogram:** Echo to be done once patient is confirmed to meet all other inclusion requirements, beginning cycle 3 Day 1 predose and every 2 cycles for 6 months, then every 3 cycles. A ±7 day window will be applied.
16. **Troponin I and BNP:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. Will be performed per the SOA and will be repeated if abnormal and clinically significant.

SCHEDULE OF ACTIVITIES PART 2B – Combination Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment) [1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2[c]**	**Day 7**	**Day 10[b]**	**Day 15**	**Day 21[c]**	**Day 1**	**Day 7**		

17. **Alk Phos Fractionation**: Obtain alkaline phosphatase (ALP) fractionation (bone, liver) per the SOA and as clinically indicated. With each ALP increase in AE grade level once at the grade level, fractionation will be obtained and an appropriate clinical evaluation will be conducted to determine the suitability of the patient continuation in the trial.
18. **Registration**: patient number and dose level allocation assigned by Pfizer Inc.
19. **Study Treatment**: PF-06952229 will be administered orally for 7 days on, 7 days off, during a 28 day cycle. Day 1 safety laboratory tests must be reviewed by the Investigator prior to dosing at the beginning of each cycle for dosing confirmation. For Part 2B mCRPC patients will receive PF-06952229 in combination with enzalutamide. Patients will self dose as described above, with the exception of doses that will be administered on site. Patients must maintain their original dosing schedule regardless of dose reductions or holds. Patients will be required to return all bottles of PF-06952229 as well as the completed patient diary for drug accountability. On days of scheduled clinic visits, morning (AM) dosing should be undertaken in the clinic (ie, not at home).
20. **Tumor Assessments**: Tumor assessments will include CT or MRI of chest, abdomen and pelvis, and MRI of the brain. If a brain MRI is medically contraindicated, a CT scan with contrast (unless contrast is medically contraindicated) may be performed, however the same modality should be used on an individual patient throughout the study. Other disease sites may be imaged if disease is suspected. Tumor assessments will be performed at Screening and every 8 weeks (±7 days) for the first year, then every 12 weeks (±7 days). Bone scans will be performed as medically indicated. Tc-99m bone scans (required for CRPC at baseline) will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Patients who are found to have hemorrhage in other organs will discontinue treatment with PF-06952229 and enter the follow-up portion of the trial. Tumor assessments with continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Given the exploratory nature of the study, confirmation of response (complete response (CR)/partial response (PR)) is preferred (see RECIST version 1.1). Tumor assessments should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation. Patients should have a confirmatory scan for PD and can remain on trial if they are receiving clinical benefit upon discussion with investigator and sponsor MD. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. FDG-PET will be performed per standard of care.

    Bone Scans for mCRPC: 99mTc-methylene diphosphonate radionuclide bone scintigraphy should be performed every 8 weeks for first 24 weeks, then every 12 weeks (up to 2 years), then every 16 to 24 weeks (±14 days). Changes in lesions that are considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form (see Appendices).

    Prostate specific antigen (PSA) assessment to be performed on Screening (for historical progression per Prostate working Group 2), C1D1 (-14 days) and Day 1 of Cycle 4, 7, 10 and every 3rd cycle thereafter as well as the End of Treatment visit. Please see Appendix for Prostate Cancer Working Group 2 (PCWG2)- Soft Tissue Response Criteria.

    CCI [redacted]

    Gleason Score should be collected at diagnosis.

SCHEDULE OF ACTIVITIES PART 2B – Combination Dose Expansion

Protocol Activity	Screening (≤28 days prior to enrollment) [1]	Active Treatment Phase†- One Cycle = 28 days								End of Treatment/ Withdrawal[23]	Post-Treatment Follow-Up[24]
		Cycles 1 & 2						Cycles 3+			
Visit Identifier (Visit Window)[a]		**Day 1**	**Day 2**[c]	**Day 7**	**Day 10**[b]	**Day 15**	**Day 21**[c]	**Day 1**	**Day 7**		

21. **Adverse Event (AE) Assessments**: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
22. **Concomitant Treatments**: All concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF including supportive care drugs, eg, anti-emetic treatment and prophylaxis, radiotherapy on study is permitted (eg, skeletal administration for CRPC), drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, infusions).
23. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks as applicable for disease assessments).
24. **Post Treatment Follow-Up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, ECOG, abbreviated physical exam, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
25. **Survival Follow-Up:** Subsequent to the follow-up period, overall survival (OS) follow-up will be conducted by telephone every 8 weeks (±7 days) until end of the entire study (2 years after last patient first treatment). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call.

Pharmacokinetic, ECG, CCI [redacted] Sampling Schedule for Part 2B - Combination Dose Expansion

Visit Identifier		Screen	Cycle 1					Cycle 2				Cycle ≥3	EOT
Study Day			**Day 1**	**Day 2****	**Day 7**	**Day 15**	**Day 21****	**Day 1**	**Day 2****	**Day 7**	**Day 10 (-24 hrs)**	**Day 7**	
Dose of PF-06952229 in clinic[1]			X*	X	X	X	X	X*	X	X		X	
Pharmacokinetics (PK)													
Predose (if dosing day)			N, E	N	N, E	N	N,E	N, E	N	N	N	N	N
First 8 Patients only (min)	0.5 hours (±5 min)		N				N	N					
	1 hour (±10 min)		N				N	N					
2 hours (±15 min)			N		N	N	N	N		N			
First 8 Patients only (min)	4 hours (±25 min)		N				N	N					
	6 hours (±40 min)		N				N	N					
	12 hours (-180 min)		N				N	N					
12-Lead ECG[2]													
0		X	X	X	X	X	X			X		X	X
2 hours (±15 min)			X		X	X	X						
CCI [redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													

Visit Identifier	Screen	Cycle 1					Cycle 2				Cycle ≥3	EOT
Study Day		Day 1	Day 2**	Day 7	Day 15	Day 21**	Day 1	Day 2**	Day 7	Day 10 (-24 hrs)	Day 7	

Abbreviation: PK = pharmacokinetic; CCI [redacted]; EOT = End of Treatment; N=PF-06952229; E=Enzalutamide; CCI [redacted]

* On Day 1 of Cycle 1 and Cycle 2 only a single dose of PF-06952229 to be given to evaluate PF-06952229 PK sampling up to 24 hr time point (i.e. pre-dose on Day 2 of Cycle 1 and Cycle 2).

** Day 2 and Day 21 visit for first 8 subjects (min).

1. **Dose of PF-06952229 in Clinic:** On days of scheduled clinic visits, morning (AM) dosing should be undertaken in the clinic (ie, not at home).
2. **Triplicate 12-Lead ECG:** The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) will be performed approximately 2 minutes apart to determine mean QTcF interval. All 12-lead ECGs should be confirmed by a qualified person at the institution. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥45 msec from the baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

CCI [redacted]

1. INTRODUCTION

1.1. Mechanism of Action/Indication

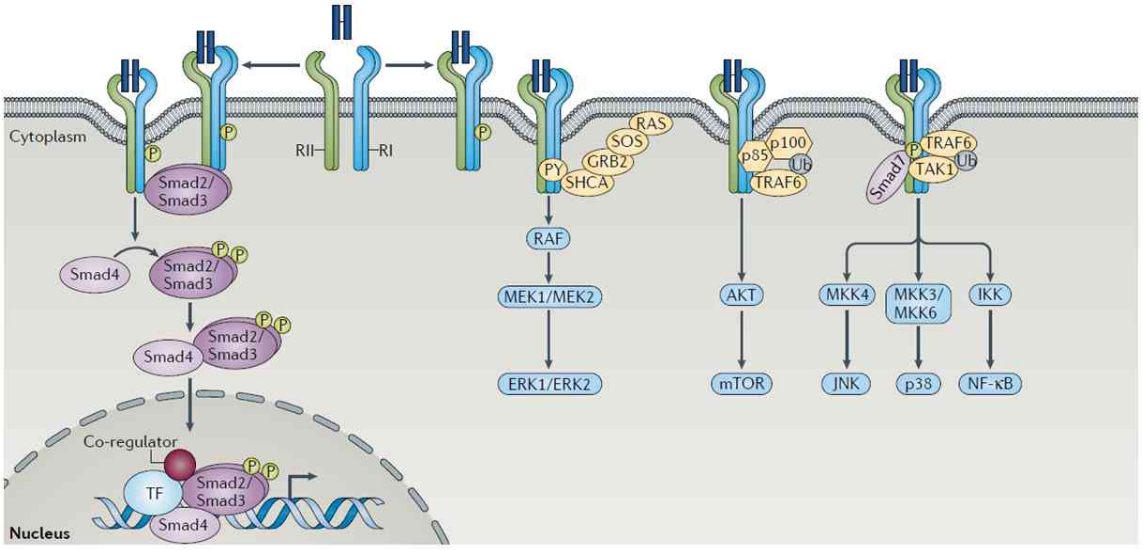
PF-06952229 is an orally bioavailable small molecule inhibitor of the serine/threonine kinase receptor transforming growth factor beta receptor 1 (TGFβR1). This receptor has pleiotropic effects on a number of transforming growth factor beta receptor (TGFβ)-mediated signaling pathways that impact the growth and proliferation of malignancies. In this clinical study, PF-06952229 is being investigated as monotherapy to treat patients diagnosed with advanced/metastatic solid tumor, and with metastatic castration-resistant prostate cancer (mCRPC) in Part 1A and Part 2A, respectively, and as combination therapy with enzalutamide to treat patients diagnosed with mCRPC in Part 1B and Part 2B.

1.2. Background and Rationale

1.2.1. TGFβ

Elevated TGFβ expression by tumor and stromal cells in the tumor microenvironment, and activation of TGFβ receptor intracellular signaling is observed in many cancers.[8] Activated TGFβR1 phosphorylates the signaling intermediate proteins termed mothers against decapentaplegic homolog 2 and 3 (SMAD2 and SMAD3), which assemble into complexes with SMAD4, and translocate to the nucleus, where they regulate the expression of TGFβ target genes (Figure 1). In addition, non-SMAD signaling may also be initiated downstream of TGFβ receptors, which can lead to the activation of various pathways such as phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), c-jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38), and extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAP).[9]

Figure 1. Canonical and Non-Canonical TGFβ signaling[10]



The activation of the TGFβ pathway in cancer cells can induce epithelial to mesenchymal transition (EMT) in which epithelial cells lose their apico-basal polarity and cell-cell adhesion, to become highly migratory mesenchymal cells, leading to metastasis. In addition, EMT has been linked to tumor cell evasion of immune surveillance.[11] TGFβ has been shown to be a potent immunosuppressive agent on both innate and adaptive immune cells, including dendritic cells, macrophages, natural killer (NK) cells, and CD4+ and CD8+ T cells. Conversely, TGFβ plays a key role stimulating the differentiation of immune-suppressive regulatory T (Treg) cells. Finally, inhibition of the TGFβR1 pathway in preclinical models has led to tumor growth inhibition.

Patient stratification based on gene expression studies reveals elevated TGFβ pathway activation in cohorts with the worst prognosis.[12] TGFβ expression has been associated with poor prognosis in a number of cancers, eg, prostate[17], colorectal[13], pancreatic[14], and lung.[15] The TGFβ pathway has also been described to play a key role in resistance to therapy. Patients with innate resistance to programmed death ligand 1 (PD-L1)/ programmed cell death 1 (PD-1) antibody treatment show elevated pre-treatment tumor TGFβ signatures.[23] In prostate cancer, TGFβ plasma levels strongly predict progression[16,17] and androgen depleting therapies, including enzalutamide, induce expression of TGFβ-dependent genes, and promote EMT and bone metastasis in castration resistant prostate cancer.[18] EMT has also been linked to chemotherapy resistance in colorectal cancer.[19,20] Collectively these findings demonstrate key roles for TGFβ pathways in disease progression and resistance to therapy in a broad spectrum of tumors, and support inhibiting the TGFβ pathway for the treatment of cancer.

1.2.2. Tumors and Combination Therapies

High TGFβ signatures and EMT expression are found in a variety of tumors, including metastatic breast cancer[21], metastatic castration-resistant prostate cancer (mCRPC)[16,17], squamous cell cancer of the head and neck[22], melanoma, mesothelioma, metastatic pancreatic cancer,[23] colorectal cancer,[24,25,26] renal cell carcinoma, and hepatocellular cancer.[27,28] These tumor types will be investigated in Part 1A of this protocol, a dose exploration of PF-06952229. Subsequent investigations in Part 1B, Part 2A, and Part 2B of the protocol will be undertaken in patients with mCRPC which was selected based on nonclinical data, unmet medical need, and preliminary Part 1A data.

These preliminary data were noted in 1 patient who was treated with 8 previous regimens for mCRPC, was treated with PF-06952229 on 30 May 2019 where the patient was reported to have a PSA of 125.3 ng/ml and a soft tissue mass of 11 mm in its longest dimension. By 13 Nov 2019, PSA was reduced to 1.6 ng/ml and the soft tissue mass was reported as 8 mm. By 04 Mar 2020 the soft tissue lesion was reported to be 0 mm in its longest dimension with a subsequent PSA measurement of 0.477 ng/ml. The patient continues to work, has an ECOG performance score of 1, and reports feeling well.

Metastatic prostate cancer treated with androgen deprivation therapy (ADT) is associated with increased TGFβsignaling. Enzalutamide resistance in preclinical prostate cancer models show increased TGFβ, EMT, cell migration and proliferation.[18,43] Therefore, this

provides the basis for further investigation of PF-06952229 in monotherapy and in combination with enzalutamide in mCRPC.

1.2.2.1. Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Prostate cancer is the most common non cutaneous cancer in US men with an estimated 164,000 new cases expected to be diagnosed in 2018.[29] It is a slow growing disease which occurs in prostate gland of the male reproductive system.[41] However some prostate tumors can grow relatively quickly and at a later stage of the disease, the cancer cells may metastasize to other parts of the body, particularly the bones and lymph nodes. Treatment options for prostate cancer include surgery, radiation therapy, hormone therapy and chemotherapy. Most hormone dependent cancers become resistant to treatment after one to three years and resume growth despite hormone therapy.[42] These metastatic castration-resistant prostate cancers respond poorly to reduction of available androgen/testosterone/ dihydrotestosterone (DHT) by either chemical or surgical means.

Metastatic progression, poor prognosis, and drug resistance in prostate cancer treated with androgen deprivation therapy (ADT) are associated with increased TGFβ signaling. Enzalutamide resistance in preclinical prostate cancer models show increased TGFβ, EMT, cell migration and proliferation.[18,43] TGFβ inhibition decreases TGFβ-induced EMT markers in prostate cancer cells.[18] In addition enzalutamide in combination with galunisertib (TGFBRi) inhibits signaling pathway (pSMAD2/3) and tumor growth (along with reversing EMT) in a preclinical prostate cancer model.[44] Based on these data, combining a TGFβ inhibitor such as PF-06952229 with enzalutamide may be a beneficial treatment option for patients with mCRPC.

1.2.3. Nonclinical Pharmacology

PF-06952229 is a selective TGFβR1 inhibitor with minimal kinase inhibitory activity/binding to TGFβR2. It is a potent inhibitor of TGFβR1 with an IC_{50} value of 0.8 nM as measured by a competition binding enzyme assay. Consistent with TGFβ action on immune cells, PF-06952229 inhibits TGFβ-induced SMAD2 phosphorylation (pSMAD2), a direct target of the TGFβR1 pathway, across several species with average unbound IC_{50} values of 57 nM in human PBMC, 26 nM in Cynomolgus monkey PBMCs, 38 nM in rat splenocytes, and 16 nM in mouse splenocytes. PF-06952229 also reverses TGFβ-mediated suppression of interleukin-2(IL-2) secretion, a marker of activation in human T cells with an EC_{50} value of 12 nM (unbound). PF-06952229 also potently inhibits TGFβ induced pSMAD2 in human MDA-MB-231 and mouse 4T1 breast cancer cell lines with IC_{50} values of 17 and 25 nM (unbound), respectively.

