A PHASE 1 STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF ESCALATING DOSES OF A VACCINE-BASED IMMUNOTHERAPY REGIMEN (VBIR) FOR PROSTATE CANCER (PF-06753512)

Compound:	PF-06753512
Compound Name:	Not applicable
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	Not applicable
Protocol Number:	B7791001
Phase:	Phase 1

DOCUMENT HISTORY

Document	Version Date	Summary of Changes and Rationale
Amendment 8	29 May 2020	Overall reasons for Amendment 8: • Change in Study Design (Section 3): Cohort 3B will be reduced from 40 to 18 participants total. Rationale: As regards the two cohorts with mCRPC, there is now sufficient sample size (n=33) to make an internal decision about further development of Pr Ca VBIR, based upon preliminary efficacy and safety. As such, there is no need to enroll additional participants. • Change in Study Design (Section 3): Cohort 5B will be reduced from 40 to 15 participants total. Rationale: Fifteen patients is considered a sufficient sample size to provide preliminary efficacy, safety, PK and biomarker data for the regimen. • Change in Study Design (Section 3): Deletion of Cohort 10B. Rationale: Studies of progression on novel-hormone therapy with abiraterone, with a switch to enzalutamide + Pr Ca VBIR, are no longer useful in defining Proof of Concept for this study. • Deletion of inclusion criteria for Cohort 10B patients – Section 4.1.3. Rationale: The combination of PrCa VBIR and enzalutamide will not be evalauted. • Section 4.2 Exclusion criterion for COVID-19/SARS-CoV2 infection added. Rationale: Guidance regarding COVID-19/SARS-CoV2 infection was required.

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		• Revisions to Objectives and Endpoints (Section 2). Rationale: For consistency with changes in Study Design. • DTH and skin punch biopsy were deleted. Rationale: No additional patients will be enrolled. • Clinical and safety information was updated, including risk of myocarditis. Rationale: New safety information from the VBIR PrCa PF-06753512 January 2020 IB (adenovirus, plasmid DNA and anti-CTLA4 tremelimumab) and from safety reports has been incorporated. • Cardiac troponin I testing was added at screening and post-baseline time points (SOA and Section 7). Rationale: Based on emerging safety information cardiac monitoring was added to mitigate the risk of myocarditis. • Enzalutamide rationale, PK, safety, dosing and product administration information was deleted (Sections 1.3.3, 1.5, 1.6, 3.1.2 and 5). Rationale: The combination of PrCa VBIR and enzalutamide will not be evaluated. • Section 5.4.3 Added recommendations for dose interruptions/delays due to Non-related Adverse Events. Rationale: Dose interruptions due to reasons other than treatment-related toxicity include guidance for COVID-19/SARS-CoV2 infection.
Amendment 7	22 November 2019	• Overall reasons for Amendment 7: Increased Cohort 3B and 5B sample size. Addition of new

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		Cohort 10B. Rationale: ESOE assessment and evaluation of regimen in combination with enzalutamide. • New Schedule of Activities (SOA): Updated for Part B Expansion Cohorts. Rationale: New SOA required for Part B. • Section 1.2 Background and Rationale: Updated prostate cancer statistics; rationale for Part B participant populations. Rationale: Provide background to support changes in Part B Dose Expansion Cohorts. • Section 1.3 PF-06753512: Updated components of the PrCa VBIR regimen. Rationale: Sunitinib will not be tested with the PrCa VBIR regimen; added rationale for combination with PF-06801591 and enzalutamide. • Section 1.5 Pharmacokinetics of tremelimubab, PF-06801591 and Enzalutamide: Updated PK data, added enzalutamide PK data; deleted sunitinib PK data. Rationale: New PK data available; enzalutamide combination added; sunitinib will not be tested with the PrCa regimen. • Section 1.6 Starting Dose Rationale: Modified background information and starting dose rationale for PrCa VBIR components. Rationale: Updated PF-06801591 information; added enzalutamide and deleted sunitinib background information and starting dose rationale. • Section 2.1 and 2.2 Part A Objectives and Endpoints: Deleted objectives and endpoints of

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		combination with sunitinib. Rationale: Sunitinib will not be tested with the PrCa VBIR regimen. • 2.3 Part B Objectives and Endpoints: Added Part B (Expansion) objectives and endpoints. Rationale: Part B Objectives and endpoints are listed. Anti-tumor activity objectives and endpoints are defined for the different Part B Cohort populations. • Study Design Section 3.1.1 Part A: Findings from Part A added. Rationale: To support Part B Cohorts, regimens and doses. • Change in Study Design Section 3.1.2 Part B: Modified Expansion Cohorts: a) Sunitinib cohorts (5A and 4B) were deleted; b) Expansion Cohorts 3B and 5B were expanded from 15 to 40 participants total; c) Expansion Cohort 10B (PrCa VBIR + enzalutamide) was added. Rationale for deletion of Sunitinib Cohorts: In previous versions of Study B7791001, sunitinib was proposed to be combined with PrCa VBIR because of preclinical evidence showing the positive effect of combining sunitinib with VBIR. However, recent work in the field of immunotherapy has focused intensive efforts on checkpoint inhibitors as stimulants of T-cell-modulated anti-cancer therapy. Given more recent evidence of successful use of checkpoint inhibitors in metastatic prostate cancer, the use of sunitinib was replaced with that of tremelimumab (anti-CTLA-4) and RN-888 (anti-PD-1) antibodies. Rationale for Expansion of Cohorts 3B and 5B: to further evaluate the Expansion Doses for each, the metastatic participants and the biochemical

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		relapse prostate cancer populations. Rationale for adding Expansion Cohort 10B: Enzalutamide resistance may be associated with increased expression of anti-PD-1. Cohort 10B will evaluate the anti-tumor response induced by PrCa VIBR + enzalutamide in participants with mCRPC whose disease progressed on abiraterone. • Change in Study Design Section 3.1.2.1 Part B: Cohort 10B lead-in was added including the mTPI decision chart and dose de-escalation schema. Rationale: The dose-de-escalation lead-in will be implemented to determine the most appropriate regimen for Cohort 10B. • Change in Study Design Section 3.1.2.1 Drug regimens and doses for Part B Expansion Cohorts defined. Rationale: Safety data from Cohorts 3B and 7A support Part B Expansion regimens and doses. • Change in Section 4 Participant selection: Added Inclusion and Exclusion Criteria for Part B Cohorts. Rationale: Eligibility criteria defined for new populations in Part B Expansion Cohorts. • Delete population specific exclusion criteria 26 to 36. Rationale: to facilitate review of eligibility in different participant populations. • Changes in Section 5 Study Treatments: supply for Part B defined, dose modifications for toxicity and prohibited medications amended. Rationale: Sections were updated based on

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		regimens and doses for each of Part B Cohorts. [redacted]
Amendment 6	11 May 2018	**The reasons for Amendment 6 include:** • Change: Clarification was provided for the Inclusion/Exclusion Criteria (Inclusion #10(a), #13, #14; Exclusion #2 and #38 (removed), [previously numbered #6, #10, #20, #23, and #29]. Rationale: (Pre-Secondary Hormone) Inclusion #10(a): 'PSA progression defined as a minimum of 2 consecutive rising levels, with an interval of ≥1 week between each determination.' The reduction from 3 to 2 consecutive rising levels does not effect the safety for the patient population. Rationale: (Biochemical Relapse) Inclusion #13: Refined the definition for relapsing prostate cancer post-definitive local therapy. 'Hormone sensitive (androgen dependent) relapsing prostate cancer post definitive local therapy. Relapse is defined as a subsequent detectable PSA (0.2 ng/ml) that increases on 2 or more determination after radical prostectomy. At least 2 PSA values with PSA1 < PSA2, each value separated by at least 2 weeks.' Rationale: (Biochemical Relapse) Inclusion #14: Refined the definition for 'High risk of development of metastatic disease defined as PSA doubling time less than or equal to 10 months (calculated considering at least 3 months before treatment administration).' PSA

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		doubling time change from 12 to 10 months does not effect the safety of the patient population. Rationale: (Post-Secondary Hormone) Inclusion #18: (a) 'PSA progression defined as a minimum of 2 consecutive rising levels, with an interval of ≥1 week between each determination.' The change from 3 to 2 consecutive rising PSA levels does not effect the safety of the population. Rationale: Exclusion #2: Removed – 'Cancer-raleted pain requiring scheduled opioid narcotics for control (as needed, ≤2 times per week is allowed).' The removal of Exclusion Criteria #2 does not effect the safety of the patient population. Rationale: Exclusion #5 (previously #6) – Provided clarification on palliative radiation therapy prior to- and during study participation. 'Radiation therapy within 4 weeks of starting study treatment, except: palliative radiotherapy to a limited field is allowed after consultation with the sponsor's medical monitor at any time during study participation, including during screening.' Rationale: Exclusion #9 (previously #10) – Provided clarification on Concurrent chemotherapy in the hormone sensitive setting is acceptable, provided the time from last treatment is >4 weeks from first dose. Removed "Prior or"and lessened the last treatment from ≥6 months to >4 weeks. The changes do not effect the safety of the patient population. Rationale: Exclusion #19 (previously #20) – Provided clarification which maintains syncopal episode within 12 months of registration as an exclusionary criteria; however, this excludes episodes of vasovagal etiology. Rationale: Exclusion #22 (previously #23) – Provided clarification. Patients may

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		participate in the follow-up status of a research study, provided no interventional drug(s), treatment or non-drug treatment is involved. Rationale: (Pre-Secondary Hormones) Exclusion #28 (previously 29): removed entire exclusion criteria "Metastasis to organ other than lymph nodes and/or bones." The change does not effect the safety of the patient population. Rationale: (Post-Secondary Hormones) Previous Exclusion #38 – removed. The removal of this exclusion criteria does not effect the safety of the patient population. • Change: Section 1.3 PF-06753512 – 'Four cohorts in Part A will evaluate escalating doses of an anti-programmed cell death protein 1 (PD-1) antibody, PF-06801591, given SC in conjunction with each immunization at a site local to the vaccine vector delivery site.' Rationale: Administrative change to correct a typographical error. [redacted] Rationale: The Prostate Cancer Clinical Trials Working Group 3 (PCWG3) is an international working group of clinical and translational experts in prostate cancer that convened in June 2012 and worked through February 2015 to update the recommendations of PCWG2 in light of a changing therapeutic landscape.[40] Section 3.1 Study Overview – Figure 1 Study Schema: • Change: Provided clarification on an intermediate dose level (Cohort 6.5A). Added 'If in Cohort 6A the tremelimumab 80 mg dose

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		level is not well tolerated, enrollment may switch to Cohort 6.5A where patients will receive Adenovirus 6 x 10^{11}VP + pDNA 5 mg + tremelimumab 40 mg + PF-06801591 300 mg. If 80 mg tremelimumab is well tolerated in Cohort 6A, enrollment will proceed to Cohort 7A as shown in Figure 1.' Rationale: Protocol allows for an intermediate dose for each component that may be evaluated if the side effect profile of the highest dose level is unfavorable. Therefore, additional cohorts than those depicted in Figure 1 may be evaluated. • Administrative Changes include: • Typographical error corrections. • Updating the Prostate Cancer Working Group 2 to the updated modified PCWG3 – see Appendix 5.
Amendment 5	17 August 2017	The reasons for Amendment 5 include: • Addition of testing for acetylcholine receptor (AChR) antibodies at screening. In addition, samples are to be drawn for central evaluation upon suspicion of potential myasthenia gravis (MG) – Schedule of Activities, Section 7.1.6. Rationale – Additional evaluation included to exclude patients who test positive at screening as agreed with FDA and to confirm requirement for evaluation if myasthenia gravis is suspected. • Inclusion of requirement for a neurologic examination as part of the Screening physical examination (PE) as well as all abbreviated PEs during Cycle 1 – Schedule of Activities and Section 7.1.3. Rationale – Neurologic examination is required to ensure adequate assessment for underlying autoimmune disorders at baseline and occurrence of adverse events during the study treatment.

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		• Addition of requirement to inform patients of the potential occurrence of immune related adverse events as part of the informed consent process as well providing patients with a Patient Information Card. – Schedule of Activities. Rationale – Additional instructions added to ensure patients are aware of the potential side effects that may be experienced after receiving the study treatment. • Clarification that more than 15 patients may be enrolled in any of the expansion cohorts – Sections 3.1 and 9.3. Rationale – Patients who do not receive a minimum number of doses or who experience more than a two week interruption in dosing for any reason may be replaced to ensure adequate evaluation of the endpoints can be conducted. • Update to Overall Study Design – Figure 1 and Sections 3.1, 3.4, 7.1.2, 7.2.3, 7.5.1, 7.5.2 and 9.6.1.3. Rationale – Inclusion of Cohort 9A and clarification that cohorts with dose combinations other than those depicted in the figure may be evaluated. • Revision to exclusion criteria #12 – Section 4.2. Rationale – Criteria revised to further clarify the exclusion for patients with history of or active autoimmune disorders. • Addition of exclusion criteria #13 which includes exclusion for positive AChR antibodies and/or abnormal neurologic examination at screening indicating possible MG – Section 4.2. Rationale – Additional exclusion criteria has been included as agreed upon with the FDA. [redacted]

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		• Inclusion of definitions for the pharmacokinetic (PK) and immunogenicity analysis sets – Section 9.1. Rationale – As PK and immunogenicity assessments are a secondary endpoint, the population of patients who will be evaluated for these analyses has been included. • Revisions to the recommended management algorithms for liver, skin, neural, endocrine, renal or pulmonary toxicity/pathology, and diarrhea or colitis – Appendix 7. Rationale – Section updated to tabular format for consistency in guidance used across other checkpoint inhibitor programs at Pfizer. • Inclusion of a recommended management algorithm for myasthenia gravis – Appendix 7. Rationale – Algorithm included to provide investigators with guidance for the treatment of an adverse event observed in this study. • Administrative changes – Sections 3.1 and 5.1, 5.4, 5.4.3.2, Appendix 1. Rationale – Administrative changes.
Amendment 4	06 April 2017	The reasons for Amendment 4 include: • Inclusion of an additional cohort in the dose expansion phase, Cohort 5B, to include the evaluation of VBIR with PF-06801591 in the biochemically relapsed patients. – Schedule of Activities, Sections 1.3, 3.1, 3.1.2, 7.1.2, 7.5.1, 7.5.2, 9.3, and Figure 1. Rationale: Given the potential benefit of adding PF-06801591 with PrCa VBIR, the combination will be evaluated in the biochemically relapsed patient population after the safety has been established in the more advanced patient population. • [redacted]

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		CCI [redacted] • Inclusion of a -7 day window for screening tumor assessments. – Schedule of Activities. Rationale – Additional time allowed to provide flexibility in scheduling. • Tumor assessment to be performed every 8 weeks (±5 days) – Schedule of Activities. Rationale – Timeframe revised for consistency in collection time across all sites. CCI [redacted]

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		assessment. • Inclusion of additional blood samples for tremelimumab and PF-06801591 PK evaluation. – Schedule of Activities. Rationale: Additional sampling included to allow for evaluation of the steady state trough concentrations of tremelimumab and PF-06801591. • Inclusion of a Month 9 dosing visit in the Maintenance Period for Cohorts 6A through 8A and Cohorts 2B, 3B and 5B. – Schedule of Activities. Rationale: Protocol correction as the PF-06801591 should continue to be administered monthly in the Maintenance Period. Therefore, patients in these cohorts should return to the clinic for Month 9 to receive PF-06801591. • Update to the starting dose of PF-06801591 to 130 mg. – Sections 1.6.6 and 5.4.3.4. Rationale: Starting dose rounded for ease of bilateral administrations. • Inclusion of clarification that tremelimumab dose levels below the starting dose listed may be evaluated based on emerging safety data for tremelimumab and PF-06801591. – Section 3.1, 5.4.3.4 and Table 4. Rationale: Clarification added to allow for possibility of lower tremelimumab doses if needed. • Requirements for contraception revised from 28 to 90 days. – Sections 4.1.2 and 4.3. Rationale: Timeframe for required contraception increased to ensure adequate coverage of the monoclonal antibodies to be administered.

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		• Post-secondary hormone patients are required to have only one of the three criteria listed in the inclusion criteria in order to be included. – Section 4.1.3. Rationale: Criteria revised to allow for more patients to be considered for inclusion in the study without impacting the safety or scientific value of the trial. • Clarification on the timepoint at which several entry criteria must be met included. – Section 4.2 and 4.2.1. Rationale: Administrative clarification. • Required washout for abiraterone changed to 2 weeks from first dose. – Section 4.2. Rationale – Given the short half-life of the compound, two weeks is sufficient for a washout prior to initiating treatment in this study. • Blood pressure limits changed to 160/100 mmHg despite optimal medical therapy – Section 4.2. Rationale – Criteria revised to allow for more patients to be considered for inclusion in the study given the target patient populations. • Inclusion of the lower abdomen as an injection site for tremelimumab – Section 5.4. Rationale – Additional injection site included for ease of administration. • Editorial and administrative changes – Sections 2.2, 3.1.2, 7.4, 9.6.1, 9.6.4 and Appendix 3. Rationale: Administrative changes and corrections.
Amendment 3	08 September	The reasons for Amendment 3 include:

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	2016	• Inclusion of Cohorts 6A through 8A in Part A to evaluate escalating doses of PF-06801591 in combination with PrCa VBIR. In addition, Cohorts 2B and 3B will be modified to evaluate the selected doses in Part B. – Schedule of Activities including new tables to include assessments for these cohorts, Sections 1.3, 1.3.1, 1.4.2, 1.6.6, 2.1, 2.2, 3.1, 3.1.1, 3.1.2, 3.1.3, 3.2, 3.4, 5.1, 5.2, 5.3, 5.3.1, 5.3.2, 5.4, 5.4.2, 5.4.3.4, 5.5, 5.7.4, 5.7.8, 7.1.2, 7.2.3, 7.5.2, 9.2.1, 9.3, 9.6.1.3, 9.6.2 and 16, Figure 1, Removal of Table 1 and inclusion of Appendix 7. Rationale: Pre-clinical studies indicate the efficacy of the PrCa VBIR may be increased when given in combination with an anti-PD-1 antibody. • Update to visit names in the Maintenance Treatment Period – Schedule of Activities. Rationale – Administrative correction. • Inclusion of tremelimumab PK and ADA assessments in the Maintenance Treatment Period – Schedule of Activities. Rationale – Assessment included to allow for continued evaluation with additional dosing and administrative change. • [redacted] Rationale – Less frequent assessment is considered sufficient for evaluation of the relevant study endpoints. Therefore, the sampling has been reduced to limit the blood draws required by the patients.

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		• Clarification on when sunitinib can be taken on study visit days. – Schedule of Activities. Rationale – Administrative clarification. • Clarification a month is 28 days for the Maintenance Treatment Period schedule. – Schedule of Activities. Rationale – Administrative clarification. • Clarification that enrollment in Cohort 2B may be delayed – Sections 3.1 and 3.1.2. Rationale – Enrollment of pre-secondary hormone patients may be delayed to allow for adequate assessment of the safety of PrCa VBIR when given in combination with PF-06801591 in the post-secondary hormone population. • Clarification that intermediate dose cohorts or cohorts with lower treatment intensity compared to cohorts with an acceptable safety profile may be evaluated. – Section 3.1. Rationale – Administrative clarification. • Revisions to the inclusion and exclusion criteria for biochemical relapse patients – Sections 4.1.2 and 4.2.2. Rationale – Criteria revised to more clearly define the desired patients to be included. • Additional exclusion criteria included for pre-secondary and post-secondary hormone patients – Sections 4.2.1 and 4.2.3. Rationale – Additional criteria included to more accurately define the desired patient population. • Requirement for at least approximately 30% of post-secondary hormone patients to have measurable disease per RECIST v1.1 with the exception of metastases to the liver and for

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		patients to have both PSA progression and measurable disease on imaging assessments – Section 4.1.3. Rationale – These patients will be included to allow for a higher chance to observe objective responses according to RECIST. • Additional instructions on how to calculate PSA doubling time included. – Sections 4.1.2, 4.2.1 and 4.2.3. Rationale – Additional instructions included to ensure consistency in the assessment across all sites. • Clarification on allowed prior use of ADT – Section 4.2.2. Rationale – Revised to ensure a more homogenous patient population across all study sites. • The vastus lateralis muscle is the preferred site of injection when possible rather than the deltoid muscle. – Section 5.4. Rationale – Given the prevalence of disease in the pelvic lymph nodes, the vastus lateralis muscle is the preferred site of injection to allow for drainage to lymph nodes where disease may be present in a higher number of patients. • Additional information included on the preferred injection site for tremelimumab – Section 5.4. Rationale – Administrative clarification. • New section provided to cover tremelimumab dose reductions and interruptions and to include additional criteria for patients who receive PrCa VBIR in combination with PF-06801591 – Sections 5.4.3.1 and 5.3.4.2. Rationale – Given the known side effects observed with other anti-CTLA4 and

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		anti-PD-1 antibodies, additional instructions have been included to address some of the side effects seen when these two class of agents are combined. • Inclusion of additional evaluations for potential Hy's Law cases - Section 7.1.2. Rationale – Additional assessments added for more thorough evaluation. • Clarification on when baseline central nervous system (CNS) imaging is required. – Section 7.4. Rationale – Administrative clarification. • Clarification that patients must receive at least 80% of their planned dose of a component to be evaluated for the MTD determination. – Section 9.1. Rationale – Administrative clarification. • Clarification that lower doses than those with an acceptable safety profile may be evaluated. – Section 9.2.1. Rationale – Administrative clarification. • Clarification responses are not required to be confirmed – Appendix 4. CCI [redacted] • Administrative changes. – Schedule of Activities, Sections 1.3, 1.4.2, 2.1, 3.1.3, 5.1, 5.3, 5.4, 5.4.3.1, 7.1.2, 7.1.3,7.1.5, 7.4, 9.6.4, Table 9 and Appendix 1.
Amendment 2	24 March 2016	The reasons for Amendment 2 include: • Inclusion of a Maintenance Treatment Period to