In vivo, pSMAD2 acts as a responsive and predictive pharmacodynamic biomarker of TGFβR1 inhibition in MC38 and 4T1 tumors. Modeling of the pharmacokinetic/pharmacodynamic relationship in tumors derives an IC50 of 5-10 nM for inhibition of phosphorylation of SMAD2 in good agreement with the in vitro cell based potencies. As a single agent, PF-06952229 showed no tumor growth inhibition (TGI) in the 4T1 primary tumors, which are known to be refractory to various therapeutic agents.

However, PF-06952229 shows significant inhibition of spontaneous lung metastasis in this model that was associated with a decrease in EMT and increase in immune-activation gene signatures in the 4T1 primary tumors.

In the MC38 murine syngeneic colorectal tumor model, PF-06952229 shows dose-dependent TGI as a single agent. No significant TGI activity (-3%) was observed relative to the vehicle treated group at a dose of 10 mg/kg twice daily (BID) (7 days on/7 days off) while 86% TGI relative to the vehicle treated group was observed at 30 mg/kg BID (7 days on/7 days off). The efficacious concentration (C_{eff}) of PF-06952229 was defined in the MC38 syngeneic tumor model as the average concentration resulting in statistically significant TGI in a monotherapy setting (30 mg/kg BID, 7 day on/7 day off regimen). The average unbound plasma concentration at this dose was 23 nM. In addition, when PF-06952229 (7 days on/7 days off regimen) was evaluated in combination with an anti-murine specific PD-1 antibody (αPD-1, dosed at 5 mg/kg twice a week for 2 weeks) in the MC38 model, there was a strong combinatorial effect observed even at the lower dose of PF-06952229 (10 mg/kg BID 7 days on/7 days off). The TGI relative to control treated animals of 10 mg/kg BID + αPD-1 was 88% and for 30 mg/kg BID + αPD-1 was 99%. Based on these data and current literature, there is a rationale for combinations with PF-06952229 in the clinic.

1.2.4. Nonclinical Pharmacokinetics

The nonclinical pharmacokinetic/toxicokinetic, absorption, distribution, metabolism, and excretion (ADME) properties of PF-06952229 have been evaluated in vitro and in vivo to support nonclinical safety evaluations and to assess the potential relevance to humans. The oral pharmacokinetics (PK) of PF-06952229 in nonclinical species indicated moderate to high oral absorption and bioavailability. Systemic exposure increased with dose in pivotal toxicity studies in rats and monkeys. PF-06952229 was highly bound to plasma proteins across species and, in general, demonstrated limited distribution into red blood cells. In vitro studies suggest PF-06952229 may be a substrate for the efflux transporters such as human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The moderate to high bioavailability observed in nonclinical species indicate that oral absorption was not limited by these efflux transporters.

The primary clearance mechanism of PF-06952229 was cytochrome P450 (CYP) 3A4-mediated metabolism (f_m ~0.9), with limited to no renal or biliary excretion. Consequently, significant changes in PF-06952229 exposure are anticipated following co-administration with strong CYP3A4 inhibitors or inducers. Following co-administration of PF-06952229 with enzalutamide (a strong inducer of CYP3A) a 70% decrease (AUC_R ~0.3) in PF-06952229 AUC was predicted. No unique human metabolites were observed in vitro compared to metabolite profiling in rat.

Assessments based on in vitro drug-drug interaction (DDI) studies and the predicted systemic exposure in humans following the projected efficacious dose indicate a low potential for DDI due to PF-06952229-mediated inhibition of CYP 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 or uridine diphosphate-glucuronosyltransferase (UGT) 1A4, 1A6, 1A9, 2B7 and 2B15. However, PF-06952229 may have the potential to inhibit CYP3A (time-dependent) and UGT1A1 (reversible) at concentrations associated with the projected efficacious dose. The

potential for DDI due to PF-06952229-mediated inhibition of organic anion-transporting polypeptides (OATP) 1B1 and 1B3, organic anion transporter (OAT) 1 and OAT3, organic cation transporter (OCT) 2, multi-antimicrobial extrusion protein (MATE) 1, and MATE2K is low. However, PF-06952229 has the potential to inhibit intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) at the projected efficacious dose.

In humans, the predicted plasma CL and V_{ss} of PF-06952229 are 5 mL/min/kg and 3 L/kg respectively, providing an effective $t_{½}$ of approximately 7 hours. PF-06952229 is estimated to exhibit an oral bioavailability of approximately 65% and fraction absorbed × fraction escaping gut metabolism (Fa×Fg) of approximately 1. Based on the predicted human PK parameters and the unbound efficacious concentration (C_{eff}) defined in the MC38 syngeneic tumor model, the efficacious oral dose of PF-06952229 in humans is projected to be 225 mg twice daily (BID).

1.2.5. Nonclinical Safety

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- **Liver:** Hepatocellular hemorrhage, necrosis and mixed cell infiltration in the liver with associated transaminase increases were observed at ≥10 mg/kg BID in the rat pivotal study; non-reversible in one female rat at the highest dose.

- **Skeletal System:** Cartilage hypertrophy/dysplasia was observed in both rats and monkeys, across the exploratory and pivotal studies. The findings were partially reversible in rat and reversible in monkey in pivotal studies. The bone/cartilage findings are considered to be related to the primary pharmacology of PF-06952229, in growing animals with open growth plates and are not expected to be relevant for adult patients.

- **Lung:** Minimal hemorrhage that was generally accompanied by minimal mixed cell inflammation was observed in the rat pivotal study at doses of PF-06952229 ≥5 mg/kg BID.

- **Other Findings:** Among other findings consistently seen in rats and monkeys was decrease in plasma phosphorous at ≥ 10 mg/kg BID.

Rat was the more sensitive nonclinical species with respect to PF-06952229-related toxicities. Based on the pivotal studies, the STD_{10} and the HNSTD in rat and monkey at the end of the dosing period were 20 and 100 mg/kg BID, respectively. Sex-combined, unbound systemic maximum plasma concentration (C_{max}) and area under the concentration time profile from time 0 to 24 hours (AUC_{24}) values at the STD_{10} in rat were 75.9 ng/mL (165 nM) and 873 ng·h/mL (1900 nM·h), respectively. At the STD_{10} in rats, the C_{max} and AUC_{24} exposure multiples are 42x and 39x, respectively to the predicted exposure at the starting dose of 20 mg BID. Sex-combined, unbound systemic C_{max} and AUC_{24} values at the HNSTD in monkey were 159 ng/mL (346 nM) and 2300 ng·h/mL (5010 nM·h), respectively. At the HNSTD in monkeys, the C_{max} and AUC_{24} exposure multiples are 88x and 102x, respectively to the predicted exposure at the starting dose of 20 mg BID.

Based on published data, attenuation of TGFβ pathway in nonhealing wounds may contribute to the loss of tissue homeostasis, epidermal hyperproliferation, and the inability of keratinocytes to migrate and epithelialize a wound. Therefore PF-06952229-mediated inhibition of TGFβR1 may have effects on wound healing.[52]

Overall, the nonclinical safety profile of this PF-06952229 has been adequately characterized to support progression into clinical trials in advanced cancer patients.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06952229 may be found in the Investigator's Brochure, which is the SRSD for this study.

1.2.6. Clinical Pharmacokinetics

Preliminary PF-06952229 concentration-time data is available from a total of 13 patients at dose levels of 20, 40, 80, 150, 250 and 375 mg BID as of 24 Jul 2019. It should be noted that due to the limited number of patients, the overall PK interpretation should be considered preliminary.

Upon oral administration on an empty stomach, PF-06952229 appeared to be rapidly absorbed after first dose with the C_{max} being achieved between 1 to 4 hours. After reaching C_{max}, PF-06952229 concentrations declined in a monophasic manner. In general, there was a dose-dependent increase in PF-06952229 exposures over the studied dose range. Additional information on clinical pharmacokinetics of PF-06952229 can be found in the Investigator's Brochure.

1.2.7. Clinical Safety

Since the modification of the patient entry criteria that led to the lifting of the FDA partial clinical hold, no hemorrhagic events have been reported as of 19 Jun 2020. For additional information on AEs reported as of 19 Jun 2020, please see Appendix 10.

1.3. Starting Dose Rationale

The selection of the starting dose and regimen for this first-in-patient (FIP) study was based on the nonclinical toxicology and PK results, which are in accordance with the International Conference on Harmonization (ICH) S9 Guidance (October 2009) for the intended population. Results from nonclinical toxicity studies indicate that the rat is the most sensitive species, and in the pivotal study the Severely Toxic Dose in 10% of animals (STD_{10}) for PF-06952229 was at 20 mg/kg twice daily (BID). Key findings in this study were the microscopic findings of hepatocellular hemorrhage, hepatocyte necrosis and mixed cell infiltration in the liver and elevated transaminases that were non-reversible in one female at 20 mg/kg BID. The human equivalent dose for the STD_{10} (20 mg/kg BID) dose in rat is approximately 194 mg BID (assuming a body weight of 60 kg). Per ICH-S9 Guidance, one-tenth of the STD_{10} can be considered as the appropriate starting dose. Given the predicted human disposition and half-life ($t_{½}$) of approximately 7 hours, the starting dose has been selected to be 20 mg administered orally (PO) BID. The human unbound steady-state C_{av} and C_{max} of PF-06952229 at the proposed starting oral dose of 20 mg BID [daily (PO) 40 mg/day] is projected to be 0.94 ng/mL (2.0 nM) and 1.8 ng/mL (3.9 nM), respectively. The respective margins relative to the STD_{10} of 20 mg/kg BID in rat are 39× and 42× for C_{av} and C_{max}, respectively. The respective margins relative to the highest non-severely toxic dose (HNSTD) of 100 mg/kg BID in monkey are 102× and 88× for C_{av} and C_{max}, respectively.

1.3.1. Intermittent Dosing Schedule Rationale

PF-06952229 will be administered PO BID on a 7-day on/7-day off schedule in a 28-day cycle. An intermittent dosing schedule was selected to mitigate the risk of potential cardiovascular toxicity based on the nonclinical cardiovascular findings observed with galunisertib, a dual inhibitor of TGFβR1 and TGFβR2 when dosed continuously[50] and with

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These effects were not observed in the 8-week pivotal study (8330539) up to 20 mg/kg BID on a 5-day on 5-day off dosing schedule (5 cycles+ 3 days, 28 total doses). CCI [redacted] A 7-day on 7 day-off dosing schedule, as was used in the mouse MC38 efficacy study, resulted in a slightly lower dose intensity over 28 days compared to 5-day on 5-day off schedule used in pivotal toxicology study, but with approximately similar predicted TGI. Based on ICH S9 Guidance, a nonclinical treatment schedule of 5- or 7-day on and 5- or 7-day off, alternating weeks (2-dose cycles), would support a clinical dosing schedule of 7 days on and 7 days off. Following consideration of all available data and practical considerations, a 7-day on 7-day off intermittent dosing schedule was selected for the FIP study. Depending on the observed half-life, alternative dosing schedules may be considered, if deemed appropriate according to the aforementioned guidance and supported by available toxicology and clinical data. Modifications the current schedule would be implemented through a protocol amendment.

1.4. PF-06952229 Rationale for Development

The TGFβ signaling pathway is associated with the invasive and metastatic process, resistance to immunotherapy, targeted therapy, and conventional chemotherapy. PF-06952229 is a potent, small molecule inhibitor of TGFβ signaling pathways and may overcome these treatment failures. Based on these and other characteristics, PF-06952229, in combination with other oncology and immuno-oncology drugs is anticipated to be efficacious in resistant and/or relapsed TGFβ/EMT-dependent cancers.

1.5. Study Rationale

TGFβ pathways play key roles in disease progression and resistance to therapy in a broad spectrum of tumors, supporting its inhibition for the treatment of cancer.[28] High TGFβ signatures and EMT expression are found in a variety of tumors making them promising targets for treatment with a TGFβ inhibitor in combination with either oncology or immuno-oncology drugs and may be particularly efficacious in resistant and/or relapsed TGFβ/EMT-dependent cancers. Based on published nonclinical data and Part 1A preliminary data from this study, this clinical trial will focus on treatment of mCRPC (Section 1.2).

Early human data have been generated for PF-06952229. Observations of bleeding events that resulted in an FDA partial clinical hold, led to mitigations being put in place within the study that included additional requirements for MRI brain scans, enrollment exclusions, and patient and study discontinuation criteria. Except for an observation of bleeding events that

resulted in the partial clinical hold and which to date have not recurred, the toxicity profile of PF-06952229 has been acceptable.

Additionally, published clinical data utilizing other inhibitors of this target (TGFβR1) support the safety and pharmacology. Based on the current available clinical data, TGFβ inhibitors have been generally safe and well-tolerated on an intermittent dosing schedule (14 days on and 14 days off) in a number of small Phase 1 trials[44,46,47] and one Phase 2 trial.[48] The most data available are from the galunisertib (LY2157299) program in which the notable Grade 3 or higher treatment-related adverse events (AE)s were: 1) in Phase 1 and 2 studies in patients with advanced solid tumors and glioblastoma, decreased platelet, neutrophil, lymphocyte or white blood cell (WBC) counts were the most common, with rare cases (generally 1 case) of central nervous system (CNS) ischemia, thrombosis/embolism, dyspnea, febrile neutropenia[44,48] 2) in Phase 1 studies of Japanese patients with advanced solid tumors or pancreatic cancer, decreased neutrophil or white blood cell counts were most common with rare cases (generally 1 case) of biliary tract infection, duodenal ulcer, hypophosphatemia, increased lipase, sepsis, small intestinal hemorrhage, cholecystitis, duodenal stenosis, and hepatobiliary disorders.[46,47] Of particular importance, no cardiac untoward events were observed in these studies, which included a thorough cardiac evaluation based on an array of clinical cardiac assessments. (See IB for more details.) Clinical efficacy data available on TGFβ inhibitors are quite limited and it is premature to determine the potential for efficacy at this time.

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1.5.2. Rationale for Safety Monitoring Plan

1.5.2.1. Cardiac Disorders

Valvulopathy – Inhibition of the TGFβ pathways was associated in galunasertib nonclinical studies with a number of cardiac toxicities that were characterized by aneurysms and valvulopathy with associated degenerative and inflammatory changes.[50] CCI [redacted]

CCI [redacted] In addition, only patients with stable cardiac disease will be enrolled and monitored with periodic assessments of vital signs, electrocardiograms (ECGs), cardiac biomarkers (troponin, high-sensitivity C-reactive protein [hs-CRP], brain natriuretic peptide [BNP]), and Doppler echocardiography. Patients with any Grade 3 treatment-related cardiac event will be discontinued from the trial.

1.5.2.2. Hepatobiliary Disorders

Transaminasemia – Elevated transaminases with associated hepatocyte necrosis were observed in rat at the STD_{10} in the pivotal PF-06952229 toxicology study. At the highest non-severely toxic dose (HNSTD) in monkey, there were minimal reversible alanine transaminase (ALT) elevations (<2-fold) without associated microscopic findings. To mitigate potential hepatoxicity, standards adapted from the Food and Drug Administration (FDA)'s DILI guidance (July 2009) for patient exclusion, hepatic monitoring and discontinuation criteria are incorporated into the protocol.