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		outline dosing frequency and assessments to be performed post Cycle 2 – Schedule of Activities, Sections 3.1, 3.1.3, 5.4 and 6.2. Rationale: Pre-clinical data indicates maintenance boost vaccinations with pDNA (and tremelimumab if the patient is assigned to receive tremelimumab) are effective to maintain the T cell response. • Window for collection of tumor assessments increased to every 8-12 weeks – Schedule of Activities Section. Rationale: Revised to more accurately reflect the standard of care imaging interval for patients. • Clarification on the pre-secondary hormone patients to be enrolled by removing references to M1. – Section 1.2, 3, 4.1.1, 4.2.1. Rationale: Update to ensure the population described throughout the document is consistent with the inclusion criteria. • Clarification that patients for whom treatment with any secondary hormone has failed, not just abiraterone or enzalutamide, are considered to have met the post-secondary hormone patient population definition – Section 1.2, 3.1, 4.1.3, 4.2.3. Rationale: Based on emerging treatment options for patients with prostate cancer, the protocol has been revised to appropriately define this patient population. [redacted] Rationale: Administrative change. [redacted]

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		CCI [redacted] • Study revised to allow post-secondary hormone patients to be enrolled in the dose escalation portion of the study – Section 3. Rationale: Allowing patients with more advanced disease will not impact the assessment of the safety of PrCa VBIR and will make the dose escalation available to more potential patients. • Study schematics and overall design revised to separate the study in to dose escalation and dose expansion portions – Sections 3.1, 3.2, 3.4, 9.1, 9.3. Rationale: Updated to simplify the schematic and description of the study design. • Minimum PSA threshold removed for patients enrolled in Part A of the study – Section 4.1.1 and 4.1.3. Rationale: Criteria revised to allow for additional patients to be considered during dose escalation. A minimum PSA level is not required to adequately assess the safety of the study treatments. • Update to exclusion criteria for prior chemotherapy. The criteria previously listed under post-secondary hormone patients has been moved to the criteria for all patients – Section 4.2. Rationale: Allowance for prior chemotherapy in the hormone sensitive setting applies to pre-secondary hormone patients as well as post-secondary hormone patients.

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		• Clarification that the analyses of Adverse Events is the primary analysis – Section 9.5.1. Rationale: Administrative Clarification. • Temporal collection added as an appropriate way to collect temperature – Schedule of Activities and Section 7.1.3. Rationale: Administrative clarification. • Window for collection of timed sampling added – Sections 7.2.1 and 7.2.2. Rationale: Administrative Clarification. • Administrative edits – Schedule of Activities, Appendix 3 and 4. Rationale: Administrative edits.
Amendment 1	02 October 2015	The reasons for Amendment 1 include: • Inclusion of an additional 6 months of follow-up after the last dose of study treatment – Schedule of Activities, Sections 3.1, 6.3 and 8.2. Rationale – Additional follow-up included to allow for continued observation of patients to better characterize duration of potential treatment effect. • Removal of Day 99 visit from Cycle 1 – Schedule of Activities. Rationale – Assessments from this visit were moved to either the Cycle 1 Day 85 or Cycle 2 Day 1 visit to reduce the number of visits required for the patients. • Addition of collection of baseline Gleason score – Schedule of Activities and Section 7.7.1. Rationale – Inadvertent exclusion from prior

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		protocol version. • Inclusion of instructions for calculation of visit windows – Schedule of Activities. Rationale – Clarification. • Inclusion of additional ECG, MUGA and creatinine clearance evaluations in Cohort 7 – Schedule of Activities for Cohort 7 and Section 7.1.2. Rationale – Additional assessments added given the known toxicities of sunitinib. • Inclusion of language indicating historical PSA and imaging assessments may be requested – Schedule of Activities and Section 7.4. Rationale – Historical disease information may be collected to allow for assessment of the disease history. • Guidance provided should QTc prolongation be observed for patients dosed in Cohort 7 – Schedule of Activities for Cohort 7 and Section 7.1.4. Rationale – Additional language added given the known toxicities of sunitinib. • Additional background information included – Section 1.2, 1.3 and 1.6.1. Rationale – Editorial changes. • Revisions to the primary objective and endpoint of the study – Sections 2.1 and 2.2. Rationale – Additional objectives included to provide more clarity on the safety objective of the study. • Inclusion of evaluation of prostate cancer using irRECIST criteria rather than irRC – Sections 2.2, 6.4, 7.4, 9.4 and Appendix 4.

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		Rationale – Recent published articles indicate irRECIST may be a more reliable and convenient method for evaluating disease status following treatment with immunotherapy products. • Revision of the definition of biochemically relapsed – Sections 3.1 and 4.1.2. Rationale – Definition updated to more accurately reflect the intended patient population to be enrolled. • Revisions to the DLT criteria and clarification that patients who experience a DLT should be removed from study treatment– Sections 3.2 and 6.4. Rationale – DLT criteria revised to include definitions more appropriate for the treatment being administered and the anticipated safety profile of those compounds. • Inclusion of section on late onset toxicities – Section 3.3. Rationale – Additional information added to clarify how the study would be impacted with the observation of toxicity meeting the DLT criteria after the DLT observation period. • Revision to inclusion criteria – Sections 4.1.1 and 4.1.3. Rationale – clarification that patients who have local recurrence of disease would be eligible for study participation and clarification on definition for measurable disease. • Revisions to dose modifications for adenovirus, tremelimumab and sunitinib – Table 4 and Table 5. Rationale – Revised to require discontinuation of treatment should Grade 4 events occur given the expected safety profile of the compounds being

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		administered. • Inclusion of instructions regarding concurrent treatment with denosumab or bisphosphates – Section 5.7.3. Rationale – Clarification. • Inclusion of amylase and lipase in the required blood chemistry panel – Schedule of Activities, Section 7.1.2. Rationale – Analytes added to adequately monitor the safety of the patients. • Inclusion of instructions for inclusion of lymph nodes in disease assessments and evaluation of bone scans – Section 7.4 and Appendix 5. Rationale – Updated to provide additional instructions consistent with the PCWG2 as well as instruction on not including the use of certain lymph nodes in disease assessments given the mechanism of action for the PrCa VBIR. • Administrative changes or corrections – Schedule of Activities and Sections 3.1, 5.4, 5.7.2, 7.1.2, 8.14.3, 9.1, 9.3, 9.5.3, 16.
Original protocol	31 March 2015	Not Applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

SCHEDULE OF ACTIVITIES

SCHEDULE OF ACTIVITIES FOR DOSE EXPANSION COHORTS:

- 3B (mCRPC: PrCa VBIR (80 mg tremelimumab +300 mg PF-06801591);
- 5B (as of Amendment 7) (BCR: PrCa VBIR +80 mg treme +130 mg PF-06801591); and

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 on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Protocol Activity	**Screen**[1] (≤28 days)		**Treatment Period**														**Post Treatment**				
		Cycle 1									**Cycle 2**						**End of Treatment**[28]	**Follow- Up (Months after EOT visit)**			
Study Day		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**							**Month 1**[29]	**Month 2**	**Month 4**	**Month 6**
Cycle Day											**Day 1**		**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28 to 35 days**			
Visit Window (Days)			**±1**	**±2**	**±2**	**±2**	**±4**	**±2**	**±4**	**±2**	**±2**		**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
Informed consent[2]	X																				
Tumor history[3]	X																				
Medical history[4]	X																				
Complete physical examination[5]	X																X				
Abbreviated physical examination[5]		X		X		X		X		X	X		X	X	X			X	X	X	X
Assessment of skin thickness at administration sites	X																				
Height	X																				
Weight	X	X									X						X				
Vital signs[6]	X	X	X	X	X	X		X		X	X		X	X	X		X	X	X	X	X
Performance status[7]	X	X				X		X		X	X		X	X	X		X	X	X	X	X
Gleason score[8]	X																				

Protocol Activity	Screen[1] (≤28 days)	Treatment Period														Post Treatment				
		Cycle 1									Cycle 2					End of Treatment[28]	Follow- Up (Months after EOT visit)			
Study Day		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**							**Month 1[29]**	**Month 2**	**Month 4**	**Month 6**
Cycle Day											**Day 1**		**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28 to 35 days**			
Visit Window (Days)			**±1**	**±2**	**±2**	**±2**	**±4**	**±2**	**±4**	**±2**	**±2**		**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
Laboratory																					
Unique Screening Labs[9]	X																				
Hematology[10]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Coagulation[12]	X			X		X		X		X							X	X			
Cardiac Troponin-I (cTnI) 15[13]	X					X		X		X	X			X							
Urinalysis[14]	X			X		X		X		X	X		X	X	X		X	X			
(12 lead) ECG[15]	X										X						X	X			
ECHO or MUGA	X																X				
Registration																					
Registration[16]		X																			
Study Treatment																					
Adenovirus administration[17]		Refer to Schedule of Study Treatment, Pharmacokinetics and Tremelimumab and PF-06801591 Immunogenicity Assessments																			
Plasmid DNA administration[17]																					
Tremelimumab administration[17]																					
PF-06801591 administration[17]																					
Tumor Assessment																					
CT scan, MRI scan or bone scan[18]	X	X[18]																			
Other samplings																					
CCI [redacted]	[redacted]																				
AChR antibody[20]	X																				
CCI [redacted]	[redacted]																				

Protocol Activity	Screen[1] (≤28 days)	Treatment Period														Post Treatment				
		Cycle 1									Cycle 2					End of Treatment[28]	Follow- Up (Months after EOT visit)			
Study Day		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**							**Month 1[29]**	**Month 2**	**Month 4**	**Month 6**
Cycle Day											**Day 1**		**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28 to 35 days**			
Visit Window (Days)			**±1**	**±2**	**±2**	**±2**	**±4**	**±2**	**±4**	**±2**	**±2**		**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
CCI																					
											X										
Pharmacokinetics and Tremelimumab ADA		Refer to Schedule of Study Treatment, Pharmacokinetics and Tremelimumab and PF-06801591 Immunogenicity Assessments																			
Pharmacokinetics and PF-06801591 ADA																					
Other clinical assessments																					
AEs[26]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Concomitant medications and non-drug supportive interventions[27]		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X

* Visit windows during the treatment period are to be calculated based on the previous dosing visit.
Abbreviations: AChR = acetylcholine receptor; ADA = anti-drug antibodies; AEs = adverse events; CT = computed tomography; CCI
ECG = electrocardiogram; ECHO = echocardiogram; CCI ; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan;
CCI

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. May be collected more than 28 days prior to study entry. As part of the consenting process, participants will be informed of the potential occurrence of immune related adverse events and will be provided with a Patient Information Card.
3. **Tumor History:** Will be collected within 28 days prior to study entry. Includes details of primary diagnosis and treatment history. If available, historical PSA results and imaging assessments (eg, CT scans, MRIs or bone scans) may also be requested.
4. **Medical History**: Includes history of disease process other than prostate cancer (active or resolved) and significant concurrent illness. Includes prior treatments and any current medical treatment for any condition.
5. **Complete and abbreviated physical examinations**: A neurologic examination must be conducted at Screening to look for potential signs suggestive of autoimmune disorders. In addition, all abbreviated physical examinations conducted during Cycle 1 must include a neurologic examination.
6. **Vital signs:** Includes temperature and blood pressure (BP) to be recorded in the seated position after approximately 5 minutes of rest.
7. **Performance status**: Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
8. **Gleason score:** The Gleason score at the time of initial diagnosis and/or time of most current recurrence should be collected.

9. **Unique Screening Labs**: To include hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, and human immunodeficiency virus (HIV). Samples will be analyzed locally.
10. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. If baseline assessment was performed within 72 hours of Cycle 1 Day 1, repeat is not required. Samples will be analyzed locally.
11. **Blood Chemistry**: Should include sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, amylase, lipase, and CCI . If baseline assessment was performed within 72 hours of Cycle 1 Day 1, repeat is not required. Samples will be analyzed locally.
12. **Coagulation**: Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
13. **Cardiac Troponin**: For participants undergoing screening, circulating levels of cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range within 28 days before study entry, preferably using the central laboratory kits provided. See Section 7.1.7 for full details.
14. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
15. **Triplicate 12 leads ECGs**: At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF is prolonged (>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.
16. **Registration**: Participant number and dose level allocation operated by Pfizer Inc.
17. **Investigational Product Administration:** Treatment to be administered after all other assessments required on that day have been performed.
18. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Screening images may be obtained within 5 weeks of registration. Imaging obtained as part of standard of care but within 28 days (-7 days) of registration may be used for screening assessment. Imaging may include chest, abdomen and pelvis CT or MRI scans or bone scans. Bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic participants to rule out CNS metastases. CT or MRI scans, as well as bone scans, when indicated, are to be done every 8 weeks (±5 days) with the first one to occur 8 weeks after C1D1 until disease progression that requires new treatment modality, permanent discontinuation, or death. Disease progression will be confirmed with two consecutive timepoints at least 4-6 weeks apart in the absence of rapid clinical deterioration. Tumor assessment should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. CCI

20. **Acetylcholine receptor (AChR) antibody:** Sample to be sent to the central laboratory for analysis. CCI Treatment decisions will be made based on the clinical diagnosis.

CCI

26. **Adverse Event (AE) Assessments**: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.03. Participants must be followed for AEs for 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 6 months should the participant commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including the 6 month follow-up period. Serious adverse events occurring after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
27. **Concomitant Treatments**: All concomitant medications and non-drug supportive interventions should be recorded in the CRF.
28. **End of Treatment Visit**: The End of treatment visit will be completed at the timepoint when a decision is made to discontinue study treatment. This can occur during Cycles 1 or 2 or during the Maintenance Treatment Phase of the study. Obtain these assessments if not completed in the past two weeks (past 6 weeks for tumor assessments).
29. **Follow up**: At least 28 days, and no more than 35 days after discontinuation of study treatment, participants will return to complete the required assessments. Participants will then return at Month 2, Month 4 and Month 6 to complete the required assessments.

SCHEDULE OF ACTIVITIES FOR DOSE ESCALATION (Amendment 6); COHORTS 1A THROUGH 4A, COHORTS 6A THROUGH 9A AND DOSE EXPANSION COHORTS 1B THROUGH 3B AND 5B –

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 on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Protocol Activity	**Screen[1] (≤28 days)**	**Treatment Period**														**Post Treatment**				
		Cycle 1									**Cycle 2**					**End of Treatment[27]**	**Follow- Up (Months after EOT visit)**			
Study Day		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**						**Month 1[28]**	**Month 2**	**Month 4**	**Month 6**
Cycle Day											**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28 to 35 days**			
Visit Window (Days)			**±1**	**±2**	**±2**	**±2**	**±4**	**±2**	**±4**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
Informed consent[2]	X																			
Tumor history[3]	X																			
Medical history[4]	X																			
Complete physical examination[5]	X															X				
Abbreviated physical examination[5]		X		X		X		X		X	X	X	X	X			X	X	X	X
Assessment of skin thickness at administration sites	X																			
Height	X																			
Weight	X	X									X					X				
Vital signs[6]	X	X	X	X	X	X		X		X	X	X	X	X		X	X	X	X	X
Performance status[7]	X	X				X		X		X	X	X	X	X		X	X	X	X	X
Gleason score[8]	X																			
Laboratory																				
Unique Screening Labs[9]	X																			
Hematology[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation[12]	X			X		X		X		X						X	X			
Urinalysis[13]	X			X		X		X		X	X	X	X	X		X	X			

Protocol Activity	Screen[1] (≤28 days)	Treatment Period														Post Treatment				
		Cycle 1									Cycle 2					End of Treatment[27]	Follow- Up (Months after EOT visit)			
Study Day		Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 71	Day 85	Day 113						Month 1[28]	Month 2	Month 4	Month 6
Cycle Day											Day 1	Day 29	Day 57	Day 85	Day 99		28 to 35 days			
Visit Window (Days)			±1	±2	±2	±2	±4	±2	±4	±2	±2	±2	±2	±2	±4			±4	±4	±4
(12 lead) ECG[14]	X										X					X	X			
ECHO or MUGA	X															X				
Registration																				
Registration[15]		X																		
Study Treatment																				
Adenovirus administration[16]		Refer to Schedule of Study Treatment, Pharmacokinetics and Tremelimumab and PF-06801591 Immunogenicity Assessments																		
Plasmid DNA administration[16]																				
Tremelimumab administration – Starting at Cohort 3A[16]																				
PF-06801591 administration – Starting at Cohort 6A[16]																				
Tumor Assessment																				
CT scan, MRI scan or bone scan[17]	X							X[17]												
Other samplings																				
CCI [redacted]																				
AChR antibody[19]	X																			
CCI [redacted]																				

Protocol Activity	Screen[1] (≤28 days)	Treatment Period														Post Treatment				
		Cycle 1									Cycle 2					End of Treatment[27]	Follow- Up (Months after EOT visit)			
Study Day		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**						**Month 1[28]**	**Month 2**	**Month 4**	**Month 6**
Cycle Day											**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28 to 35 days**			
Visit Window (Days)			**±1**	**±2**	**±2**	**±2**	**±4**	**±2**	**±4**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
Pharmacokinetics and Tremelimumab ADA		Refer to Schedule of Study Treatment, Pharmacokinetics and Tremelimumab and PF-06801591 Immunogenicity Assessments Table																		
Pharmacokinetics and PF-06801591 ADA																				
Other clinical assessments																				
AEs[25]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and non-drug supportive interventions[26]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Visit windows during the treatment period are to be calculated based on the previous dosing visit.
Abbreviations: AChR = acetylcholine receptor; ADA = anti-drug antibodies; AEs = adverse events; CT = computed tomography; CCI
ECG = electrocardiogram; ECHO = echocardiogram; CCI cell; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan;
CCI

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. May be collected more than 28 days prior to study entry. As part of the consenting process, participants will be informed of the potential occurrence of immune related adverse events and will be provided with a Patient Information Card.
3. **Tumor History:** Will be collected within 28 days prior to study entry. Includes details of primary diagnosis and treatment history. If available, historical PSA results and imaging assessments (eg, CT scans, MRIs or bone scans) may also be requested.
4. **Medical History**: Includes history of disease process other than prostate cancer (active or resolved) and significant concurrent illness. Includes prior treatments and any current medical treatment for any condition.
5. **Complete and abbreviated physical examinations**: A neurologic examination must be conducted at Screening to look for potential signs suggestive of autoimmune disorders. In addition, all abbreviated physical examinations conducted during Cycle 1 must include a neurologic examination.
6. **Vital signs:** Includes temperature and blood pressure (BP) to be recorded in the seated position after approximately 5 minutes of rest.
7. **Performance status**: Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
8. **Gleason score:** The Gleason score at the time of initial diagnosis and/or time of most current recurrence should be collected.
9. **Unique Screening Labs**: To include hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, and human immunodeficiency virus (HIV). Samples will be analyzed locally.
10. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. If baseline assessment was performed within 72 hours of Cycle 1 Day 1, repeat is not required. Samples will be analyzed locally.

11. **Blood Chemistry**: Should include sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, amylase, lipase, and CCI . If baseline assessment was performed within 72 hours of Cycle 1 Day 1, repeat is not required. Samples will be analyzed locally.
12. **Coagulation**: Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
13. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
14. **Triplicate 12 leads ECGs**: At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF is prolonged (>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.
15. **Registration**: Participant number and dose level allocation operated by Pfizer Inc.
16. **Investigational Product Administration:** Treatment to be administered after all other assessments required on that day have been performed.
17. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Screening images may be obtained within 5 weeks of registration. Imaging obtained as part of standard of care but within 28 days (-7 days) of registration may be used for screening assessment. Imaging may include chest, abdomen and pelvis CT or MRI scans or bone scans. Bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic participants to rule out CNS metastases. CT or MRI scans, as well as bone scans, when indicated, are to be done every 8 weeks (±5 days) with the first one to occur 8 weeks after C1D1 until disease progression that requires new treatment modality, permanent discontinuation, or death. Disease progression will be confirmed with two consecutive timepoints at least 4-6 weeks apart in the absence of rapid clinical deterioration. Tumor assessment should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. CCI
19. **Acetylcholine receptor (AChR) antibody:** Sample to be sent to the central laboratory for analysis. CCI Treatment decisions will be made based on the clinical diagnosis.
20. **Circulating Tumor Cells**: Approximately 10 mL of blood will be collected for evaluation of circulating tumor cells by the central laboratory.
21. **Serology**: Approximately 10 mL of blood will be collected for central evaluation of IgG antibody responses against the vaccine.
22. **Peripheral Blood Mononuclear Cells**: Approximately 50 mL of blood will be collected for central evaluation of immune response. In addition, the samples may also be used for T cell receptor (TCR) sequencing analysis.
23. **Myeloid Derived Suppressor Cells:** Approximately 5 mL of blood will be collected for central evaluation of circulating MDSC.
24. **Fresh Tumor Tissue Samples:** In the dose escalation portion of the study and Cohort 2B in the dose expansion portion, optional biopsies can be performed at screening and/or Cycle 2 Day 1 (-21 days) at the discretion of the investigator and upon agreement from the participant. Additional unscheduled on-treatment biopsies or biopsies at other timepoints may be collected, if indicated, and agreed upon by the sponsor and investigator and agreed to by the participant. In the dose expansion Cohorts 3B and 4B, mandatory pre-treatment and on-treatment at Cycle 2 Day 1 (-21 days) biopsies will be obtained in at least approximately 5 participants in each cohort. If the participant discontinues study treatment before Cycle 2 Day 1, the biopsy can be performed as part of the End of Treatment visit.
25. **Adverse Event (AE) Assessments**: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.03. Participants must be followed for AEs for 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 6 months should the participant commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including the 6 month follow-up period. Serious adverse events occurring after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

26. **Concomitant Treatments**: All concomitant medications and non-drug supportive interventions should be recorded in the CRF.
27. **End of Treatment Visit**: The End of treatment visit will be completed at the timepoint when a decision is made to discontinue study treatment. This can occur during Cycles 1 or 2 or during the Maintenance Treatment Phase of the study. Obtain these assessments if not completed in the past two weeks (past 6 weeks for tumor assessments).
28. **Follow up**: At least 28 days, and no more than 35 days after discontinuation of study treatment, participants will return to complete the required assessments. Participants will then return at Month 2, Month 4 and Month 6 to complete the required assessments.