1.5.2.3. Metabolism and Nutrition Disorders

Hypophosphatemia – Decreased serum phosphate was observed in the PF-06952229 nonclinical toxicology studies. The relevance of this finding in adults is unclear and substantive changes in serum phosphorus are not anticipated in the population to be enrolled in this clinical trial. Nevertheless, to mitigate any potential risk, serum phosphate will be included with requisite serum chemistry monitoring and regularly assessed throughout the study. Any confirmed treatment-related Grade 3 hypophosphatemia that does not resolve to baseline will result in dose modification or discontinuation from the trial.

1.5.2.4. Musculoskeletal and Connective Tissue Disorders

Bone/Skeletal disorders - Physeal and cartilage hypertrophy observed in the PF-06952229 toxicology studies is thought to be due to primary pharmacology of drug on bone physiology and in growing animals with open growth plate. Therefore, this finding is not anticipated since substantive bone remodeling is not expected in adults. Nevertheless, during the trial, with each Common Terminology Criteria for AE (CTCAE) grade level increase in total alkaline phosphatase, bone and liver fractionation will be obtained and an appropriate clinical evaluation will be conducted to determine the suitability of the patient continuation in the trial.

1.5.2.5. Respiratory, Thoracic and Mediastinal Disorders

Minimal hemorrhage in the lung that was generally accompanied by minimal mixed cell inflammation was observed in the rat pivotal study at PF-06952229 doses ≥10 mg/kg/day. There was no effect on respiratory function in the single dose safety pharmacology study in rats at 40 mg/kg. During the clinical trial, respiratory AEs and CT/MRI findings will be monitored closely, and an appropriate clinical evaluation will be conducted to determine the suitability of the patient continuation in the trial.

1.6. Overview of Enzalutamide

Enzalutamide will be provided by Pfizer as capsules for oral administration. More detailed information about the known and expected benefits and risks and reasonably expected AEs of enzalutamide may be found in the Investigator's Brochure, which is the SRSD for this study.

2. STUDY OBJECTIVES AND ENDPOINTS

Part 1A - PF-06952229 Single Agent Dose Escalation Phase in Patients With Advanced/Metastatic Tumors.

Primary Objective(s):	Primary Endpoint(s):
• 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.	• First-cycle DLTs. • AEs as graded by NCI CTCAE version 5.0. • Laboratory abnormalities as graded by NCI CTCAE version 5.0.
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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	• Pharmacokinetic parameters of PF-06952229. o Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, and as data permit, AUC_{inf}, CL/F, V_z/F, and $t_{1/2}$. o 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}). • PSA50 Response Rate for prostate cancer patients. • Response assessment will be based on PCWG2 for prostate cancer and RECIST 1.1 for other tumor types.
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Part 1B - Dose Escalation of PF-06952229 in Combination With Enzalutamide in Patients with mCRPC

Primary Objective(s):	Primary Endpoint(s):
• 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.	• First cycle DLTs in combination with enzalutamide for mCRPC. • AEs as graded by NCI CTCAE version 5.0. • Laboratory abnormalities as graded by NCI CTCAE version 5.0.
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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.	• 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}). • PSA50 Response Rate • Response assessment will be based on PCWG2 and RECIST 1.1.
CCI [redacted]	[redacted]

Part 2A - PF-06952229 Single Agent Dose Expansion Phase in mCRPC

Primary Objective(s):	**Primary Endpoint(s):**
• 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.	• AEs as graded by NCI CTCAE version 5.0. • Laboratory abnormalities as graded by NCI CTCAE version 5.0. • PSA50 Response Rate. • Response assessment will be based on PCWG2 and RECIST 1.1.
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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).	• ORR based on PCWG2 and RECIST 1.1. and time to event endpoints (DoR, PFS, OS, TTP, TTR). • 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}). • Assessment of levels of intra-tumor T cells (eg, CD8 IHC);
CCI [redacted]	[redacted]
[redacted]	[redacted]

Part 2B - Dose Expansion of PF-06952229 in Combination With Enzalutamide in Patients With mCRPC

Primary Objective(s):	Primary Endpoint(s):
• 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.	• AEs as graded by NCI CTCAE version 5.0. • Laboratory abnormalities as graded by NCI CTCAE version 5.0. • PSA50 Response Rate. • Response assessment will be based on PCWG2 and RECIST 1.1.
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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).	• ORR based on PCWG2 and RECIST 1.1. and time to event endpoints (DoR, PFS, OS, TTP, TTR). • Pharmacokinetic parameters of PF-06952229 (in at least 8 subjects). ○ 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}). • Peak and trough concentrations at selected cycles. • Assessment of levels of intra-tumor T cells (eg, CD8 IHC);
CCI [redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open-label, multi-center, multiple-dose, dose-escalation and expansion, safety, tolerability, PK, and PD 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 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 with enzalutamide conducted in patients who were previously treated for metastatic castration-resistant prostate cancer (mCRPC). The starting dose of PF-06952229 will be based on safety, PK, and potential efficacy, but will not exceed the MTD or MAD of Part 1A. Because of the potential DDI between enzalutamide and PF-06952229, the maximum PF-06952229 dose for the combination may be higher than the monotherapy MTD, but not higher than 800 mg BID.. Based on evolving PK, PD, and safety profiles, assessed in Part 1A, Part 1B may commence before reaching the MTD in Part 1A, 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.

The biomarker studies will be used to help understand the in vivo mechanism of action of the agent(s) studied as well as potential mechanisms of resistance. The studies may help in the future development of PF-06952229 as a single agent, or in combination with other compounds, and may provide information on tumor sub-types that may respond to the Investigational Product.

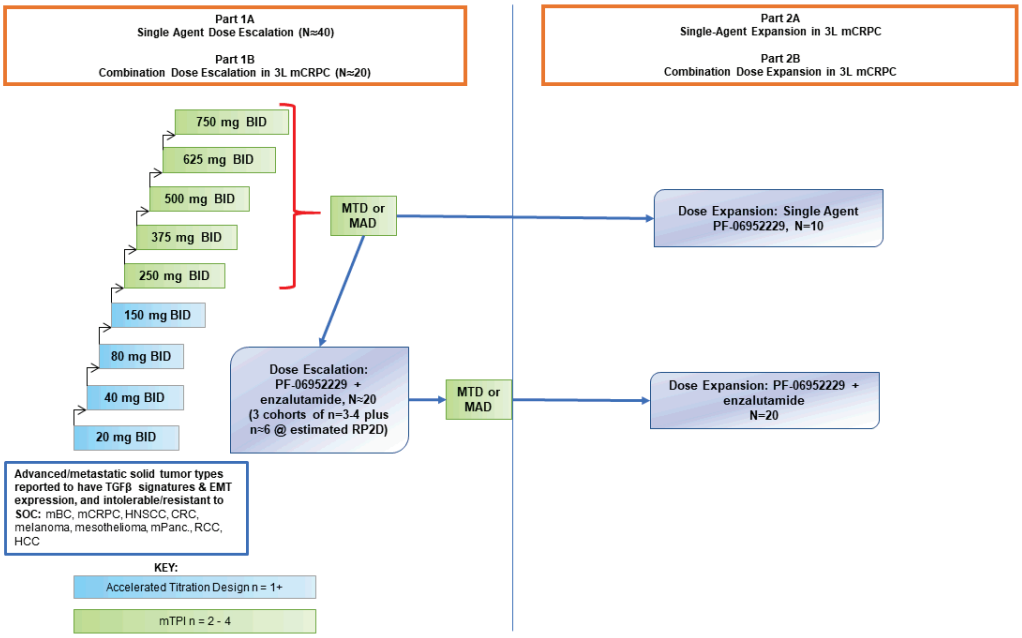
Approximately 90 patients are to be enrolled in this study. The total sample size may vary depending on the number of the dose levels with patients enrolled and the actual number of patients at each dose level. A maximum sample size of 40 patients may be needed to establish and confirm MTD in Part 1A, and approximately 20 patients may be needed for Part 1B. A maximum of 10 and 20 patients are planned for the expansion cohorts in Part 2A and Part 2B, respectively.

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, for 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 and PD time points may be reconsidered and amended during the study based on the emerging safety and PK and PD data.

Figure 2. Study Schema



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3.1.1. Part 1 Dose Escalation

3.1.1.1. Part 1A – Single Agent PF-06952229 in Advanced/Metastatic Solid Tumors

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.

3.1.1.2. Starting Dose

The starting dose of PF-06952229 will be 20 mg given twice daily (BID) orally as a regimen of 7 days on/7 days off in 28- day cycles. The rationale for selecting this starting dose is provided in Section 1.3.

3.1.1.3. Criteria for Dose Escalation

The initial dose escalation in Part 1A begins with an accelerated titration design followed by a standard escalation phase that will use a modified target probability interval (mTPI) approach. Initial dose levels for Part 1A are provided in Table 1 and intermediate dose levels may be considered if needed.

Table 1. PF-06952229 Dose Levels

DOSE LEVEL (DL)*	DOSE	Percent Increase From Previous Dose
DL -1	10 mg BID	-
DL 1** Starting dose	20 mg BID	-
DL 2	40 mg BID	100%
DL 3	80 mg BID	100%
DL 4	150 mg BID	88%
DL 5	250 mg BID	66%
DL 6	375 mg BID	50%
DL 7	500 mg BID	33%
DL 8	625 mg BID	25%
DL 9	750 mg BID	16.7%

*The proposed doses, schedule(s), and PK time points may be reconsidered or amended during the study based on the emerging safety and PK data. Intermediate doses may be considered when deemed necessary based on on-going evaluation of safety and toxicity data.
**Starting dose DL1. De-escalation to a lower dose level (DL-1) may be considered if DLT(s) at the starting dose are observed (see Table 2 on mTPI Dose Decision Rules).

In principle, all patients must be evaluated for a minimum DLT observation period of 28 days. However, if a patient discontinues close to Day 28 for reasons other than toxicity and due to an evident non drug-related event, the patient may be deemed evaluable for safety if safety assessments have been unremarkable and the investigator and sponsor's medical monitor both agree that the patient is evaluable for DLT safety observation.

The dose escalation in the study will stop if any of the following criteria is met:

- Approximately 40 patients have been achieved in Part 1A monotherapy dose escalation, or approximately 20 patients have been achieved in Part 1B combination dose escalation;
- 6 - 12 patients 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.

3.1.1.3.1. Acceleration Phase

The dose escalation in Part 1A – Monotherapy Dose Escalation will use the Accelerated Titration Design (ATD) as proposed by Simon[7] followed by a standard escalation phase that will use a mTPI approach. During the accelerated phase, initial cohorts will contain a minimum of 1 patient until the first instance of first-course CTCAE clinically significant grade ≥2 toxicity (as agreed upon by investigator and sponsor). With the occurrence of clinically significant grade ≥2 toxicity, a minimum of 2 additional patients will be treated at

that dose. If these 2 patients do not develop CTCAE grade ≥2 toxicity then the accelerated phase of the study with a minimum of 1 patient cohort will be continued. The dose escalations in this phase are in increments of approximately 80 - 100%, until reaching 250 mg BID, after which the design will revert to a standard escalation approach (mTPI) in order to obtain more comprehensive PK data. The accelerated phase will revert to standard escalation (see below for underlying methodology) if there is a second occurrence of first-course cycle CTCAE grade ≥2 or first instance of first-course cycle DLT.

3.1.1.4. Standard (mTPI) Escalation Phase

The proposed mTPI method for this protocol includes stopping rules and dose escalation/finding criteria which prevent the target DLT rate to reach ≥33% for determining the MTD. Targeting a DLT rate of 27.5% and an acceptable DLT interval (22.5% to 32.5%) will be utilized in both Parts 1A – Monotherapy Dose Escalation (beginning at Dose Level 5) and 1B – Combination Dose Escalation, and will also be used to monitor the DLTs so as not to cross toxicity boundaries in the expansion of a cohort. At least 3 DLT-evaluable patients will be required for the dose escalation decision based on mTPI beginning at Dose Level 5. Note provided the DLT rate for cardiac toxicity does not exceed 10%. The decision rules use a Beta (1,1) prior.

Table 2. mTPI Dose Decision Rules

DLT	n=1	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	E
1	D	S	S	S	S	S	E	E	E	E	E	E
2		DU	D	D	S	S	S	S	S	S	S	E
3			DU	DU	D	D	S	S	S	S	S	S
4				DU	DU	DU	DU	D	S	S	S	S
5					DU	DU	DU	DU	DU	D	S	S
6						DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

Source: https://udesign.laiyaconsulting.com/
E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial.

3.1.1.5. Part 1B – PF-06952229 in Combination With Enzalutamide in mCRPC

Part 1B is a dose-escalation of PF-06952229 in combination with enzalutamide conducted in patients who were previously treated for mCRPC. The starting dose of PF-06952229 will be based on safety, PK, and potential efficacy, but will not exceed the MTD or MAD of Part 1A. Because of the potential DDI between enzalutamide and PF-06952229, the maximum PF-06952229 dose for the combination may be higher than the monotherapy MTD, but not

higher than 800 mg BID. In addition to safety and tolerability, PF-06952229 PK exposure data may be reviewed for informed dose escalation. Based on evolving PK, PD and safety profiles, assessed in Part 1A, Part 1B may commence before reaching the MTD in Part 1A, and will follow an mTPI design as described in Section 3.1.1.4.

Enzalutamide (a CYP3A4 inducer) is predicted to decrease the PK of PF-06952229 (a CYP3A4 substrate) by 70% (Section 1.2.4). PF-06952229 is not expected to impact the PK of enzalutamide, therefore a fixed dose of enzalutamide is 160 mg QD, administered on a continuous basis. Dose modifications to enzalutamide will not be allowed during the DLT evaluation period.

3.1.2. Part 2 Dose Expansion

3.1.2.1. Part 2A – Single Agent PF-06952229 in mCRPC

PF-06952229 will be evaluated as a monotherapy in patients with mCRPC in this dose expansion cohort. An additional 10 patients will be enrolled to confirm the safety of the MTD determined in Part 1A (monotherapy dose escalation) and estimate the effect of anti-tumor activity of PF-06952229 as a monotherapy in patients with mCRPC.

3.1.2.2. Part 2B – PF-06952229 in Combination with Enzalutamide in mCRPC

PF-06952229 will be evaluated in combination with enzalutamide in patients with mCRPC in this dose expansion cohort. An additional 20 patients will be enrolled to confirm the safety of the MTD determined in Part 1B (combination dose escalation) and estimate the effect of anti-tumor activity of PF-06952229 in combination with enzalutamide in patients with mCRPC. Enzalutamide will be administered per the protocol.

3.2. 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 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.

3.3. 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.

3.4. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further investigation based on Phase 1 dose escalation and expansion study results. Based on the safety, tolerability, and PK/PD data from the Part 1A Monotherapy Dose Escalation cohorts, the single agent recommended dose for expansion will be selected as an estimate of monotherapy RP2D. After expansion cohorts with larger sample size and sufficient data, the final RP2D will be made by the sponsor based on the recommendation from investigators and study team. The determination of RP2D will be based on safety, tolerability, and early signs of clinical efficacy and benefit.

Based on the safety, tolerability, and PK/PD data from Part 1B combination dose escalation, the combination recommended dose for expansion will be selected as an estimate of combination RP2D. Similarly, the final combination RP2D will be determined after the combination expansion cohort. Combination RP2D may be different from monotherapy RP2D due to potential overlap toxicity or DDI.

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4. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. For Part 1A (monotherapy dose escalation phase): Histological or cytological diagnosis of a solid tumor that is advanced/metastatic, patients are intolerant to standard treatment, resistant to standard therapy or for which no standard therapy is available for the following tumor types:

    - Breast cancer;
    - Prostate cancer (mCRPC - testosterone less than 50 ng/dL);
    - Squamous cell cancer of the head and neck;
    - Melanoma;
    - Mesothelioma;
    - Pancreatic cancer;
    - Colorectal cancer;
    - Renal cell carcinoma;
    - Hepatocellular cancer.

2. For Part 1B (Combination Dose Escalation Phase): histological or cytological diagnosis of mCRPC (castration is defined as having a serum testosterone less than 50 ng/dL due to medical or surgical castration), patients who are intolerant to standard treatment, resistant to standard therapy, or refuse to standard therapy.

3. Part 2A and Part 2B:

   - Histologically or cytologically confirmed prostate adenocarcinoma metastatic disease.

   - Effective castration with serum testosterone levels <0.5 ng/mL (1.7 nmol/L).

   - Having received 3 or more cycles of prior docetaxel therapy (before or after abiraterone).

   - Having PD while receiving abiraterone acetate within 12 months of abiraterone treatment initiation (≤12 months).

   - Progressive disease (PD) by:

     a. Progression in measurable disease per RECIST 1.1 criteria. Patient with measurable disease must have at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded). Each lesion must be at least 10 mm when measured by computed tomography (CT) (CT scan thickness no greater than 5 mm) or magnetic resonance imaging (MRI). Lymph nodes should be ≥15 mm in short axis. As defined by PCWG2, if lymph node metastasis is the only evidence of metastasis, it must be ≥20 mm in diameter when measured by spiral CT or MRI. Previously irradiated lesions, primary prostate lesion, and bone lesions will be considered non-measurable disease, or

     b. Appearance of 2 or more new bone lesions (PCWG2). They must be confirmed by other imaging modalities (CT; MRI) if ambiguous results, or

     c. Rising PSA defined (PCWG2) as at least 2 consecutive rises in PSA to be documented over a reference value (measure 1) taken at least 1 week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (second beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the second measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the second measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to enrollment. A PSA value of at least 2 ng/mL is required at study entry.

   - Prior abiraterone acetate must be stopped at least 2 weeks before study treatment.

4. Patients must have recently obtained archival tumor tissue available for submission to the sponsor (except for Part 2A – monotherapy dose expansion). Patients enrolled in Part 1 and Part 2 should have access to their archival formalin-fixed paraffin-embedded material, collected within 6 months of screening, containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or whenever possible, consent to undergo a biopsy during screening. The sponsor should be contacted if obtaining a new biopsy is not medically feasible for approval to enroll, prior to initiating screening activities.

5. Patients entering the study in the subgroup(s) requiring mandatory pre- and on-treatment tumor biopsies in Part 2A and 2B must have a tumor amenable to biopsy and consent to these planned biopsy procedures. The sponsor should be contacted if obtaining a pre-treatment and on treatment biopsies is not medically feasible for approval to enroll, prior to initiating screening activities.

6. Age ≥18 years.

7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

8. Adequate bone marrow function (see Appendix 3), including:

   - Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
   - Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
   - Hemoglobin ≥9 g/dL.

9. Adequate renal function, including serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution. In equivocal cases, a 24-hour urine collection test can be used to estimate the creatinine clearance more accurately.

10. Adequate liver function, including:

    - Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome;
    - Aspartate and alanine aminotransferase (AST and ALT) ≤2.5 x ULN, ≤5.0 x ULN if there is liver involvement by the tumor;
    - Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).

11. Serum phosphate within normal range (if abnormal, must be nonclinically significant per the Investigator and approval for patient inclusion after agreement from sponsor.

12. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for alopecia and those listed in the specific exclusion criteria.

13. For Part 1A monotherapy dose escalation: serum pregnancy test (for females of childbearing potential) negative at screening.

14. For Part 1A monotherapy dose escalation: female patients of nonchildbearing potential must meet at least 1 of the following criteria:

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and must have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    - Have medically confirmed ovarian failure.

    All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

15. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

16. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

4.2. Exclusion Criteria

Patients with any of the characteristics/conditions listed below will not be included in the study:

Any labs may be repeated for confirmation. Only the lab result requiring confirmation must be repeated, not the entire panel.

1. For Parts 1B; current or prior treatment with enzalutamide within 24 days prior to first dose

1. For 2A and 2B:

    - Prior chemotherapy other than docetaxel for prostate cancer, except estramustine, adjuvant/neoadjuvant treatment completed >3 years ago;

    - Less than 28 days elapsed from prior treatment with chemotherapy, immunotherapy, radiotherapy, or surgery to the time of study enrollment.

2. Central Nervous System (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by baseline brain MRI (or CT with contrast if MRI is medically contraindicated), clinical symptoms, cerebral edema, and/or progressive growth. If contrast is medically contraindicated, a non-contrast CT scan may be performed.

3. Patients with a history of CNS metastases or cord compression.

4. Liver metastases at baseline as evidenced by CT scan or MRI that may be at risk for bleeding, such as those that are >1 cm,

5. Patients with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement). **Note**: Patients with indwelling catheter for drainage, or requirement for drainage no more frequently than monthly will be allowed.

6. Any other active malignancy within 3 years prior to study entry, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.

7. Patients with a history of clinically significant tumor bleeding (except for bleeding in a post-operative setting), coagulopathy or arterio-venous malformations (AVM) or aneurysms in the CNS, liver, lung or other major organ of the body. Patients with known Osler-Weber-Rendu disease, Hemophilia A, Hemophilia B (Christmas Disease), Von Willibrand's Disease, Factor 13 deficiency and Factor 7 deficiency, antibodies to Factors 8 and 7, history of other bleeding diatheses and abnormal INR values.

8. Evidence of a tumor that compresses or invades major blood vessels or tumor cavitation that in the opinion of the investigator is likely to bleed.

9. Major surgery within 4 weeks prior to first dose.

10. Prior organ transplantation including heart and allogeneic stem-cell transplantation.

11. Radiation therapy within 4 weeks prior to study entry. Note: Patients who have received radiotherapy must have recovered from any reversible side effects, such as nausea and vomiting.

12. Last anti-cancer therapy including investigational drug(s) within 28 days (or 5 half-lives, whichever is shorter) prior to study entry excluding hormonal therapy.

13. Active and clinically significant bacterial, fungal, or viral infection, including known hepatitis B virus (HBV), known hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) - related illness. In equivocal cases, with positive serology, those patients with a negative viral load are potentially eligible provided the other entry criteria are met. Note: Inclusion of patients with well controlled HIV, HBV or HCV can be discussed with sponsor on a case by case basis.

    - COVID-19/SARS-CoV2: Refer to Appendix 8 for further information.

14. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism; deep venous thrombosis (DVT); arterial occlusive disease; ongoing cardiac dysrhythmias of National Cancer Institute (NCI) CTCAE Grade ≥2, atrial fibrillation of any grade that is uncontrolled, or QTcF interval >470 msec at screening. Note: There is an exception where a cardiac rhythm device/pacemaker is fitted and results in QTcF >470 msec.

15. Anticoagulation therapy with heparin, low molecular weight heparin, vitamin K antagonists, anti-platelet agents, or factor Xa inhibitors throughout the study and for at least 28 days post the last dose of study treatment. (If anticoagulation therapy is medically indicated on trial, patients should stop treatment with PF-06952229. For those requiring temporary anticoagulant therapy, resumption of PF-06952229 treatment may be permitted after discussion with the Sponsor. In any other case, study treatment should be permanently discontinued, and the patient should enter the follow-up portion of the trial.)

16. Moderate or severe heart valve function defect including moderate or severe valve stenosis or regurgitation.

17. Evidence or history of septal aneurysm, other heart aneurysm, or any aneurysm of the major vessels.

18. Grade ≥3 cardiac troponin I at baseline.

19. Left ventricular ejection fraction (LVEF) of ≤50% or significant valvular regurgitation.

20. Hypertension that cannot be controlled by medications (>150/90 mmHg despite optimal medical therapy) or requiring more than 2 medications for adequate control.

21. Clinically significant non-healing or healing wounds.

22. For patients entering the combination with enzalutamide arm, history of seizures other than isolated febrile seizure in childhood.

23. Has a history of a cerebrovascular accident or transient ischemic attack less than 6 months ago.

24. Known or suspected hypersensitivity to active ingredient/excipients of PF-06952229 or enzalutamide.

25. Other acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

26. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

27. For Part 1A Monotherapy Dose Escalation: Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

28. For Part 1B Combination Dose Escalation, Part 2A Monotherapy Expansion, and Part 2B Combination Dose Expansion: fertile male patients and female partners of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose for monotherapy (Part 2A) or for at least 3 months after the last dose for combination therapy (Part 1B and Part 2B).

29. Inability to consume or absorb study drug, including but not limited to:

    - Active inflammatory gastrointestinal (GI) disease, known diverticular disease or previous gastric resection or lap-band surgery. Impairment of gastro-intestinal function or GI disease that may significantly alter the absorption of PF-06952229, such as history of GI surgery with may result in intestinal blind loops and patients with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhea of CTCAE Grade >1.

30. Current use or anticipated need for food or drugs that are known strong and moderate CYP3A4/5 inhibitors, including their administration within 10 days or 5 half-lives of the CYP3A4/5 inhibitor, whichever is longer, prior to first dose of investigational product. A list of CYP3A4/5 inhibitors are provided in Appendix 9 (Section 5.7).

31. Current use or anticipated need for drugs that are known strong and moderate CYP3A4/5 inducers, including their administration within 10 days or 5 half-lives of the CYP3A4/5 inducer, whichever is longer, prior to the first dose of investigational product (See Section 5.7). A list of CYP3A4/5 inducers is provided in Appendix 9.

32. Have initiated bisphosphonates or approved receptor activator of nuclear factor kappa B -ligand (RANK-L) targeted agents (for example, denosumab) <14 days prior to study entry, unless there is agreement with the medical monitor.

33. Active, known or suspected autoimmune diseases including inflammatory bowel disease (including ulcerative colitis and Crohn's disease), rheumatoid arthritis, systemic progressive sclerosis, systemic lupus erythematosus (SLE), autoimmune vasculitis (eg, Wegener's Granulomatosis), CNS or motor neuropathy considered to be of autoimmune origin (eg, Gullian-Barre Syndrome, Myasthenia Gravis, Multiple Sclerosis).

4.3. Lifestyle Requirements

In this study, fertile male patients and female patients who are of childbearing potential will receive PF-06952229. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 28 days after the last dose of monotherapy (Part 1A and Part 2A) or for at least 3 months after the last dose of combination therapy (Part 1B and Part 2B). The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient and his or her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

All sexually active male patients must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of monotherapy (Part 1A and Part 2A), and for at least 3 months after the last dose of combination therapy (Part 2A and Part 2B).

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity ultraviolet B (UVB) light sources such as tanning beds, tanning booths and sunlamps. Patients should be encouraged to apply sunscreen/sunblock daily.

Patients should not eat or drink products containing grapefruit from 7 days prior to enrollment until end of the study or discontinuation.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, Investigational Medicinal Product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the Investigational Medicinal Products are PF-06952229 and enzalutamide.

Refer to the respective IBs for further information on PF-06952229 and enzalutamide.

5.1. Allocation to Treatment

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will e-mail or fax a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a patient identification number and supply this number to the site. The patient identification number will be used on all study-related documentation at the site.

No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the patient's enrollment;
- Specification of the dose level for that patient and;
- Permission to proceed with dosing the patient.

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

5.2. Patient Compliance

On PK clinic days, all doses of study treatments will be administered by the appropriately designated study staff at the investigational site.

Patients will be required to return all unused study treatment at the beginning of each cycle. The number of tablets/capsules returned by the patient will be counted, documented, and recorded.

On drug start and stop days, compliance telephone calls will occur for a minimum of the first 2 cycles to ensure compliance to the study drug schedule. Additionally, a patient diary will be provided to the patients to aid in patient compliance with the dosing instructions and used to support the accountability process. The diary will be maintained by the patient to include missed or changed doses (PF-06952229 and enzalutamide, where applicable). The number of PF-06952229 tablets remaining will be documented and recorded at each clinic visit or Day 1 of each cycle. The patient diary may also be used to support this part of the accountability process. CCI [redacted]

Enzalutamide will be administered in accordance with the protocol. All PF-06952229 and enzalutamide administration will be documented on the corresponding investigational product administration case report form (CRF). The information regarding diary completion, requirement to return all bottles and accountability documentation will also be performed on patients receiving enzalutamide (where applicable).

5.3. Investigational Product Supplies

PF-06952229 and enzalutamide will be supplied by Pfizer. Study centers will receive PF-06952229 and enzalutamide (for Part 1B and Part 2B) prior to enrollment of the first patient.

The clinical site pharmacy will dispense the supply that is appropriate for the patient.

5.3.1. Dosage Form(s) and Packaging

PF-06952229 will be provided as tablets for oral administration. The 5 mg, 25 mg, and 125 mg tablets will be supplied in separate bottles and labeled according to local regulatory requirements.

5.3.1.1. Enzalutamide

Enzalutamide will be provided by Pfizer as capsules for oral administration. The enzalutamide 40 mg capsules will be supplied in bottles and labeled according to local regulatory requirements.

5.3.2. Preparation and Dispensing

The study treatment should be dispensed at each visit per the schedule of treatment. A qualified staff member will dispense the investigational product in the bottles provided, in quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site at the next study visit.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of all investigational agents or drugs used in this study, including but not limited to: PF-06952229 and enzalutamide.

Dose adjustments or discontinuations should be managed according to the Section 5.4.4 below. However, per the investigator's discretion, other dose adjustments may be discussed with the sponsor.

Any unused product or waste material should be disposed of in accordance with local requirements.

5.4. Administration

5.4.1. PF-06952229

Patients will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

PF-06952229 will be administered twice a day (BID) on an intermittent basis (7 days on/7 days off). A cycle is defined as 28 days, regardless of missed doses or dose delays.

PF-06952229 will be administered orally on an empty stomach without adjustment for body size at every cycle, CCI [redacted] No food or liquids other than water will be consumed for 2 hours before and 1 hour following each dose throughout the study.

Patients should be instructed to take their medication at approximately the same time each day (approximately every 12 hours) and to not take more than the prescribed dose at any time.

On days of scheduled clinic visits (see the Schedule of Activities for Parts 1 and 2), morning (AM) dosing of PF-06952229 should be undertaken in the clinic (ie, not at home). On those days where the morning dose of PF-06952229 is held due to a specific study visit, the second BID dosing should be taken no sooner than 8 hours, and no later than 16 hours post the first BID dosing (allowable treatment window ±4 hours). On Day 1 of Cycle 1 and Cycle 2 in Part 1B and Part 2B, only a single dose of PF-06952229 to be given to evaluate PF-06952229 PK sampling up to 24 hr time point (ie, pre-dose on Day 2 of Cycle 1 and Cycle 2).

If a patient misses a dose by more than 4 hours, he/she must be instructed not to "make it up" but to resume the subsequent dose as prescribed.

If a patient vomits 1 hour or more after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses and site should discuss dosing with sponsor.

If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of PF-06952229.

In Part 1B and Part 2B of the study, PF-06952229 is given in combination with enzalutamide in patients with mCRPC. After an appropriate dose of PF-06952229 is selected in the combination dose escalation cohort (Part 1B), the combination will be tested in a dose expansion cohort (Part 2B) of enzalutamide and PF-06952229.

A dosing diary will be given to the patient to support at-home dosing.