SCHEDULE OF ACTIVITIES FOR MAINTENANCE TREATMENT PERIOD (COHORT 1A AND 1B)

Protocol Activity	Maintenance Treatment Period*						
Study Month**	**Month 10**	**Month 12**	**Month 14**	**Month 16**	**Month 18**	**Month 20**	**Month 22 and every 2 months thereafter**
Visit Window (Days)	±7	±7	±7	±7	±7	±7	±7
Abbreviated physical examination	X	X	X	X	X	X	X
Weight		X			X		
Vital signs[1]	X	X	X	X	X	X	X
Performance status[2]	X	X	X	X	X	X	X
Laboratory							
Hematology[3]	X	X	X	X	X	X	X
Blood Chemistry[4]	X	X	X	X	X	X	X
Coagulation[5]	X		X		X		X[15]
Urinalysis[6]	X		X		X		X[15]
(12 lead) ECG[7]		X			X		
Study Treatment							
Plasmid DNA Administration[8]	X	X	X	X	X	X	X
Tremelimumab administration – Starting at Cohort 3A[8]	X	X	X	X	X	X	X
Tumor Assessment							
CT scan, MRI scan or bone scan[9]	X[9]						
Other Samplings							
PK and Tremelimumab ADA – Starting at Cohort 3A	X		X		X		X[15]
CCI							
Other clinical assessments							
AEs[13]	X	X	X	X	X	X	X
Concomitant medications and non-drug supportive interventions[14]	X	X	X	X	X	X	X

***** When a decision is made to discontinue study treatment during the Maintenance Treatment Period, the End of Treatment visit assessments should be performed. The participant will then enter the Post Treatment Period of the study.

****** Study visit is based on completion of two cycles in the treatment period. Visit window for the first maintenance treatment visit is to be calculated based on the Cycle 2 Day 85 dosing date. The first dose in the maintenance period should occur 56 days after the C2D85 dosing date. A month is defined as 28 days.

1. **Vital signs:** Includes temperature and blood pressure (BP) to be recorded in the seated position after approximately 5 minutes of rest.
2. **Performance status**: Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.

3. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Samples will be analyzed locally.
4. **Blood Chemistry**: Should include sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, amylase, lipase, and CCI Samples will be analyzed locally.
5. **Coagulation**: Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
6. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
7. **Triplicate 12 leads ECGs**: At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF is prolonged (>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.
8. **Investigational Product Administration:** Treatment to be administered after all other assessments required on that day have been performed.
9. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans or bone scans. CT or MRI scans, as well as bone scans, when indicated, are to be done every 8 weeks (±5 days) until disease progression that requires new treatment modality, permanent discontinuation, or death. Disease progression will be confirmed with two consecutive timepoints at least 4-6 weeks apart in the absence of rapid clinical deterioration.

CCI

13. **Adverse Event (AE) Assessments**: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.03. Participants must be followed for AEs for 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 6 months should the participant commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including the 6 month follow-up period. Serious adverse events occurring after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
14. **Concomitant Treatments**: All concomitant medications and non-drug supportive interventions should be recorded in the CRF.
15. To be assessed every 4 months.

SCHEDULE OF ACTIVITIES FOR MAINTENANCE TREATMENT PERIOD (DOSE ESCALATION COHORTS 6A THROUGH 9A AND DOSE EXPANSION COHORTS 3B AND 5B)

Protocol Activity		**Maintenance Treatment Period***												
Study Month**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**Month 13**	**Month 14**	**Month 15**	**Month 16**	**Month 17**	**Month 18**	**Month 19**	**Month 20**	**Month 21**	**Month 22 and every month thereafter**
Visit Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Abbreviated physical examination		X		X		X		X		X		X		X[1]
Weight				X						X				
Vital signs[2]		X		X		X		X		X		X		X[1]
Performance status[3]		X		X		X		X		X		X		X[1]
Laboratory														
Hematology[4]		X		X		X		X		X		X		X[1]
Blood Chemistry[5]		X		X		X		X		X		X		X[1]
Coagulation[6]		X				X				X				X[9]
Cardiac Troponin-I (cTnI)[7]	X			X										
Urinalysis[8]		X				X				X				X[9]
(12 lead) ECG[10]				X						X				
Study Treatment														
Plasmid DNA Administration[11]		X		X		X		X		X		X		X[1]
Tremelimumab administration[11]		X		X		X		X		X		X		X[1]
PF-06801591 administration[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Assessment														
CT scan, MRI scan or bone scan[12]								X[12]						
Other Samplings														
PK and Tremelimumab ADA		X				X				X				X[9]
PK and PF-06801591 ADA		X				X				X				X[9]
CCI [redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted][6]
Other clinical assessments														
AEs[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and non-drug supportive interventions[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* When a decision is made to discontinue study treatment during the Maintenance Treatment Period, the End of Treatment visit assessments should be performed. The participant will then enter the Post Treatment Period of the study.

** Study visit is based on completion of two cycles in the treatment period. Visit window for the first maintenance treatment visit is to be calculated based on the Cycle 2 Day 85 dosing date. The first dose in the maintenance period should occur 28 days after the C2D85 dosing date. A month is defined as 28 days.

1. To be assessed every 2 months.
2. **Vital signs:** Includes temperature and blood pressure (BP) to be recorded in the seated position after approximately 5 minutes of rest.
3. **Performance status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
4. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Samples will be analyzed locally.
5. **Blood Chemistry:** Should include sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, amylase, lipase, and CCI [redacted] Samples will be analyzed locally.
6. **Coagulation:** Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
7. **Cardiac Troponin**: For participants undergoing screening, circulating levels of cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range within 28 days before study entry, preferably using the central laboratory kits provided. See Section 7.1.7 for full details.
8. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
9. To be assessed every 4 months.
10. **Triplicate 12 leads ECGs:** At each time point, three consecutive 12 lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF is prolonged (>500 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
11. **Investigational Product Administration:** Treatment to be administered after all other assessments required on that day have been performed.
12. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans or bone scans. CT or MRI scans, as well as bone scans, when indicated, are to be done every 8 weeks (±5 days) until disease progression that requires new treatment modality, permanent discontinuation, or death. Disease progression will be confirmed with two consecutive timepoints at least 4-6 weeks apart in the absence of rapid clinical deterioration.

CCI [redacted]

16. To be assessed every 6 months.

17. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.03. Participants must be followed for AEs for 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 6 months should the participant commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study related procedure and/or receiving investigational product, through and including the 6 month follow up period. Serious adverse events occurring after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
18. **Concomitant Treatments:** All concomitant medications and non drug supportive interventions should be recorded in the CRF.

Schedule of Study Treatment – Cohorts 1A and 2A

Protocol Activity	Screen (≤28 days)	Treatment Period														Post Treatment	
		Cycle 1									Cycle 2					End of Treatment	Follow-Up
Study Day		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**						
Cycle Day											**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 99**		
Visit Window (days)			**±1**	**±2**	**±2**	**±2**	**±4**	**±2**	**±4**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**		
Study Treatment																	
Adenovirus[1]		X									X						
Plasmid DNA[2]						X		X		X		X	X	X			

1. Adenovirus will be administered intramuscularly on Day 1 of each cycle.
2. Plasmid DNA vaccinations will be administered intramuscularly using an electroporation device on Day 29, Day 57 and Day 85 of each cycle.

Schedule of Study Treatment, Pharmacokinetics, and Tremelimumab Immunogenicity Assessments – Cohort 3A

Protocol Activity	Screen (≤28 days)	Treatment Period															Post Treatment				
		Cycle 1										Cycle 2					End of Treatment	Follow- Up (Months after EOT visit)			
Study Day		**Day 1**	**Day 3 -6**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**						**M1**	**M2**	**M4**	**M6**
Cycle Day												**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28-35 days**			
Visit Window (hours)				**±24 hr**	**±48 hr**	**±48 hr**															
Visit Window (days)							**±2**	**±4**	**±2**	**±4**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
Study Treatment																					
Adenovirus[1]		X										X									
Plasmid DNA[2]							X		X		X		X	X	X						
Tremelimumab[3]		X					X		X		X	X	X	X	X						
Pharmacokinetics and Tremelimumab Immunogenicity																					
PK for tremelimumab[4]		X	X	X	X	X	X		X		X	X	X				X		X	X	X
ADA for tremelimumab[5]		X					X				X		X				X		X	X	X

Abbreviations: ADA = Anti-drug antibody.

1. Adenovirus will be administered intramuscularly on Day 1 of each cycle. Tremelimumab will be administered after the adenovirus. Both adenovirus injections should be administered prior to administering the tremelimumab.
2. Plasmid DNA vaccinations will be administered intramuscularly using an electroporation device on Day 29, Day 57 and Day 85 of each cycle. Tremelimumab will be administered after the plasmid DNA. Both pDNA vaccinations should be administered prior to administering the tremelimumab.
3. Tremelimumab will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. Tremelimumab will be administered after the adenovirus or plasmid DNA.
4. Blood samples for determination of tremelimumab drug concentrations will be collected at pre-dose (within 6 hrs prior to tremelimumab dose) on Day 1, any time between Day 3 to Day 6 (48 to 120 hr), Day 8 (168 hr ±24 hours), Day 15 (336 hr ±48 hours), and Day 22 (504 hr ±48 hours) after the Day 1 tremelimumab dose; and additionally at pre-dose (within 6 hrs prior to tremelimumab dose) on Day 29, Day 57 and Day 85 of Cycle 1; at pre-dose (within 6 hrs prior to tremelimumab dose) on Day 1 and Day 29 of Cycle 2; at the End of Treatment (EOT) visit; and at 2, 4 and 6 months after EOT during the follow-up period.
5. Blood samples for detection of anti-drug antibodies (ADA) against tremelimumab will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to tremelimumab dosing.

Schedule of Study Treatment, Pharmacokinetics, Tremelimumab and PF-06801591 Immunogenicity Assessments – Cohorts 6A through 9A

Protocol Activity	Screen (≤28 days)	Treatment Period															Post Treatment				
		Cycle 1										Cycle 2					End of Treatment	Follow- Up (Months after EOT visit)			
Study Day		**Day 1**	**Day 3 -6**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**						**M1**	**M2**	**M4**	**M6**
Cycle Day												**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28-35 days**			
Visit Window (hours)				**±24 hr**	**±48 hr**	**±48 hr**															
Visit Window (days)							**±2**	**±4**	**±2**	**±4**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
Study Treatment																					
Adenovirus[1]		X										X									
Plasmid DNA[2]							X		X		X		X	X	X						
Tremelimumab[3]		X					X		X		X	X	X	X	X						
PF-06801591[4]		X					X		X		X	X	X	X	X						
Pharmacokinetics and Tremelimumab Immunogenicity																					
PK for tremelimumab[5]		X					X		X		X	X	X				X		X	X	X
ADA for tremelimumab[5]		X					X				X		X				X		X	X	X
PK for PF-06801591[6]		X	X	X	X	X	X		X		X	X	X				X		X	X	X
ADA for PF-06801591[7]		X					X				X		X				X		X	X	X

Abbreviations: ADA = Anti-drug antibody.