5.4.2. Food Requirements

5.4.2.1. Food Requirements CCI [redacted]

Oral PF-06952229 will be administered BID with at least 8-oz (240 mL) of water on an empty stomach. No food or liquids other than water will be consumed for at least 2 hours before and 1 hour following each dose throughout the study. CCI [redacted]

CCI [redacted]

CCI

[redacted]

5.4.3. Enzalutamide Administration

Enzalutamide capsules are to be self-administered once daily on an outpatient basis and can be taken with or without food.

Patients receiving enzalutamide should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

If a patient misses a dose by more than 8 hours, he/she must be instructed not to "make it up" but to resume the subsequent dose as prescribed. If a patient vomits 1 hour or more after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses and site should discuss dosing with sponsor.

A dosing diary will be given to the patient to support at-home dosing.

5.4.4. Recommended Dose Modifications

Dose modifications for enzalutamide due to toxicity or intolerable side effects are described in Sections 5.4.5 and Section 5.4.6.

Every effort should be made to administer PF-06952229 on the planned dose schedule (28-day cycle, 7 days on/7 days off).

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modifications should be based on the worst

toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

- No dose adjustments or reductions are allowed and patients are to discontinue the study treatment at any signs of medically significant cardiac toxicity.

- Patients will continue to receive the reduced dose as a result of AEs even after toxicity recovery.

- Patients who experience a second discreet DLT-equivalent toxicity will be discontinued from the study unless they are expected to continue to receive clinical benefit after discussion with the sponsor medical monitor or designee.

- Despite dose reductions or delays of PF-06952229 the patient will retain the same 28-day cycle of 7 days on and 7 days off. Note: If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

- In the case where a patient is at a dose level deemed to be above a safe level (MTD determined below this dose level) discussion between the Investigator and the sponsor to determine what is in the best interest of the patient.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery, and if required, dose reduction during a given treatment cycle;

- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;

- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

5.4.5. Dosing Interruptions

Patients experiencing Grade 3 or 4 potentially PF-06952229 treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment interrupted.

Consider permanent discontinuation of study treatment for related Grade 4 AEs of any duration. An exception to this such as emesis, as well as clinically insignificant laboratory abnormalities that resolve within 3 days on optimum treatment should be discussed between the investigator and Pfizer or its delegate.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

Doses may be held for up to 2 weeks until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or may even delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. Patients must maintain their original dosing schedule regardless of dose reductions or holds. The need for a dose reduction at the time of treatment resumption should be based on dose reduction criteria, unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the patient may need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

For enzalutamide, if a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect (at the PI's discretion), withhold dosing for 1 week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg). Please contact Sponsor's medical monitor for any questions.

5.4.6. Dose Delays

Re-treatment following treatment interruption for PF-06952229 treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC ≥1,000/mm^3;
- Platelets count ≥50,000/mm^3;
- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or at the investigator's discretion, Grade ≤2 if not considered a safety risk for the patient).

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 4 weeks of treatment interruption, PF-06952229 may be resumed. Refer to the Dose Reductions section for AEs that require dose reduction at the time of treatment resumption.

If these conditions are not met, treatment resumption must be delayed for up to a maximum of an additional 2 weeks. If patients require discontinuation of PF-06952229 for more than 6 weeks at any time during the study, then study treatment should be permanently discontinued unless the investigator's benefit/risk assessment suggests otherwise after discussion with the sponsor's medical monitor or designee.

If a treatment interruption continues beyond Day 14 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

If patients require discontinuation of study drug for more than 4 weeks at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise and after discussion with the sponsor's medical monitor.

For enzalutamide, if a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect (at the PI's discretion), withhold dosing for 1 week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg). Please contact Sponsor's medical monitor for any questions.

5.4.7. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-06952229 dose may need to be reduced when treatment is resumed.

Dose reduction/discontinuation of PF-06952229 should be considered before or concurrently with enzalutamide (for patients receiving combination of PF-06952229 and enzalutamide).

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved within 2 weeks.

Dose reduction of PF-06952229 associated with treatment related toxicity by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and case report form (CRF).

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intrapatient dose re-escalation is not allowed.

Patients experiencing a DLT during the 28 day safety window and who in the judgment of the investigator and sponsor are benefiting from therapy may resume dosing at the next lower dose level once adequate recovery is achieved.

Hold PF-06952229 for related Grade 3 AEs with subsequent dose-reduction, if such AEs return to Grade ≤1 or baseline within two weeks.

Exclusions to this include emesis, and clinically insignificant laboratory abnormalities that resolved within two days on optimum treatment and dose reduction may not be required.

Patients who require a treatment interruption >4 weeks should discontinue the study drug thought to be responsible for the treatment interruption.

Table 3. Dose Modifications for PF-06952229 - Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Serum bilirubin (Guidance for non-Gilbert's Syndrome patients. Agreement between sponsor and investigator is required for these patients).	Continue at the same dose level	Continue at the same dose level	When serum bilirubin ≥2 x ULN: Hold administration until recovery to Grade 0-1 within 2 weeks, serum bilirubin <2 xULN or baseline and reduce by 1 dose level. Discontinue dose if dose delay is more than 2 weeks.* If toxicity reoccurs despite reduction, patient may be dose reduced again by another dose level upon recovery to Grade 0-1 or baseline within 2 weeks unless the patient is in the first dose group, then only 1 dose reduction is allowed. Prompt palliative measures are strongly encouraged (eg, anti-emetics).	Patients who experience related Grade 4 non- hematologic toxicities despite optimal medical intervention should be discontinued from the study. *
Thrombocytopenia	Continue at the same dose level.	Continue at the same dose level.	Hold PF-06952229 until platelets ≥75,000/mm3. For platelet counts 10,000 – 25,000/mm^3, continue monitoring every 3 days until recovery to ≥25,000/mm3 (Grade 3 or less) within 2 weeks. For platelet counts ≤10,000/mm3 monitor daily until recovery to ≥25,000/mm3 (Grade 3 or less) within 2 weeks. Reduce PF-06952229 by 1 dose level. If toxicity reoccurs despite dose reduction, patient may either be held until recovery within 2 weeks and continuation at same dose, or undergo further dose reduction by another dose	Consider Permanent discontinuation of study drugs for related Grade 4 AEs of any duration.

Table 3. Dose Modifications for PF-06952229 - Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
			level unless the patient is in the first dose group, then only 1 dose reduction is allowed.	
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, within 2 weeks then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.*	Permanent discontinuation of study drugs for related Grade 4 AEs of any duration. * (Exclusion to this discontinuation for emesis, and clinically insignificant laboratory abnormalities that resolve within two days on optimum treatment, additional exclusions will require agreement between the investigator and sponsor).
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline within 2 weeks, then resume treatment at the same dose level.**	Permanent discontinuation of study drugs for related Grade 4 AEs of any duration.** (Exclusion to this will require agreement between the investigator and sponsor).
Acute reductions in hemoglobin	Mild symptoms; investigate for tumor hemorrhage or other sources of bleeding.	Moderate symptoms. For acute hemoglobin reduction ≥2g/dL, hold dose and investigate for tumor hemorrhage or other sources of bleeding.	For acute unexplained G ≥3 anemia (hemoglobin <8.0 g/dL), restore blood/blood volume and investigate for tumor hemorrhage or other sources of bleeding. Consider permanent discontinuation. Continuation will require agreement with Sponsor, hemoglobin >9.0 g/dL and complete resolution of the tumor hemorrhage/ bleeding event.	For acute unexplained G ≥4 anemia, replace blood/blood volume and investigate for tumor hemorrhage or other sources of bleeding. Permanent discontinuation of study drug.

*Patients may continue on trial if they are receiving clinical benefit after discussion between the investigator and sponsor.
**Cycle will not be extended to cover for the missing doses.

Nausea, vomiting, or diarrhea should follow guidance for the below:

Table 4. Nausea, Vomiting, or Diarrhea, Cardiac Toxicity Dose Modification Guidance

Initial management or low-grade symptoms	Follow-up or higher-grade symptoms
Dyspepsia Consider starting or giving prescription antacids (not PPIs.	For Grade ≥2, consider dose interruption until dyspepsia back to baseline. Can restart at starting dose or dose modify (eg, 1 level) depending on the severity of symptoms and other contributing factors. Consider referral to gastroenterology for evaluation of Helicobacter pylori, possible endoscopy if Grade ≥2 symptoms persist despite appropriate therapy with antacids and dose interruption.
Diarrhea Prescribe loperamide or diphenoxylate/atropine; begin if diarrhea ≤ Grade 1.	Grade 2: interrupt PF-06952229; restart when it is Grade ≤1 at same dose or at dose reduction, depending on severity of symptoms and other contributing factors.
Nausea/emesis Pretreatment with antiemetics is not required for PF-06952229. Patient education regarding this common side effect is essential, and prescriptions for prochlorperazine, 5-HT3 antagonists, or other antiemetics of choice should be given along with instructions and indications for use if nausea/emesis is Grade 1.	Grade 2: interrupt PF-06952229; consider adding a second antiemetic per NCCN guidelines; restart PF-06952229 when it is Grade ≤1 at same dose or at a dose reduction based on the severity of symptoms.
Cardiac Toxicity	No dose adjustments or reductions are allowed, and patients are to discontinue the study treatment at any signs of medically significant cardiac toxicity.

For enzalutamide, if a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect (at the PI's discretion), withhold dosing for 1 week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg). Please contact Sponsor's medical monitor for any questions.

5.4.8. Study Stopping Rules and Patient Discontinuation

If the incidence of all bleeding events (all Grades) that are related to PF-06952229 is observed above 25%, the trial will be suspended.

All Grade 3 or Grade 4 bleeding events that are related to PF-06952229 will result in trial discontinuation for any patient who experience such clinical findings.

Any subsequent Grade 3 or Grade 4 bleeding event that is related to PF-06952229 will trigger a full review of overall safety of PF-06952229 and an assessment of the benefit/risks of this molecule in the studied patient population.

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take home investigational products.

5.6. Investigational Product and Study Treatment Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product and study treatment supplies. All investigational products and study treatment will be accounted for using a drug accountability form/record. All bottles of study treatments must be returned to the investigator by the patient at every visit and at the end of the trial.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician (including bisphosphonates or approved RANK ligand (RANK-L) targeted agents (for example, denosumab).

All concomitant treatments, blood products, as well as nondrug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

Anticoagulation therapy with heparin, low molecular weight heparin, vitamin K antagonists, anti platelet agents, or factor Xa inhibitors is prohibited throughout the study and for at least 28 days post the last dose of study treatment. If anticoagulation therapy is medically indicated on trial, patients should stop treatment with PF-06952229. For those requiring temporary anticoagulant therapy, resumption of PF-06952229 treatment may be permitted after discussion with the Sponsor. In any other case, study treatment should be permanently discontinued, and the patient should enter the follow-up portion of the trial.

Because inhibition of CYP3A4/5 isoenzymes may increase PF-06952229 exposure leading to potential increases in toxicities, the use of known strong and moderate inhibitors are not permitted within 10 days or 5 half-lives of the CYP3A4/5 inhibitors, whichever is longer prior to the first dose of PF-06952229. A list of CYP3A4/5 inhibitors is provided in Appendix 9.

Because induction of CYP3A4/5 isoenzymes may decrease PF-06952229 exposure leading to potential decrease in efficacy, the use of strong or moderate CYP3A4/5 inducers is not permitted within 10 days or 5 half-lives of CYP3A4/5 inducers, whichever is longer prior to the first dose of PF-06952229. A list of CYP3A4/5 inducers is provided in Appendix 9.

5.7.1. Proton-Pump Inhibitors

Acid reducing agents (ARAs) may decrease PF-06952229 absorption and exposure. The potential impact to absorption and exposure may be the greatest with proton pump inhibitors (PPIs). When possible patients who are currently taking PPIs should be switched to antacids

or H2-Receptor antagonists (see below) at least 14 days prior to Cycle 1 Day 1 and continue with these alternative ARAs throughout the study.

In Part 1A, Part 1B, and Part 2B, if the patient starts the study treatment period currently taking a PPI, the dose and frequency should be recorded in the appropriate CRF page and the patient should maintain this treatment until after Cycle 2 Day 1 visit, to allow for more accurate estimation of the impact of CCI enzalutamide (Part 1B, and Part 2B) on PF-06952229 exposure. If the patient stops or alters treatment with PPI during this period, this should be recorded in the CRF.

5.7.2. Antacids or H2-Receptor Antagonists

Recommendations about the use of antacids or H2-receptor antagonists and PF-06952229 dosing include the following (but are not limited to): cimetidine, famotidine, nizatidine, ranitidine. If needed, administer H2-receptor antagonists with a staggered dosing regimen (twice daily). The dosing of PF-06952229 should occur at least 10 hours after H2-receptor antagonist evening dose and 2 hours before the H2-receptor antagonist morning dose. However, if needed, local antacids should be given at least 2 hours before or at least 2 hours after PF-06952229 administration.

5.8. Other Anti-tumor/Anti-Cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while patients are receiving study treatment. Additionally, the initiation of new concurrent vitamins or herbal supplements is not permitted unless discussed and agreed with the sponsor.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PF-06952229 with radiotherapy, PF-06952229 treatment should be interrupted during palliative radiotherapy, stopping 14 days before and resuming treatment after recovery to baseline.

5.9. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

Patients currently being treated with a gonadotropin-releasing hormone agonist (GnRH agonist) may continue treatment while on clinical study C3881001 as long as the GnRH agonist treatment has been well tolerated for at least 3 months prior to study entry. If patients have had tolerability issues with GnRH agonists, such patients may be allowed to enroll with agreement of the Pfizer medical monitor.

5.9.1. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first 14 days of Cycle 1, but they may be used to treat treatment emergent neutropenia as

indicated by the current American Society of Clinical Oncology guidelines or the relevant full prescribing information for the growth factor.

Erythropoietin or other erythropoiesis stimulating agents (ESAs) may be used at the investigator's discretion for the supportive treatment of anemia as described in current American Society of Clinical Oncology/American Society of Hematology guidelines or the relevant full prescribing information.

5.9.2. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is not permitted in the first cycle. Primary prophylaxis in subsequent cycles is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected DDI and assuming the drug is not included in the Concomitant Treatment(s) section.

5.9.3. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected DDI and assuming the drug is not included in the Concomitant Treatment(s) section.

5.9.4. Corticosteroids

Chronic systemic corticosteroid use (prednisone >15 mg/day or equivalents) for palliative or supportive purposes is permitted. However, corticosteroids use for a short duration (eg, ≤15 mg/day of prednisone, for 2 weeks) as symptomatic treatment on individual basis may be considered after discussion with sponsor's medical monitor or designee. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

5.9.5. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06952229 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06952229 is recommended at least 14 days prior to surgery. Postoperatively, the decision to reinitiate PF-06952229 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see the Schedule of Activities and Assessments sections.

6.2. Study Period

For the treatment period procedures, see the Schedule of Activities and Assessments sections.

6.3. Follow-up

For follow-up procedures see the Schedule of Activities and Assessments sections.

6.4. Patient Withdrawal

Withdrawal of Consent:

Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to Follow-Up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal Section) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Patient may permanently discontinue study treatment (definitive discontinuation). Reasons for definitive discontinuation of study treatment may include the following:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

Note that discontinuation of study treatment does not represent withdrawal from the study. If study treatment is definitively discontinued, the patient will remain in the study to be evaluated for AEs. See the Schedule of Activities for data to be collected at the time of discontinuation of study treatment and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study treatment, it must be documented on the appropriate CRF/in the medical records whether the patient is discontinuing further receipt of study treatment or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

A patient may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

At the time of discontinuing from the study, if possible, an end of treatment visit should be conducted. See the Schedule of Activities for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

Subsequent to the follow-up period, overall survival (OS) follow-up will be conducted by telephone every 8 weeks (± 7 days) until end of the entire study (2 years after last patient first treatment). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call.