1. Adenovirus will be administered intramuscularly on Day 1 of each cycle. Tremelimumab and PF-06801591 will be administered after the adenovirus. Both adenovirus injections should be administered prior to administering the tremelimumab and PF-06801591.
2. Plasmid DNA vaccinations will be administered intramuscularly using an electroporation device on Day 29, Day 57 and Day 85 of each cycle. Tremelimumab and PF-06801591 will be administered after the plasmid DNA. Both pDNA vaccinations should be administered prior to administering the tremelimumab and PF-06801591.
3. Tremelimumab will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. Tremelimumab will be administered after the adenovirus or plasmid DNA and before the PF-06801591. Both tremelimumab injections should be administered prior to administering the PF-06801591.

4. PF-06801591 will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. PF-06801591 will be administered after the adenovirus or plasmid DNA and after the tremelimumab.
5. Blood samples for determination of tremelimumab drug concentrations and for detection of ADA against tremelimumab will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to tremelimumab dosing.
6. Blood samples for determination of PF-06801591 drug concentrations will be collected at pre-dose (within 6 hrs prior to PF-06801591 dose) on Day 1, any time between Day 3 to Day 6 (48 to 120 hr), Day 8 (168 hr ±24 hours), Day 15 (336 hr ±48 hours), and Day 22 (504 hr ±48 hours) after the Day 1 PF-06801591 dose; and additionally at pre-dose (within 6 hrs prior to PF-06801591 dose) on Day 29, Day 57 and Day 85 of Cycle 1; at pre-dose (within 6 hrs prior to PF-06801591 dose) on Day 1 and Day 29 of Cycle 2; at the End of Treatment (EOT) visit; and at 2, 4 and 6 months after EOT during the follow-up period.
7. Blood samples for detection of ADA against PF-06801591 will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to PF-06801591 dosing.

Schedule of Study Treatment, Pharmacokinetics, and Tremelimumab Immunogenicity Assessments – Expansion Cohort 1B

Protocol Activity	Screen[1] (≤28 days)	Treatment Period														Post Treatment				
		Cycle 1									Cycle 2					End of Treatment	Follow- Up (Months after EOT visit)			
Study Day		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**						**M1**	**M2**	**M4**	**M6**
Cycle Day											**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28-35 days**			
Visit Window (hours)			**±24 hr**	**±48 hr**	**±48 hr**															
Visit Window (days)						**±2**	**±4**	**±2**	**±4**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
Study Treatment																				
Adenovirus[1]		X									X									
Plasmid DNA[2]						X		X		X		X	X	X						
Tremelimumab[3]		X				X		X		X	X	X	X	X						
Pharmacokinetics and Tremelimumab Immunogenicity																				
PK for tremelimumab[4]		X				X		X		X	X	X				X		X	X	X
ADA for tremelimumab[4]		X				X				X		X				X		X	X	X

Abbreviations: ADA = Anti-drug antibody.

1. Adenovirus will be administered intramuscularly on Day 1 of each cycle. Tremelimumab will be administered after the adenovirus. Both adenovirus injections should be administered prior to administering the tremelimumab.
2. Plasmid DNA vaccinations will be administered intramuscularly using an electroporation device on Day 29, Day 57 and Day 85 of each cycle. Tremelimumab will be administered after the plasmid DNA. Both pDNA vaccinations should be administered prior to administering the tremelimumab.
3. Tremelimumab will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. Tremelimumab will be administered after the adenovirus or plasmid DNA.
4. Blood samples for determination of tremelimumab drug concentrations and for detection of ADA against tremelimumab will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to tremelimumab dosing.

Schedule of Study Treatment, Pharmacokinetics, and Immunogenicity Assessments – Expansion Cohorts, 3B and 5B

Protocol Activity	Screen (≤28 days)	Treatment Period														Post Treatment				
		Cycle 1									Cycle 2					End of Treatment	Follow- Up (Months after EOT visit)			
Study Day		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 113**						**M1**	**M2**	**M4**	**M6**
Cycle Day											**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 99**		**28-35 days**			
Visit Window (hours)			**±24 hr**	**±48 hr**	**±48 hr**															
Visit Window (days)						**±2**	**±4**	**±2**	**±4**	**±2**	**±2**	**±2**	**±2**	**±2**	**±4**			**±4**	**±4**	**±4**
Study Treatment																				
Adenovirus[1]		X									X									
Plasmid DNA[2]						X		X		X		X	X	X						
Tremelimumab[3]		X				X		X		X	X	X	X	X						
PF-06801591[4]		X				X		X		X	X	X	X	X						
Pharmacokinetics and Tremelimumab Immunogenicity																				
PK for tremelimumab[5]		X				X		X		X	X	X				X		X	X	X
ADA for tremelimumab[5]		X				X				X		X				X		X	X	X
PK for PF-06801591[6]		X				X		X		X	X	X				X		X	X	X
ADA for PF-06801591[6]		X				X				X		X				X		X	X	X

Abbreviations: ADA = Anti-drug antibody.

1. Adenovirus will be administered intramuscularly on Day 1 of each cycle. Tremelimumab and PF-06801591 will be administered after the adenovirus. Both adenovirus injections should be administered prior to administering the tremelimumab and PF-06801591.
2. Plasmid DNA vaccinations will be administered intramuscularly using an electroporation device on Day 29, Day 57 and Day 85 of each cycle. Tremelimumab and PF-06801591 will be administered after the plasmid DNA. Both pDNA vaccinations should be administered prior to administering the tremelimumab and PF-06801591.
3. Tremelimumab will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. Tremelimumab will be administered after the adenovirus or plasmid DNA and before the PF-06801591. Both tremelimumab injections should be administered prior to administering the PF-06801591.
4. PF-06801591 will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. PF-06801591 will be administered after the adenovirus or plasmid DNA and after the tremelimumab.

5. Blood samples for determination of tremelimumab drug concentrations and for detection of ADA against tremelimumab will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to tremelimumab dosing.
6. Blood samples for determination of PF-06801591 drug concentrations and for detection of ADA against PF-06801591 will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to PF-06801591 dosing.

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APPENDICES

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Vaccine-based immunotherapy regimen (VBIR) for prostate cancer (PrCa VBIR, PF-06753512) is an anti-cancer immunotherapy regimen that is currently being developed for the treatment of patients with various stages of prostate carcinoma.

1.2. Background and Rationale

Prostate cancer is the most common cancer in American men (aside from skin malignancies). The American Cancer Society's estimates that in the United States in 2019 there will be 174,650 newly diagnosed cases of prostate cancer and over 31,000 prostate cancer-related deaths.[37] The early stages of prostate cancer are localized to the prostate, often indolent in nature, and treatable by operative resection or radiotherapy. However, the majority of patients are at a high risk of disease recurrence; and, once metastatic, of disease progression. Given this disease biology, there is a need for new therapies to provide long-term disease control while offering a better quality of life with manageable side effect profiles.

Recent advances in understanding the mechanisms of immune surveillance and the reversal of immune tolerance have yielded encouraging therapeutic advances involving manipulation of the immune system to control specific tumor types.[18,21,27,51] These approaches mostly encompass the use of single-agent therapies to enhance anti-tumor immune responses. In contrast, the regimen used in this study, referred to as PF-06753512 or PrCa VBIR, is a combination approach using a vaccine combined with immune system modulators. Using this approach, T-cell derived, anti-prostate cancer immune responses are induced, expanded and maintained long-term at the site of metastatic disease.

The study is divided in to two parts, Dose Escalation (Part A) followed by Dose Expansion (Part B). Three clinical populations have been evaluated for safety in the Part A, Dose Escalation portion of the study for the PrCa VBIR:

- Participants with metastatic castration resistant prostate cancer (mCRPC) who are either asymptomatic or minimally symptomatic with limited (non-visceral) metastatic disease before treatment with secondary hormonal manipulation (eg, abiraterone or enzalutamide). Although these novel hormone therapies are approved for treatment of this population, many patients will experience progressive disease (median radiographic progression-free-survival [RPFS] of about 16 months for enzalutamide or abiraterone) and become symptomatic which requires chemotherapy (eg, docetaxel).[2,43]

- Participants with mCRPC for whom secondary hormonal manipulation has failed. Up to 45% of patients develop resistance to novel hormone therapy within 6-9 months of treatment due to mutations in the androgen receptor (eg, AR-V7).[1,11] In addition, for approximately one third of these patients, a new phenotype emerges with highly aggressive small cell-like/undifferentiated neuroendocrine features.[8] Patients resistant to novel hormone therapy such as abiraterone and/or enzalutamide have a very poor outcome due to the absence of therapeutic alternatives. The PrCa VBIR may offer these patients a therapy that is anticipated to have few anti-androgen side effects; would delay disease progression; reduce the need for chemotherapy; and may prolong survival.

- Participants with hormone sensitive prostate cancer following definitive local therapy, who were determined to have rising prostate specific antigen (PSA) at a rate putting them at high risk for rapid development of metastatic disease (defined by a PSA doubling time <10 months). Although there is no worldwide standard-of-care in this population, Androgen Deprivation Therapy (ADT) is frequently used when the PSA rises rapidly in the apparent disease-free setting (termed "Biochemical Relapse, or BCR"). The use of androgen deprivation impacts significantly the quality-of-life (QoL) of these patients. For example, sexual/hormonal dysfunction is a significant concern for many patients considering the duration of androgen deprivation, (24 – 36 months), and its significant side effects of muscle wasting, fatigue, and reduction in libido. In this setting patients whose disease is BCR may benefit from a therapy with few androgen side effects, such as PrCa VBIR. In patients with BCR, the goal will be to prevent or delay the need for chemical castration, preserve the QoL of the patients, and ultimately delay progression to metastatic disease.

Part B, the Dose Expansion phase of the study, will evaluate participants with metastatic castrate resistant prostate cancer (mCRPC) whose disease has progressed despite novel hormonal treatment (enzalutamide or abiraterone) irrespective of the time of administration of these anti-androgen agents. Additionally, participants with biochemical relapse of disease (BCR), meaning there is no detectible metastatic disease, are included in Part B.

1.3. Overview of PrCa VBIR Regimen (PF-06753512)

An effective anti-tumor immune response should involve the activation of specific effector T cells and/or the production of functional anti-tumor antibodies targeted against antigens that are highly expressed by the patients' tumor. In this study, two antigen-delivery systems will be used in a heterologous prime/boost approach to elicit immune responses to several selected prostate cancer antigens. As these are self-antigens, the antigen delivery systems were selected to break immune tolerance and to elicit high T cell titers. The approach makes use of concomitant administration of immune modulators to drive immune response expansion as well as condition the immune suppressive tumor micro-environment to allow sustained immune-mediated killing of tumor cells.

The initial PrCa VBIR regimen for prostate cancer (PF-06753512) consisted of three basic components described below. A fourth component (described below) has now been added to the PrCa VBIR regimen, which is the anti-PD-1 antibody PF-06801591:

1. A priming immunization with a replication-deficient adenovirus (AdC68) vector, derived from a chimpanzee-specific AdC68 that expresses three selected prostate cancer-specific antigens, administered intramuscularly (IM).

2. Plasmid deoxyribonucleic acid (DNA) booster vaccinations, encoding the same antigens, administered IM with an electroporation device (intramuscular TriGrid Delivery System (TDS-IM)).

3. Low dose anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) monoclonal antibody (tremelimumab) delivered subcutaneously (SC) in conjunction with each immunization at a site as close as possible to the vaccine vector delivery site. The anti-CTLA4 administration is aimed at enhancing the vector-elicited immune response by blocking a natural mechanism for limiting antigen-specific T cell expansion.

4. In addition to the 3 agents described above, PF-06801591 will be added to treatment with PrCa VBIR. PF-06801591 is a humanized, hinge region-stabilized IgG4 monoclonal antibody (mAb) specific for human PD-1. This antibody can selectively and reversibly bind to human PD-1 and block the interaction between PD-1 and PD-L1/programmed death-ligand 2 (PD-L2). The administration of PF-06801591 will help maintain the PrCa VBIR-induced T cell response over time, by blocking the inhibitory effects against T-cells, which result from tumor-activated PD-1/programmed death-ligand 1 (PD-L1).

An overview of the rationale for the use of these three basic components of PrCa VBIR described in more detail below:

1. The three prostate cancer specific antigens (Prostate-Specific Membrane Antigen [PSMA], Prostate-Specific Antigen [PSA], and Prostate Stem Cell Antigen [PSCA]) were selected on the basis of their over expression in prostate cancer tumors and metastatic lesions.[7,13,14,23,29,35,49] The use of multiple tumor antigens within the prostate cancer vaccine will improve the probability that a greater percentage of patients will benefit from the vaccine, given that any single tumor antigen is not consistently expressed by every patient's tumor lesion with different pathological grades and clinical stage.

   Adenovirus has been shown in nonclinical and clinical studies to activate high levels of cluster of differentiation (CD) 4 and CD8 T cell and B cell responses, which are essential effector mechanisms of the immune system[5,50] (Study VR-VTR-10211). Since approximately 50% of patients in the US and Europe have pre-existing immunity to human adenovirus serotype 5,[6,12,28] a chimpanzee adenovirus C68 (AdC68) with limited seroprevalence in humans was selected for the priming vaccination.

2. Due to T cell homeostasis, T cell responses contract a couple of weeks post induction and require boost vaccinations to ensure the immune pressure is maintained on the tumor. Since humans develop neutralizing antibodies to adenovirus vectors, which prevent effective re-administration, the AdC68 priming vaccination will be followed by plasmid DNA boost vaccinations encoding PSMA, PSA, and PSCA administered IM with an electroporation device.

3. Tremelimumab (anti-CTLA4) will be given locally by SC injection in conjunction with the priming and boost vaccinations. This monoclonal antibody has been shown to increase responder frequency and enhance the breadth and magnitude of the T cell response to the selected cancer vaccine antigens.

1.3.1. Rationale for the Components of PrCa VBIR

Evidence that high titers of tumor-specific T cells can eliminate large tumor burden has recently been demonstrated in patients with refractory chronic lymphocytic leukemia (CLL) treated with chimeric antigen receptor (CAR) T cells.[36] In these clinical studies, peripheral blood mononuclear cells (PBMCs) are isolated from patients, modified ex vivo to express a tumor-antigen specific receptor and amplified before being adoptively transferred back into the patients. Complete remission was achieved in 9/12 patients who had - before therapy - a tumor burden between 3-7 pounds, highlighting the anti-tumor potency of high avidity T cells. The bolus injection of high numbers of high avidity T cells, however, resulted in tumor lysis syndrome with high fevers, most likely triggered by the systemic release of high levels of interferon (IFN) by the activated T cells. Unlike CARs, which are genetically modified T cells of high avidity, a cancer vaccine will induce polyclonal, tumor-antigen specific T cells. Vaccine induced T cells are expected to be of lower avidity due to thymic deletion of high avidity T cells specific for self-antigens. Vaccine induced T cell responses are mounted after each vaccination and generally require multiple boost vaccinations before high T cell titers are reached. The slower induction of T cells and thymic deletion of high avidity T cells might explain the good safety profile observed to date in patients treated with cancer vaccines.

A therapeutic cancer vaccine has recently shown to provide some therapeutic benefit to patients with mCRPC in a randomized Phase 2 trial.[19,22] The Prostvac vaccine consists of a Vaccinia virus prime vaccination followed by boost vaccinations using a fowlpox virus. The viruses express the PSA and the three T cell costimulatory molecules LFA-3, B7.1 and ICAM-1. Patients in the Prostvac arm had a median survival time of 25.1 months whereas patients in the control arm demonstrated a median survival time of 16.6 months which was statistically significant with a p-value of 0.0061.[48] Therefore, Prostvac provides proof of concept that induction of T cell responses specific to PSA can provide some therapeutic benefit to patients with mCRPC. PrCa VBIR may provide further therapeutic benefit to patients with prostate cancer for the following reasons:

1. PrCa VBIR utilizes the adenovirus vector for prime vaccination which has been shown in non-human primates (NHPs) to be superior to the Vaccinia based modified vaccinia virus Ankara (MVA) vector at inducing high titers of antigen-specific CD8+ T cells.[5]

2. In preclinical models using PrCa VBIR, T cell responses are amplified at each prime and boost vaccination with the local delivery of anti-CTLA4 (tremelimumab) administered SC at close proximity to the vaccine draining lymph nodes. Systemic delivery of an anti-CTLA4 monoclonal antibody in combination with cancer vaccines has recently been demonstrated to enhance the potency of two prostate cancer vaccines, namely Prostvac and GVAX[30,53] In both non-randomized studies, the patients that received the cancer vaccine with anti-CTLA4 lived much longer than patients who received the cancer vaccine as monotherapy, as predicted by the Halabi nomogram, a nomogram for predicting survival in men with CRPC.[17] Using preclinical models, local delivery of anti-CTLA4 at close proximity of the vaccine draining lymph nodes was demonstrated to be superior at enhancing vaccine induced T cell responses when compared to systemic delivery of anti-CTLA4 in combination with a cancer vaccine. These data suggest that local delivery of tremelimumab in the PrCa VBIR will activate higher tumor-antigen specific T cell titers than achieved when using systemic delivery of anti-CTLA4, in addition to eliminating the initial high systemic exposure to anti-CTLA4.

3. PrCa VBIR delivers, in addition to the PSA antigen, two more prostate specific antigens, namely PSCA and PSMA which are expressed in the majority of bone (PSCA) and lymph node (PSMA) metastatic lesions in prostate cancer patients.[23,49] Most of the metastatic lesions in prostate cancer patients are indeed found in the bone and lymph nodes.

4. MDSCs have been found at high levels in prostate cancer patients[54] and have been shown to blunt response to immunotherapy in metastatic melanoma patients treated with an anti-CTLA4 monoclonal antibody (ipilimumab, BMS). In these studies it was demonstrated that patients with low levels of MDSCs at baseline responded better to anti-CTLA4 treatment than patients with higher pre-treatment MDSC levels.[24]

5. The PD-1/PD-L1 signaling pathway plays a critical role in mediating T-cell immune suppression in the local tumor environment. Thus, anti-PD-1 monoclonal antibody (PF-06801591) when given with PrCa VBIR is anticipated to help induce high titers of tumor-specific T cells active long term at the tumor site.

Additional details of the pre-clinical studies can be found in the Investigator's Brochure.

1.3.2. Safety and Part B Expansion Dose for PF-06753512 (PrCa VBIR) combined with PF-06801591 (anti PD-L1 antibody)

As of 11 November 2019, 69 participants had been enrolled in the B7791001 study in Cohorts 1A and 2A (n=7), which include escalating doses of AdC68 (PF-06755992) ranging from 4×10^{11} VP to 6×10^{11} VP and a fixed dose of pDNA (PF-06755990) of 5 mg; Cohorts 3A (n=6) and 1B (n=20), which include 6×10^{11} VP AdC68, 5 mg of pDNA, and 80 mg oftremelimumab; Cohort 6A (n=7) and 5B (n=12), which include 6×10^{11} VP AdC68, 5 mg of pDNA, 80 mg of tremelimumab, and 130 mg of PF-06801591; Cohort 9A (n=3), which includes 6×10^{11} VP AdC68, 5 mg of pDNA, 40 mg of tremelimumab and PF-06801591

130 mg; and Cohort 7A (n=14), which includes 6×10^{11} VP AdC68, 5 mg of pDNA, 80 mg of tremelimumab and PF-06801591 300 mg.

As of 11 November 2019, the most frequently experienced (≥5 participants) treatment related AEs were fatigue and influenza like illness (27 participants; 39.1% each), diarrhoea (14 participants; 20.3%), nausea and pyrexia (10 participants; 14.5% each), decreased appetite, and myalgia (9 participants; 13.0% each), injection site pain, alanine aminotransferase increased, headache, and amylase increased (8 participants; 11.6% each), aspartate aminotransferase increased, lipase increased, and arthralgia (7 participants; 10.1% each), pruritus (6 participants; 8.7%), hyperthyroidism, hypothyroidism, abdominal pain, chills, vomiting, injection site discomfort, weight decreased, and hyponatraemia (5 participants; 7.2% each).

Adverse Drug Reactions (ADRs) identified for PrCa VBIR (PF-06753512) in combination with PF-06801591 include colitis and hypothyroidism.

Grade 4 myasthenia gravis and myositis as well as Grade 3 alanine aminotransferase and aspartate aminotransferase were reported in one participant dosed with PrCa VBIR in combination with PF-06801591. Myasthenia gravis and myositis have been reported with anti-PD-1, anti-PD-L1 and anti-CTLA-4 therapies. A blood sample was collected at screening for central evaluation of AChR antibodies and positive results were exclusionary. Participants should be closely monitored for early detection of signs and symptoms of myasthenia gravis and/or myositits and should be instructed to contact the investigative site immediately should they experience diplopia, ptosis of the upper eyelid, difficulty to walk, talk or swallow, muscle weakness, or shortness of breath.

Two participants on Study B7791001 experienced immune-mediated myocarditis. Both participants are in the earliest stage of prostate cancer recurrence and carried the diagnosis of "prostate cancer, biochemical relapse-only ("BCR"). There have been no reports of immune-mediated myocarditis in participants with metastatic prostate cancer.

One participant developed signs of myocardial inflammation (significant ECG changes) at 22 days after the initiation of therapy, had elevated cardiac troponin consistent with myocardial injury, an endomyocardial biopsy showed lymphocytes infiltrating the myocardium, and responded to steroids and immunosuppressive therapy. The second participant presented with multi-system organ failure at 274 days from initiation of treatment. The participant presented with significant heart failure, along with markedly elevated cardiac troponin indicating myocardial injury. The participant died within 24 hours of hospitalization. No autopsy was performed to help determine the diagnosis.

Based upon the above cases of immune-mediated myocarditis in Cohort 5B of Study B7791001, participants will be screened prior to study entry for elevations in cardiac troponin (cTnI), a biomarker for cardiac inflammation or injury; if elevated, participants will be excluded from the study. In addition, serial cardiac monitoring of cTnI will be initiated for all on-going participants in B7791001 and dosing will not occur unless the cTnI is within normal limits.

1.4. Nonclinical Safety

1.4.1. Nonclinical Toxicity Study for PrCa VBIR

The nonclinical safety of the AdC68, plasmid DNA (pDNA) and tremelimumab were assessed in a repeat-dose toxicity study in sexually-mature male monkeys. The cynomolgus monkey was considered the appropriate species for the toxicity study because of the high homology (DNA/protein) of the three antigens between monkeys and humans, and because of the lack of activity of tremelimumab in rodents. The safety of AdC68 was also evaluated following a single dose administered without tremelimumab, as part of the repeat-dose study in monkeys. In a separate study, the tissue distribution and persistence of AdC68 was characterized using quantitative polymerase chain reaction (qPCR) following a single intramuscular injection in Cotton rats, a species that was demonstrated to express encoding antigens.