If the patient refuses further visits, the patient should continue to be followed for survival (if survival is a secondary endpoint) unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study-specific evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessment

Safety assessments will include collection of AEs, serious AEs (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

For alternative safety assessment logistics during public emergencies such as the COVID-19 pandemic, refer to Appendix 8.

7.1.1. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female patients of childbearing potential, 2 negative pregnancy tests are required before receiving PF-06952229 (1 negative pregnancy test at screening and 1 at the baseline visit immediately before PF-06952229 administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit and within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1) before the patient may receive the PF-06952229. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be repeated at every treatment cycle up to Cycle 3 and every other cycle thereafter during the active treatment period, and at the end of study treatment to confirm that the patient has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study.

7.1.2. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE version 5.0) timing, seriousness, and relatedness.

7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analysed at local laboratories.

Safety Laboratory Tests

<table>
<tr><th>Hematology</th><th>Chemistry</th><th>Coagulation</th><th>Urinalysis</th><th>Pregnancy Test</th></tr>
<tr><td>Hemoglobin</td><td>ALT</td><td>PT or INR</td><td rowspan="5">Urine dipstick for urine protein: If (greater than 1+), collect 24-hr and microscopic (Reflex Testing)</td><td rowspan="5">For female patients of childbearing potential, serum or urine</td></tr>
<tr><td>Platelets</td><td>AST</td><td>PTT</td></tr>
<tr><td>WBC</td><td>Alk Phos</td><td></td></tr>
<tr><td>Absolute Neutrophils</td><td>Sodium</td><td></td></tr>
<tr><td>Absolute Lymphocytes</td><td>Potassium</td><td></td></tr>
<tr><td>Absolute Monocytes</td><td>Magnesium</td><td></td><td rowspan="4">Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)</td><td>SEROLOGY</td></tr>
<tr><td>Absolute Eosinophils</td><td>Chloride</td><td></td><td>Hepatitis B testing**</td></tr>
<tr><td rowspan="2">Absolute Basophils</td><td rowspan="2">Total calcium</td><td rowspan="2"></td><td>Hepatitis C virus Antibodies**</td></tr>
<tr><td>Human immunodeficiency virus (HIV)</td></tr>
<tr><td></td><td>Total bilirubin***</td><td></td><td></td><td></td></tr>
<tr><td></td><td>BUN or Urea</td><td></td><td></td><td>Tumor markers: PSA for mCRPC</td></tr>
<tr><td></td><td>Creatinine</td><td></td><td></td><td></td></tr>
<tr><td></td><td>Uric Acid</td><td></td><td></td><td></td></tr>
</table>

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test
	Glucose (nonfasted)			
	Albumin			
	Serum Phosphorus			
	Alkaline phosphatase bone fraction			
	Troponin I and BNP			
	Alkaline phosphatase liver fraction			
	TSH at Screening only			
	Testosterone at Screening (mCRPC patients only)			

**Viral Disease Screening: Hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti HBc), (HbcAb), hepatitis B surface antibody (anti HBs), hepatitis C virus antibodies (HCVAb), and human immunodeficiency virus testing (HIV) to be conducted by local laboratory where required by local regulations or if warranted by patient history.
***For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination to include weight, vital signs, assessment of ECOG performance status and height; height will be measured at Screening only.

7.1.5. (12-Lead) Electrocardiogram

Electrocardiogram (ECG): The Screening ECG will be a single 12-lead ECG. Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all other ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate.

If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed.

In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 501 msec. If QTcF interval reverts to less than 501 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be

held until the QTcF interval decreases to 500 msec. Patients will then restart the investigational product at the next lowest dose level.

If the QTcF interval has still not decreased to 500 msec after 2 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), then an ECG (triplicate) should be obtained at the time of the event.

When matched with PK sampling, plan the timing of ECG accordingly so that the PK collection afterwards can be around the intended time point.

7.2. Echocardiogram

Echocardiogram (Echo) will be evaluated in all patients. The following parameters will be evaluated: ventricular function (including left ventricular ejection fraction [LVEF], end systolic volume [ESV] and end diastolic volume [EDV]), qualitative evaluation of chamber size, and wall motion. A Doppler examination will be completed and should include an assessment of mitral valve, atria, right ventricle, tricuspid valve, aortic valve, pulmonic valve, great vessels, and pericardium. Additional assessments will be per the study manual.

7.3. Pharmacokinetics Assessments

7.3.1. Plasma for PK analysis of PF-06952229

Blood samples (3 mL) to provide a minimum of 1.2 mL plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) as outlined in the Schedule of Activities. The PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

Where noted in the Schedule of Activities, blood samples for PF-06952229 concentrations will be collected at approximately the same time as other assessments such as CCI, ECGs (first ECG then PK collection) and bone marrow aspirate collections etc, wherever possible.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. The exact time of the sample collection will always be noted on the CRF. If a

scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, patient, and sponsor.

PK samples will be assayed for PF-06952229 using a validated analytical method.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the Clinical Study Report (CSR).

7.3.2. Urine for Analysis of PF-06952229 Concentrations

In single agent dose expansion cohort (Part 2A), optional urine samples will be collected for 12 hours (-3 hour window) after PF-06952229 morning dosing on Cycle 1, Day 7 to measure PF-06952229 concentrations, and thereby determine the renal elimination of PF-06952229 from the body. Urine will be collected on Cycle 1, Day 7 from selected patients over the following intervals: 0 to 4 hours, 4 to 8 hours, and 8 to 12 (-3 hour window) hours post the morning dose. Patients will empty their bladder just prior to morning dosing on Cycle 1, Day 7.

At the end of each urine collection period, the total volume will be measured and recorded. Voided urine should be collected in a container. The urine will then be mixed thoroughly, and an aliquot will be withdrawn for the potential measurement of drug concentrations. The sample must be processed and shipped as indicated in the instructions provided by the sponsor. The urine samples will be assayed using a validated analytical method in compliance with Pfizer SOPs.

Samples collected for analyses of urine PF-06952229 concentration may also be used for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will not be included in the CSR.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

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CCI [redacted]

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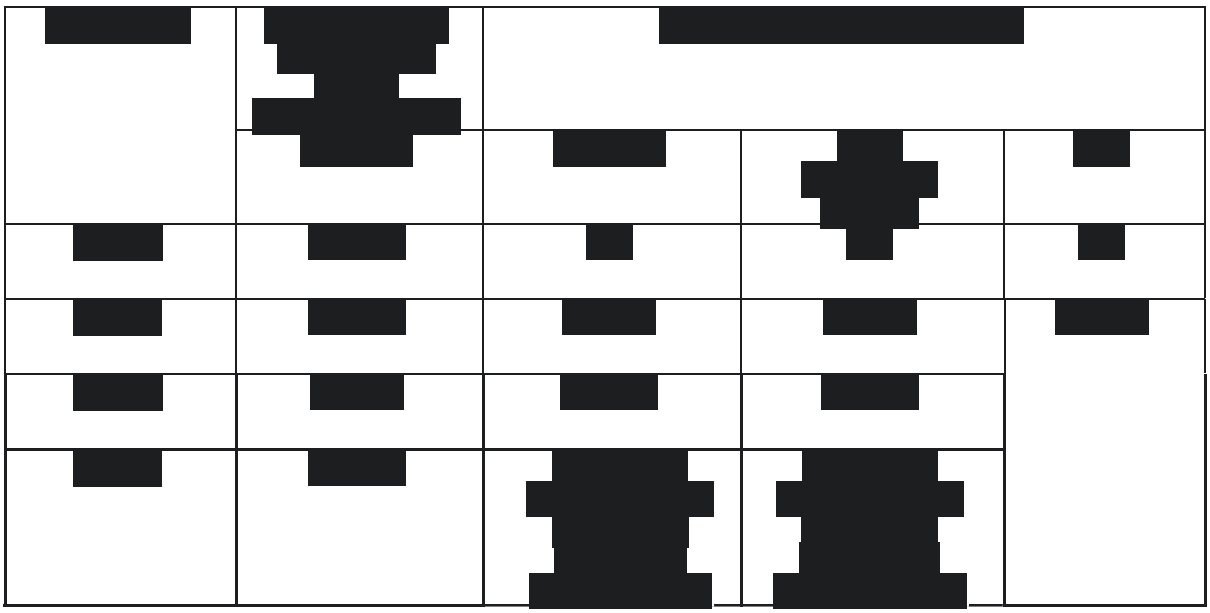

[redacted]

CCI [redacted]

CCI

[redacted]

7.6. Additional Research

Unless prohibited by local regulations or IRB/EC decision, patients will be asked to indicate on the consent form whether they will allow their banked samples to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Patients need not provide additional biospecimens for the uses described in this section; CCI [redacted] Patients may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

Details on processes for collection and shipment of these samples can be found in the Lab Manual.

7.7. Imaging Assessments

Management of Incidental Findings

An incidental finding is one unknown to the patient that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study.

CT, MRI, and PET images may be reviewed by a central review facility. The purpose of this review is to evaluate images for response. Central image review is not a complete medical review of the patient. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the principal investigator. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-patient relationship. The principal investigator will be responsible for reporting any AEs identified from incidental findings as described in the Adverse Event Reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

7.8. Tumor Response Assessments

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule of Assessments, or whenever disease progression is suspected (eg, symptomatic deterioration), at the time of withdrawal from treatment, if not done in the previous 6 weeks, after end of treatment for patients who did not end treatment due to disease progression, death, or withdrawal of consent.

Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Note: Bone scan and soft-tissue disease assessment should continue according to this schedule irrespective of whether study treatment is delayed, missed, or discontinued until the earlier of initiation of subsequent systemic anticancer therapy or permanent loss to radiographic follow-up (including hospice admission).

Tumor assessments will include CT or MRI of chest, abdomen and pelvis, and MRI of the brain. If a brain MRI is medically contraindicated, a CT scan with contrast (unless contrast is medically contraindicated) may be performed, however the same modality should be used on an individual patient throughout the study. Other disease sites may be imaged if disease is suspected. Tumor assessments will be performed at Screening and every 8 weeks (±7 days) for the first year, then every 12 weeks (±7 days). Bone scans will be performed as medically indicated. Tc-99m bone scans (required for mCRPC at baseline) will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Patients who are found to have hemorrhage in other organs will discontinue treatment with PF-06952229 and enter the follow-up portion of the trial. After 2 years, tumor assessments should be performed every 4 months thereafter. Given the exploratory nature of the study, confirmation of response (complete response (CR)/partial response (PR)) is preferred (see RECIST version 1.1). Tumor assessments should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation. Patients should have a confirmatory scan for PD and can remain on trial if they are receiving clinical benefit upon discussion with investigator and sponsor. Tumor assessments should be fixed according to the calendar, regardless of treatment delays.

mCRPC Only: For mCRPC, prostate specific antigen (PSA) assessment should also be performed on Screening (for historical progression), C1D1 (-14 days) and Day 1 of Cycles 4, 7, 10 and every 2nd cycle thereafter as well as the End of Treatment visit, and should be evaluated using Prostate Working Group 3 – Soft Tissue Response Criteria. Patients should have a confirmatory scan for PD and should remain on trial if they are receiving clinical benefit (according to discussion with site investigator and sponsor).

Confirmation of response (CR/PR) with a second consecutive scan at least 4 weeks later is preferred. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. CT or MRI scans should be completed before tumor biopsy samples are collected. If a patient is classified as having progressive disease (PD) at a post-baseline tumor assessment, then confirmation of PD by a second consecutive scan at least 4 weeks later in the absence of rapid clinical deterioration is required.

Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C1D1 (standard of care imaging may be utilized prior to the 28 days after agreement between the sponsor and investigator), (2) performed using the method requirements (ie, RECIST v. 1.1), (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. All patients' files and radiologic images must be available for source verification and for potential peer review. All study images may also be provided by the study site to an independent radiology facility (IRF) for independent evaluation. Analysis of tumor assessments for the purpose of this study will be by investigator assessments and will be collected on CRFs.

Bone scans must be acquired on all patients using Tc99- methylene diphosphonate (MDP) tracer at screening and at subsequent post-baseline tumor assessments.

7.8.1. Image Acquisition Parameters

The following image acquisition parameters must be recorded as applicable: tomographic slice thickness and reconstruction interval, pulse sequence, contrast agent (including brand name), contrast agent dose and route of administration, contrast agent injection start and stop times, and contrast agent injector type (eg, manual or power/auto injector).

7.8.2. Soft Tissue Disease Assessment

CT scans should include full coverage of chest, abdomen, and pelvis at all specified time points. If MRI is performed for the abdomen and pelvis examinations, then at least a non-contrast CT chest must be performed as well. The same method of radiological assessment must be used throughout the study. In particular, the same modality and imaging protocol used at baseline should be used at all subsequent imaging time points (eg, if MRI is initially used, MRI should be utilized throughout the study). For at least the baseline imaging examination, both pre-contrast CT (or MRI) scans of the abdomen (liver at minimum) and post-contrast CT (or MRI) scans of the chest, abdomen, and pelvis must be obtained. For the abdomen and pelvis at least single-phase (equilibrium or IVC phase) should be obtained. For all scheduled follow-up imaging examinations, post-contrast CT (or MRI) scans of the chest, abdomen, and pelvis must be obtained.

For prostate cancer soft tissue disease response and progression will be defined per modified Prostate Cancer Working Group 2 (PCWG2) (See Appendices).

Note: Soft tissue disease progression does not warrant discontinuation of tumor assessments or study treatment. Patients may continue on trial if they are receiving clinical benefit after discussion between the investigator and sponsor.

7.8.3. Bone Scan Assessment

Whole body anterior and posterior bone scans should be acquired using 25 mCi (± 10%) Tc99-MDP administered intravenously, with imaging performed 3 hours post-injection. For all follow-up bone scans, the same dose of Tc99-MDP and the same delay from injection to scanning and bed speed must be used and be recorded on source documents.

For patients with symptoms of spinal compression, MRI of the spine and base of the skull should also be performed.

Worsening bone scan does not warrant discontinuation of bone scans or study treatment discontinuation.

7.8.4. Central Independent Radiology Facility (IRF)

An IRF may evaluate imaging studies and supportive clinical data in a central and independent fashion. The IRF will comprise board-certified radiologists and nuclear medicine physicians who will identify baseline lesions and assign post-baseline time point

responses. Details regarding IRF member qualification, training, methods, procedures, and other issues relevant to IRF will be described in the IRF Charter.

All radiological studies acquired at all scheduled time points and any additional (unscheduled) radiological images acquired to evaluate for potential metastatic disease may also be requested to be sent to the IRF or sponsor. All scans sent to the IRF must be in original digital imaging and communications in medicine (DICOM) format. Electronic transfer of scan files (via file transfer protocol [FTP], hypertext transfer protocol (HTTP), or similar means) is preferred, although transfer on physical media (such as digital versatile disc [DVD] or compact disc [CDs]) is acceptable. For digital media, each disk should contain one time point for one patient. The site is expected to maintain a copy of digital data for the retention period applicable to the protocol, Good Clinical Practices (GCP)s, and federal, international and/or state legal and medical requirements. The sponsor and or designee will retain the media for the life of the study.

Note: In patients that show evidence of clinical benefit, PCWG2 advises continuing therapy in the case of an isolated PSA rise after an initial decline, until radiographic or clinical progression is manifest. PCWG2 draws the distinction between documenting progression for consistency of reporting (eg, recording the date of documented progression in a site of disease such as a lymph node that is unlikely to adversely affect prognosis) versus the decision to stop therapy.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
	Occupational exposure is not recorded.	breastfeeding. Include all AEs/SAEs associated with occupational exposure.

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a patient during the active collection period, which begins after obtaining informed consent as described in Section 8.1.4, will be recorded on the AE section of the CRF.Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;

- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or;
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or;
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes then the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 5.0 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the

following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For patients with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability**

of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy (EDP)

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE [ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital (anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death)], then the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.3.1. Medication Errors Definition

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Such medication errors occurring to a study patient are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Analysis Sets

1. Safety analysis set.

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

2. Full analysis set.

The full analysis set includes all enrolled patients.

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. 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.

5. PK analysis sets.

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

CCI [redacted]

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose Escalation

This study contains 2 parts, dose escalation with PF-06952229 (Part 1A), followed by dose escalation for PF-06952229 in combination with enzalutamide (Part 1B), and dose expansion for PF-06952229 as a monotherapy (Part 2A) and combination dose expansion of PF-06952229 with enzalutamide in patients with mCRPC (Part 2B).

Part 1A Single Agent PF-06952229 and Part 1B PF-06952229 Plus Enzalutamide Combination Dose Escalation

The dose escalation in Part 1A will start with Accelerated Titration Design (ATD) as proposed by Simon et al (Journal of the National Cancer Institute, Vol. 89, No. 15, August 6, 1997). 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[4] 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)[4] 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).

9.2.2. Statistical Methods for Determining the MTD

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 provided the DLT rate for cardiac toxicity does 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).[4] 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

9.3. Efficacy Analysis

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor response at each visit, and best overall response (and PSA50 response if prostate cancer patient). In addition, progression date, death date, date of first response and last tumor assessment date, and date of last contact will be listed. Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), Time to Response (TTR), time to progression (TTP), duration of response (DoR), and PSA50 response rate for prostate cancer patients will be summarized and presented if data permits. For these efficacy parameters, all dose levels and tumor types will be included for part 1 patients, for part 2 patients, summary will be for mCRPC patients.

The definition of each response category is provided in the Appendix for RECIST 1.1.

9.4. Analysis of Pharmacokinetics CCI [redacted]

9.4.1. Analysis of Pharmacokinetics

9.4.1.1. Single-Dose and Steady-State PF-06952229 Pharmacokinetic Analysis

Plasma PK parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC_{last}) for PF-06952229 will be estimated using noncompartmental analysis. If data permit or if considered appropriate, area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), apparent oral plasma clearance (CL/F), apparent volume of distribution (V_{ss}/F or V_z/F), accumulation ratio (R_{ac}) and linearity ratio (R_{ss}) will be also estimated. The single-dose and steady-state PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation [CV], median, minimum, maximum, geometric mean and its associated CV) by dose, cycle and day.

For PF-06952229 concentrations, concentrations will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated

CV) by dose, cycle, day and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day (single dose and steady state) using nominal times. Individual and median profiles will be presented on both linear-linear and log-linear scales.

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

The observed accumulation ratio and the linearity ratio will be summarized descriptively. Each will be analyzed after natural log transformation using a one-way analysis of variance (ANOVA) with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation and linearity ratios for each dose.

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

Urine PK parameters (Ae%, CL_R) for PF-06952229 will also be estimated and summarized.

CCI

CCI [redacted]

[redacted]

9.5. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set.

9.5.1. Analysis of the Primary Endpoint

DLT is a primary endpoint of the dose escalation components of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the Study Design section. Adverse Events constituting DLTs will be listed per dose level.

9.5.2. Analysis of Secondary Safety Endpoints

Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (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 treatment. The number and percentage of patients who experienced any 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).

Laboratory Test Abnormalities

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

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

9.5.3. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for

safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate). Data will be summarized and listed for QT, heart rate, RR and PR interval, QRS, QTcF (and other correction factors, eg, QTcB as appropriate). Individual QT (all evaluated corrections) intervals will be listed. 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, 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 Grade. Shift tables will also be provided for ECG abnormality at baseline vs on treatment (yes, no, not done: (n, %)). Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

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

9.6. Sample Size Determination

9.6.1. 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.

9.6.2. 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

9.7. Data Monitoring Committee

This study will not use a data monitoring committee (DMC). For the purpose of this protocol, Pfizer procedures for periodic safety review by a safety review team, comprised of the investigators and the sponsor, will be applied in order to review individual and summary data collected in the safety and clinical databases.

Discussions between the investigators and the sponsor regarding safety will occur in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and determine if further patient enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected and/or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable law.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed [unless a waiver of informed consent has been granted by an IRB/EC]. The investigator will retain the original of each patient's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last patient last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06952229 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (CSR synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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Appendix 1. ABBREVIATION LIST

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
ADTs	androgen depleting therapies
AE	adverse event
Ae%	percent of the cumulative amount of unchanged drug excreted into the urine
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti HBc	hepatitis B core antibody
anti HBs	hepatitis B surface antibody
ANC	absolute neutrophil count
ANOVA	analysis of variance
ARA	acid reducing agent
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATD	Accelerated Titration Design
AUC_{24h}	area under the concentration-time curve from time 0 to 24 hours after dose
AUC_{inf}	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
AUC_{last}	area under the plasma concentration versus time curve from 0 to last
$AUC_{ss,\tau}$	area under the plasma concentration curve at time of steady state
$AUC_{sd,\tau}$	area under the plasma concentration curve at standard deviation
BBS	Biospecimen Banking System
BID	twice daily
BNP	B-type natriuretic peptide
BP	blood pressure
BUN	blood urea nitrogen
C#D#	Cycle # Day #
CA 15-3	cancer antigen 15-3
C_{avg}	average concentration
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration,
CD	compact disc
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CDK	cyclin dependent kinase
CEA	carcinoembryonic antigen

Abbreviation	Term
C_{eff}	effective concentration
CI	confidence interval
CK	creatine kinase
CL_b	predicted blood clearance
CL/F	apparent clearance
CL_{ss}/F	steady state apparent clearance
CL_R	renal clearance of the drug from plasma
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRPC	castration-resistant prostate cancer
CSA	clinical study agreement
CSR	clinical study report
$C_{ss,max}$	steady state maximum plasma concentration
$C_{ss,min}$	steady state minimum plasma concentration
CT	computed tomography
CTA	clinical trial application
CCI	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome
DDI	drug-drug interaction
DHT	Dihydrotestosterone
DICOM	digital imaging and communications in medicine
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
CCI	[redacted]
DoR	duration of response
DRF	Dose-range finding
DVD	digital versatile disc
DVT	deep venous thrombosis
EC	ethics committee
EC_{50}	concentration corresponding to 50% of the maximum effect
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EDV	end diastolic volume
Eg	for example
EMT	epithelial-to-mesenchymal transition
EOT	end of treatment

Abbreviation	Term
ER	estrogen receptor
ERK	extracellular signal-regulated kinase
ESA	erythropoiesis stimulating agents
ESV	end systolic volume
EU	European Union
EudraCT	European Clinical Trials Database
F	Bioavailability (systemic availability of the administered dose)
Fa	fraction absorbed
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
CCI	[redacted]
FIH	first in human
FIP	First-in-patient
FSH	follicle-stimulating hormone
FTP	file transfer protocol
GCP	Good Clinical Practice
GI	Gastrointestinal
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone agonist
HBsAg	hepatitis B virus surface antigen
HbcAb	hepatitis B core antibody
HCVAb	hepatitis C virus antibodies
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
hERG	human ether à-go-go-related gene
HIV	human immunodeficiency virus
HNSCC	squamous cell cancer of the head and neck
HNSTD	highest non-severely toxic dose
HR	heart rate
HR+	hormone receptor positive
hs-CRP	high-sensitivity C-reactive protein
5-HT	5-hydroxytryptamine
HTTP	hypertext transfer protocol
IB	investigator's brochure
IC_{50}	50% inhibitive concentration
ICH	International Conference on Harmonisation
ID	Identification
Ie	that is
IHC	Immunohistochemistry
IL-2	Interleukin-2

Abbreviation	Term
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRF	independent radiology facility
IUD	intrauterine device
IVC	abdominal imaging at 60 to 70% after intravenous administration of contrast material
JNK	c-jun N-terminal kinase
Ka	absorption rate
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LHRH	luteinizing hormone releasing hormone
LVEF	left ventricular ejection fraction
MAP	mitogen-activated protein kinase
mBC	metastatic breast cancer
mCRPC	metastatic castration-resistant prostate cancer
mITT	modified intent to treat
mTPI	modified target probability interval
MD	multiple dose
MDP	methylene diphosphonate
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NCA	non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	natural killer
OS	overall survival
ORR	objective response rate
PACL	Protocol Administrative Change Letter
PBPK	physiologically based pharmacokinetic
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
pT	target probability
PCD	primary completion date
PCWG2	Prostate Cancer Working Group 2
PD	pharmacodynamics; progressive disease
PD-1	programmed cell death
PD-L1	programmed death ligand - 1
PE	physical examination
PEG 400	polyethylene glycol 400

Abbreviation	Term
PET	positron emission tomography
PFS	progression-free survival
PD-L1/PD-1	programmed death-ligand 1/ programmed cell death protein 1
PI	principal investigator
PK	pharmacokinetic
PO	administered orally
PPI	proton pump inhibitor
PR	pulse rate; partial response
PS	performance status
PSA	prostate specific antigen
pSMAD2	phosphorylated mothers against decapentaplegic homolog 2
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QT	time between the start of the Q wave and the end of the T wave
QTcF	Fridericia's QTc correction formula
QTcB	Bazett's QTc correction
R_{ac}	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RANK	Receptor activator of nucleus factor kappa B-ligand
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	respiratory rate
R_{ss}	linearity ratio
RUQ	right upper quadrant
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLC	small cell lung cancer
SLE	systemic lupus erythematosus
SOA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
STD	severely toxic dose
STD_{10}	severely toxic dose in 10% of the animals
$t_{½}$	terminal elimination half-life
TBili	total bilirubin
TBNK	T-cells, B-cells, Natural Killer cells
TDI	time dependent inhibition
TGFβ	transforming growth factor beta
TGFβR1	transforming growth factor beta receptor 1

Abbreviation	Term
TGI	tumor growth inhibition
T_{max}	time to maximum plasma concentration
TME	tumor microenvironment
$T_{ss,max}$	time to steady-state maximum plasma concentration
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USPI	United States Package Insert
UVB	ultraviolet B
Vd/F	apparent volume of distribution after non-intravenous administration
Vd_{ss}	steady-state volume of distribution
V_{ss}/F	apparent volume of distribution at steady state after non-intravenous distribution
V_z/F	Apparent volume of distribution during terminal phase after non-intravenous administration
WBC	white blood cell

Appendix 2. Detailed Dose Escalation/De-Escalation Scheme for mTPI design

DLT	n=1	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	E
1	D	S	S	S	S	S	E	E	E	E	E	E
2		DU	D	D	S	S	S	S	S	S	S	E
3			DU	DU	D	D	S	S	S	S	S	S
4				DU	DU	DU	DU	D	S	S	S	S
5					DU	DU	DU	DU	DU	D	S	S
6						DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

Source: https://udesign.laiyaconsulting.com/.
E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial.

Escalation/De-escalation algorithms for total number of patients treated at the current dose level (current and previous cohorts)

- With 2 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1 DLT -> remain at the same dose;
  - 2 DLTs -> de-escalate and consider current dose as intolerable.
- With 3 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1 DLT -> remain at the same dose;
  - 2 DLTs -> de-escalate;
  - 3 DLTs -> de-escalate and consider current dose as intolerable.
- With 4 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1 DLT -> remain at the same dose;

- 2 DLT -> de-escalate;
- 3-4 DLTs -> de-escalate and consider current dose as intolerable.

- With 5 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1-2 DLTs -> remain at the same dose;
  - 3 DLTs -> de-escalate;
  - 4-5 DLTs -> de-escalate and consider current dose as intolerable.
- With 6 patients treated at current dose level:
  - 0 DLT -> escalate;
  - 1-2 DLT -> remain at the same dose;
  - 3 DLTs -> de-escalate;
  - 4-6 DLTs -> de-escalate and consider current dose as intolerable.
- With 7 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2-3 DLTs -> remain at the same dose;
  - 4-7 DLTs -> de-escalate and consider current dose as intolerable.
- With 8 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2-3 DLTs -> remain at the same dose;
  - 4 DLTs -> de-escalate;
  - 5-8 DLTs -> de-escalate and consider current dose as intolerable.
- With 9 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2-4 DLTs -> remain at the same dose;

- 5-9 DLTs -> de-escalate and consider current dose as intolerable.

- With 10 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2-4 DLTs -> remain at the same dose;
  - 5 DLTs -> de-escalate;
  - 6-10 DLTs -> de-escalate and consider current dose as intolerable.
- With 11 patients treated at current dose level:
  - 0-1 DLT -> escalate;
  - 2-5 DLTs -> remain at the same dose;
  - 6-11 DLTs -> de-escalate and consider current dose as intolerable.
- With 12 patients treated at current dose level:
  - 0-2 DLTs -> escalate;
  - 3-5 DLTs -> remain at the same dose;
  - 6-12 DLTs -> de-escalate and consider current dose as intolerable.

Appendix 3. Bone Marrow Reserve in Adults

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol.5, 255-258, 1961*

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM	Head :			136.6		
AND	Cranium	165.8	0.75	124.3	13.1	**13.1**
MANDIBLE	Mandible	16.4	0.75	12.3		
	Upper Limb Girdle:			86.7		
HUMERI, SCAPULAE,	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
CLAVICLES	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
STERNUM	4	18.6		7.4		
AND	5	23.8		9.5	7.9	**10.2**
RIBS	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
	Sacrum	194.0	0.75	145.6	13.9	
PELVIC BONES	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
VERTEBRAE	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar):			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		**1497.7**		**1045.7**	**100.0**	**100.0**

Appendix 4. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

*As published in Am J Clin Oncol 5:649-655, 1982.

Appendix 5. Bone Scan Assessment Form

PCCTC Bone Scan Assessment Tool

BASELINE Scan Date: (_____/_____/_____)

Patient Identifier:	
Protocol Number:	Protocol Start Date:

Is tracer uptake related to metastatic disease?

◯Yes ◯No

NOTE: If "NO", do not fill out the form below

If yes, indicate total number of lesions related to metastatic disease
(select one)

◯1 ◯2-4 ◯5-9 ◯10-20 ◯>20

Comments		Investigator's Signature	

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PCCTC Bone Scan Assessment Tool

8 Week Scan Date: (_____/_____/_____)

Patient Identifier:	
Protocol Number:	Protocol Start Date:

Is tracer uptake related to metastatic disease?

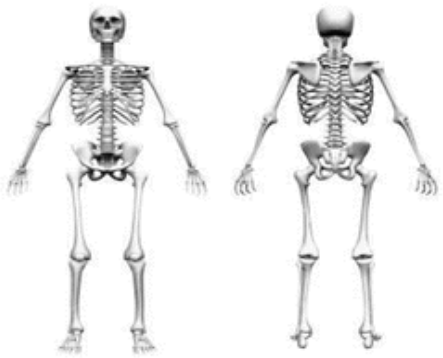
◯Yes ◯No

NOTE: If "NO", do not fill out the form below

Draw site(s) of NEW lesion(s) on skeleton

Check Region(s) of NEW Disease:

- ❑ Skull
- ❑ Thorax
- ❑ Spine
- ❑ Pelvis
- ❑ Extremities



If yes, indicate total number of NEW lesions compared to Baseline Scan (Date:___/___/___)
(select one)

◯0 ◯1 ◯2 ◯3 ◯4 ◯5 ◯>5

*Presence of new lesions at this time does not confirm progression *

Clinical Impression (circle one)

◯ Improved ◯ Stable ◯ Progression

Comments		Investigator's Signature	

Version 1.0 © 2010, MSKCC

PCCTC Bone Scan Assessment Tool

_____ Week Scan Date: (_____/_____/_____)

To be compared to 8 Week Scan

Patient Identifier:

Protocol Number: | Protocol Start Date:

Is tracer uptake related to metastatic disease?

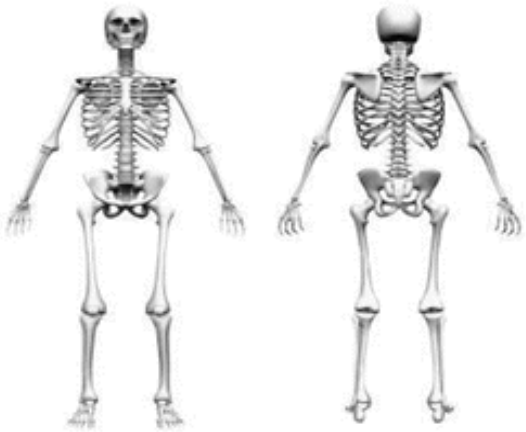
◯Yes ◯No

NOTE: If "NO", do not fill out the form below

Draw site(s) of NEW lesion(s) on skeleton

Check Region(s) of NEW Disease:

- ❑ Skull
- ❑ Thorax
- ❑ Spine
- ❑ Pelvis
- ❑ Extremities



If yes, indicate total number of NEW lesions compared to 8 Week Scan (Date:___/___/___)

(select one)

◯0 ◯1 ◯2 ◯3 ◯4 ◯5 ◯>5

Clinical Impression (circle one)

◯ Improved ◯ Stable ◯ Progression

Comments		Investigator's Signature	

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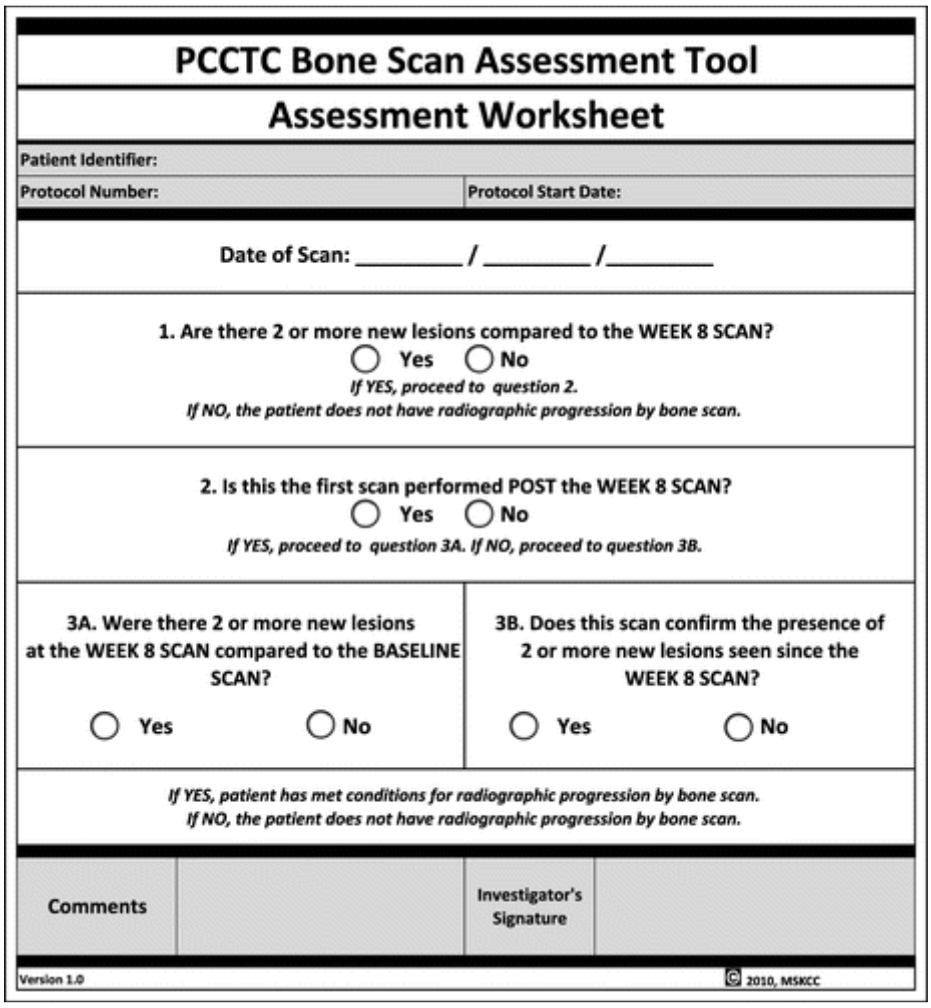

PCCTC Bone Scan Assessment Tool

Assessment Worksheet

Patient Identifier:	
Protocol Number:	**Protocol Start Date:**

Date of Scan: _____ / _____ /_____

1. Are there 2 or more new lesions compared to the WEEK 8 SCAN?

◯ Yes ◯ No

If YES, proceed to question 2.
If NO, the patient does not have radiographic progression by bone scan.

2. Is this the first scan performed POST the WEEK 8 SCAN?

◯ Yes ◯ No

If YES, proceed to question 3A. If NO, proceed to question 3B.

3A. Were there 2 or more new lesions at the WEEK 8 SCAN compared to the BASELINE SCAN?	**3B. Does this scan confirm the presence of 2 or more new lesions seen since the WEEK 8 SCAN?**
◯ Yes ◯ No	◯ Yes ◯ No

If YES, patient has met conditions for radiographic progression by bone scan.
If NO, the patient does not have radiographic progression by bone scan.

Comments		**Investigator's Signature**	

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Appendix 6. Response Evaluation Criteria In Solid Tumors (RECIST) v 1.1

Adapted from 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.

CATEGORIZING LESIONS AT BASELINE

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

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm);
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray;
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper;
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

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

Non-measurable disease

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

- Bone disease**:** Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline;
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions**:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions;
- Normal nodes**:** Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

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

Target lesions

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

- If 2 target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used;
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

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

Non-target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

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

Target disease

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

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

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

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

- Indeterminate: Progression has not been documented; and:

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

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

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

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

Non-target disease

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

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

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

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

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

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

Table 1. Objective Response Status at each Evaluation

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

Appendix 7. 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.

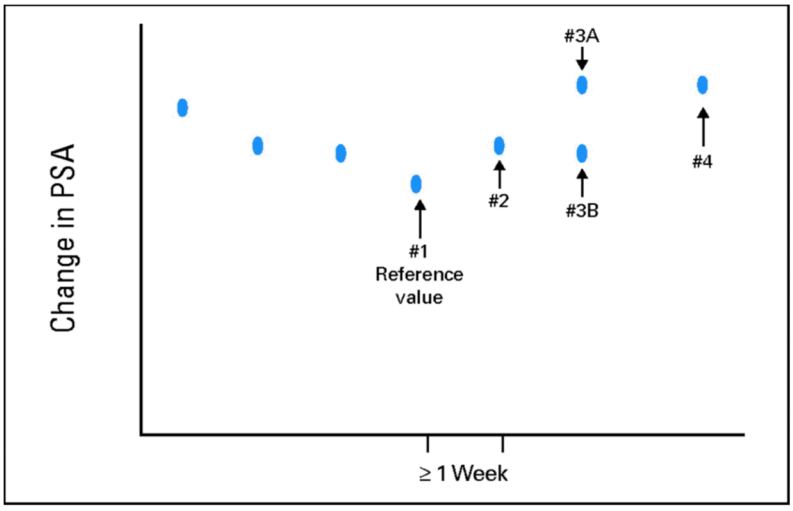
And Eisenhauer E.A., et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

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 1, #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 1, #3B) value is less than the screening PSA (Figure 1, #2) value, then an additional test for rising PSA (#4) will be required to document progression before the patient can be enrolled.

Figure 1. 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]
	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

Date Progression Detected[1]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan

[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:

Table 2. 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.

Appendix 8. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic in the US and other areas as applicable and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances, including the lifting of any quarantines and travel bans/advisories.

Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per the exclusion criterion # 13. When the infection resolves, the patient may be considered for rescreening.

Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow-up on the safety of study patients at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess patient safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the patient and the Investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study treatments(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to ADVERSE EVENT REPORTING.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol. Refer to Pregnancy Testing.

Study patients must be reminded to promptly notify site staff about any change in their health status.

Alternative Facilities for Safety Assessments

Laboratory Testing

If a study patient is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The safety laboratory evaluations included in Section 7.1.3 may be performed at a local laboratory.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the patient's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a patient requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the patient to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the patient's source documents/medical records and relevant data recorded on the CRF. Confirm that the patient is adhering to the contraception method(s) required in the protocol.

Imaging

If the patient is unable to visit the study site for imaging assessment(s), the patient may visit an alternative facility to have the imaging assessment(s) performed. Qualified study site personnel must order, receive, and review results.

Electrocardiograms

If the patient is unable to visit the study site for ECGs, the patient may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

Study Treatment

If the safety of a trial patient is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that patient from study treatment must be considered.

PF-06952229 may be shipped by courier to study patient if permitted by local regulations and in accordance with storage and transportation requirements for the PF-06952229. Pfizer does not permit the shipment of PF-06952229 by mail. The tracking record of shipments and the chain of custody of PF-06952229 must be kept in the patient's source documents/medical records.

The following is recommended for the administration of PF-06952229 for patients who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection:

- For symptomatic patients with active SARS-CoV2 infection, PF-06952229 should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the patient should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential DDIs as described in Concomitant Treatment(s) for any concomitant medication administered for treatment of SARS-CoV2 infection.

Patients receiving PF-06952229 in combination with enzalutamide in Part 1B, and Part 2B will follow the same procedures described in this section for enzalutamide.

Home Health Visits

A home health care service will be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the patient's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Adverse Event Checks

Adverse Events and Serious Adverse Events

If a patient has COVID-19 during the study, this should be reported as an adverse event (AE) or SAE and appropriate medical intervention provided. Temporary discontinuation of the study treatment is medically appropriate until the patient has recovered from COVID-19.

It is recommended that the Investigator discuss temporary or permanent discontinuation of study treatment with the study medical monitor.

Efficacy Assessments

The use of alternative measures for efficacy assessments needs to be approved by the study team.

Independent Oversight Committees

Not applicable.

Appendix 9. Prohibited Concomitant Medications Which May Result in Drug-Drug Interaction (DDI)

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are CYP3A4/5 inhibitors or inducers.

Drug Category	Drugs or Supplement	Required Washout Period Requirement
CYP3A4/3A5 Inhibitor	VIEKIRA PAK Anti-HIV retroviral drugs containing ritonavir ritonavir cobicistat troleandomycin telaprevir itraconazole indinavir voriconazole mifepristone mibefradil clarithromycin posaconazole telithromycin grapefruit juice ceritinib conivaptan nefazodone nelfinavir saquinavir ribociclib idelalisib boceprevir Erythromycin Fluconazole Atazanavir Darunavir Duvelisib Diltiazem Dronedarone Crizotinib Fedratinib Letermovir Aprepitant Lefamulin Casopitant Amprenavir Faldaprevir Imatinib Verapamil	10 days or 5 half-lives whichever is longer

Drug Category	Drugs or Supplement	Required Washout Period Requirement
	Ravuconazole Netupitant Nilotinib Istradefylline Tofisopam Cyclosporine Ciprofloxacin Voxelotor Isavuconazole Cimetidine fluvoxamine	
CYP3A4/3A5 Inducer	carbamazepine enzalutamide rifampicin mitotane avasimibe rifapentine apalutamide ivosidenib phenytoin St John's Wort extract phenobarbital semagacestat efavirenz dabrafenib cenobamate lesinurad bosentan thioridazine rifabutin Lorlatinib Nafcillin talviraline lopinavir modafinil etravirine elagolix lersivirine telotristat ethyl	10 days or 5 half-lives whichever is longer

Note 1: Half-life refers to the half-life of the parent drug and its metabolites, which are inhibitors or inducers. The longest half-life should be used to calculate the period necessary to washout a medication prior to the first dose of study treatment.

Appendix 10. Additional Clinical Safety Data

The data below are from the Part 1A of the Study C3881001 clinical database as of 19 Jun 2020. These data are preliminary and may change. At that time 27 subjects were reported to have been screened and 20 subjects were shown to have been enrolled. The tumor types enrolled were prostate cancer (11 subjects), pancreatic cancer (3 subjects), colon cancer/colorectal cancer (2 subjects), squamous cell head and neck cancer/squamous cell tongue cancer (2 subjects), breast cancer (1 subject), and mesothelioma (1 subject). One subject each was enrolled in the 20, 40, 80 and 150 mg BID accelerated titration cohorts. Six subjects in the 250 mg BID cohort and 3 patients in the 375 BID mg cohort were enrolled prior to a partial clinical hold implemented in July 2019 when 2 subjects experienced Grade 3 events of hepatic hemorrhage (250 mg BID cohort) and intracranial tumor hemorrhage (375 mg BID cohort). Two additional subjects (1 each) with epistaxis and oral hemorrhage were also reported. Subsequently, study entry criteria were modified to reduce the risks of bleeding in a protocol amendment. As of the 19 Jun 2020 database version, no additional AEs of bleeding episodes have been reported.

One hundred and nineteen AEs were reported in 20 patients. Of the 119 AEs,

- Ninety-one AEs were either Grade 1 or 2 in 17 patients.

- The most frequency reported AEs (≥3 subjects) were nausea or worsening nausea (5 subjects), cough (4 subjects), anorexia (4 subjects), nasal drainage or congestion (4 subjects), nasal congestion or intermittent nasal congestion (4 subjects), abdominal pain, or abdominal/right upper quadrant (RUQ) pain (3 subjects), vomiting (3), anemia, or intermittent anemia (3 subjects), dyspnea (3 subjects), fatigue, or worsening fatigue (3 subjects) and headache (3 subjects).Twenty-five Grade 3 AEs were reported in 14 patients.

    - 3 AEs (anemia, intracranial tumor hemorrhage, and intrahepatic hemorrhage, each in 1 patient) were reported as attributed to PF-06952229 by the investigators. Of note, no additional hemorrhagic events have been reported following the modifications made to study entry criteria.

    - 21 Grade 3 AEs considered unrelated to PF-06952229 were reported in 13 patients: 3 events of abdominal/abdominal RUQ pain, 2 events of hyponatremia, 2 events of anemia/worsening anemia, 2 events of constipation, 2 events of nausea, vomiting and dehydration, and 1 episode each of pneumonia, pulmonary embolism, musculoskeletal weakness left side, left hip pain, hyperbilirubinemia, hyperglycemia, increased ALT, increased AST, hypotension, and dysphagia.

    - 1 Grade 3 AE (fatigue) was reported and the relationship to PF-06952229 has not been reported.

- Two Grade 4 AEs (sepsis and acute respiratory failure) were reported in 2 patients; both of which were deemed to be unrelated to PF-06952229.

- One Grade 5 AE was reported due to death due to tumor progression.

Serious AEs of intracranial tumor hemorrhage, intrahepatic hemorrhage, and anemia reported in 1 patient each were considered related to PF-06952229 by the investigators. Serious AEs not related to PF-06952229 were death due to tumor progression, oral hemorrhage, acute respiratory failure, sepsis, abdominal pain, pneumonia, anemia, hyponatremia, constipation, pulmonary embolism, left hip pain, and nausea/vomiting/dehydration. Each serious, unrelated AE was reported for 1 patient each.