The repeat-dose toxicity study in monkeys used the same routes of administration and the same dose regimen for the vaccine components and tremelimumab as proposed for this study. An initial priming dose of AdC68 was followed by 3 consecutive boost doses with pDNA followed by an additional boost with AdC68, all administered at 28-day intervals. Tremelimumab was administered by SC injection at a site local to the vaccine delivery site on the same days as vaccine administration. The absolute dose of AdC68 ($6x10^{11}$ VP) was the same as the highest proposed human dose. The absolute dose of plasmid DNA (10 mg) was two times the proposed human dose. Tremelimumab was evaluated at two dose levels (50 and 150 mg) when administered with the vaccine components, and at the 150 mg/dose level in the absence of the vaccine components, using the same monthly dosing regimen.

In the repeat dose study, there was no evidence of systemic toxicity and findings were limited to the injection sites and the draining lymph nodes and are consistent with a local inflammatory reaction and generation of an immune response. Mild non-adverse increases in monocytes, fibrinogen, thyroxine and marked increases in C-reactive protein consistent with an immune response associated with AdC68 administration were observed. There were no indications of local irritation (erythema or edema) attributed to the administration of AdC68, tremelimumab or AdC68/pDNA/tremelimumab noted over the course of the dosing and recovery periods of the study. Slight, transient increase in body temperature was noted 24 hours after administration of the pDNA/tremelimumab in one animal; however, no consistent pattern was observed.

1.4.2. Nonclinical Toxicity Studies of PrCa VBIR with PF-06801591

The safety and toxicokinetics of the PrCa VBIR in combination with SC or intravenous (IV) administered PF-06801591 was evaluated in a Good Laboratory Practice (GLP) study in sexually-mature male cynomolgus monkeys. PF-06801591 was administered at a dose of 20 mg/kg by SC or IV injection concurrently with the initial AdC68 prime dose and a single pDNA boost of the PrCa VBIR (2 injections, 1-month apart). SC injections were made at a site local to the vaccine delivery site, adjacent to the tremelimumab injection site. The safety of PF-06801591 administered by SC injection according to the same dose schedule in the absence of the PrCa VBIR was also evaluated as part of this study.

There were no microscopic findings, changes in clinical pathology parameters, or other evidence of local or systemic toxicity when PF-06801591 was administered alone at 20 mg/kg SC. There was no evidence of systemic toxicity when the PrCa VBIR was administered in combination with SC or IV dosages of PF-06801591. Mild, transient increases in globulin and moderate to marked increases in C-reactive protein (CRP) were observed following administration of the PrCa VBIR in combination with PF-06801591 on Days 1 and 28. Transient increases in lymphocytes and/or monocytes, and fibrinogen were observed following administration on Day 1 only (priming dose with AdC68). These changes were considered indicative of an inflammatory response to vaccine administration. Microscopic findings of minimal to mild chronic inflammation at the vaccine injection sites, and tremelimumab and PF-06801591 SC injection sites, were consistent with generation of an immune response against the vaccine components and localized effects at the injection sites. All effects were considered nonadverse, because they were transient and/or based on the low magnitude and absence of correlating adverse clinical pathologic alterations. Increases in antigen-specific T cells were observed in all animals that received the vaccine components with tremelimumab and PF-06801591. PF-06801591 exposures were similar on Days 1 and 29 when administered as a single agent by SC injection. PF-06801591 exposures were lower on Day 29 compared to Day 1 when co-administered with the PrCa VBIR, possibly due to induction of anti-drug antibodies (ADA). Tremelimumab exposures were similar when co-administered with SC or IV PF-06801591.

Results of cytokine release assays conducted using tremelimumab and PF-06801591 in combination in human whole blood or PBMCs showed no synergistic effect on cytokine release when these agents were combined, and thus, indicate a low risk of human cytokine toxicity.

1.5. Pharmacokinetics of Tremelimumab and PF-06801591

1.5.1. Tremelimumab Pharmacokinetics After Intravenous Administration

The single-dose and multiple-dose pharmacokinetics (PK) of tremelimumab following intravenous (IV) administration have been studied in participants with varied tumor types, including solid tumors, melanoma, and prostate cancer (Studies A3671001, A3671002 and A3671004). After IV administration, tremelimumab exhibited a biphasic disposition profile. Over the dose range of 0.1 to 15 mg/kg, mean values of the maximum drug concentration (C_{max}) and the area under the concentration-time curve (AUC) increased with dose in an approximately proportional manner. Tremelimumab had a low clearance (mean values ranged from 0.119 to 0.152 mL/hr/kg), a small volume of distribution (mean values ranged from 78.1 to 85.1 mL/kg), and a long terminal disposition half-life ($t_{1/2}$; mean values ranged from 19.2 to 24.8 days). After repeated administration at 10 mg/kg once every 4 weeks, the accumulation ratio based on AUC was approximately 1.26.

PK of tremelimumab after subcutaneous administration has not been evaluated in previous studies.

1.5.2. PF-06801591 Pharmacokinetics

Single and multiple dose PK of PF-06801591 are being evaluated in the ongoing Phase 1b/2 study B8011001 (Section 1.6.4.1). Preliminary PK data from Phase 1 cohorts suggest that PF-06801591 exhibits PK characteristics typical of IgG4 monoclonal antibodies.

The mean maximum serum concentration (C_{max}) and area under the serum concentration-time curve over the dosing interval (AUC_{tau}) of PF-06801591 increased in an approximately dose-proportional manner over the dose range of 0.5 -10 mg/kg following IV administration. The CV% values for C_{max} and AUC_{tau} were 24% to 35% and 22% to 36%, respectively (n = 2-8 per dose level), following the first IV dose. After SC administration at 300 mg, PF-06801591 was slowly absorbed, with a median T_{max} of approximately 8 days (n = 15). Steady state exposure after repeated SC dosing at 300 mg every 4 weeks fell within the range observed following IV dosing at 1 and 3 mg/kg, Q3W.

1.6. Starting Dose Rationale

Below are listed the rationales for the starting doses of the various components:

1.6.1. Clinical Adenovirus C68 Dosing

Anticipated efficacy and safety were considered when selecting the AdC68 dose range for clinical testing. The dose ranges of 1 x 10^9 VP to 5 x 10^{11} VP of a modified adenovirus antigen delivery system have shown a tolerable safety profile in patients with colorectal cancer as well as dose-dependent immune responses to a self-antigen.[31] Previously, high doses of different adenovirus vectors were evaluated preclinically. The absence of germ line transmission was demonstrated in mice and baboons.[38,56] In a separate study in NHPs, a dose of 5 x 10^{12} VP/kg was found to be well tolerated.[39] Importantly, repeated administration did not appear to alter the toxicity/tolerability profile.[34] It is also important to note that these animals were dosed IV per kg body weight, making the total dose substantially higher than the highest dose planned in this study (6 x 10^{11} VP IM total dose). Furthermore, since the administration in this study is IM, the systemic safety profile is anticipated to be more favorable.[38] Higher doses of adenovirus, up to 2 x 10^{11} VP/kg (total dose in excess of 1 x 10^{13} VP), when administered directly into the hepatic artery are tolerated in patients with partial ornithine transcarbamylase deficiency.[40]

In the toxicity study of AdC68, plasmid DNA and tremelimumab in monkeys, the safety and antigen-specific T-cell responses were evaluated following administration of AdC68 at 6 x 10^{11} VP, either as a single agent or in combination with plasmid DNA and tremelimumab using the same dosing frequency as planned for the Phase 1 study. As described in Nonclinical Safety, there was no evidence of systemic toxicity in the study and findings were limited to the injection sites and the draining lymph nodes. CCI [redacted]

Based on the above safety and immune response data, a starting dose of 4 x 10^{11} VP administered IM has been selected as the starting dose for AdC68 in this study.

1.6.2. Clinical Plasmid DNA Dosing

Efficacy and safety were factors considered to select the DNA dose for clinical testing. DNA doses of 0.2 to 8 mg have been reportedly delivered in clinical trials by other sponsors using the Ichor TDS electroporation device. In NHPs, the data collected to date demonstrated that electroporation of DNA dose at 5 mg can effectively and reproducibly boost AdC68 vector primed IFNγ CD8 T cell responses to a self-antigen in the presence of tremelimumab. A DNA dose of 10 mg was well tolerated but no significant benefit on the magnitude or responder frequency of the IFNγ CD8 T cell responses was observed. Thus, a dose of 5 mg is selected for the DNA for clinical testing.

1.6.3. Clinical Tremelimumab Dosing

More than 1000 participants with cancer have been treated with tremelimumab as single-agent or in combination with another anti-cancer treatment. Clinical safety data for tremelimumab, at IV doses ranging from 0.01 to 15 mg/kg, indicate an acceptable safety profile in participants with cancer. The established maximum tolerated dose (MTD) for single-agent therapy is 15 mg/kg IV every 12 weeks, a dose level that has been extensively studied in a Phase 3 trial in participants with melanoma.[41] Diarrhea, pruritus, and rash were the most common treatment-related adverse events (AEs) associated with tremelimumab. Another important event observed related to tremelimumab was hypopituitarism.

Monthly dosing, as planned for this study, was tested in the clinic in participants with melanoma, where administration of up to 10 mg/kg IV monthly[3] was tolerated with no dose-limiting toxicity observed. The overall profile was found to be acceptable with the most frequent treatment-related AEs being diarrhea, rash, and pruritus. Frequency of Grade 3/4 AEs was 27% in the participants dosed with 10 mg/kg once every month.

The highest dose of tremelimumab will not exceed 150 mg, which equals to 2 mg/kg for a 75 kg patient, is expected to lead to a systemic exposure not exceeding that of a 2 mg/kg IV dose in a 75 kg patient. Thus, the AUC and C_{max} of this dose are expected to be lower than those of the 10 mg/kg dose of tremelimumab previously administered to participants monthly via the IV route as described above.

Given the lower doses and the different route of administration, SC rather than IV administration, this study will start at a dose level of 80 mg total dose SC. In the event that 80 mg SC is not tolerated, lower dose levels (eg, 40 mg) may be tested.

1.6.4. Clinical PF-06801591 Dosing

The starting dose of PF-06801591 will be at 130 mg, administered SC every 4 weeks (Q4W) in combination with the PrCa VBIR. Upon evaluation of the emerging safety (including late onset toxicities) and PK data of PF-06801591 from the initial PF-06801591 dosing cohort in all participants for 4 weeks or longer, a higher PF-06801591 dose of 300 mg was selected for further evaluation with escalating doses of tremelimumab. The specific dose level for PF-06801591 dosing cohorts was selected to achieve the systemic exposure that has shown to

be therapeutically effective for similar anti-PD-1 mAbs, not to exceed 300 mg due to the limitation of injection volume. The starting dose of 130 mg was selected based on data from nonclinical safety studies of PrCa VBIR in combination with PF-06801591, and known dose/exposure-response relationships of similar anti-PD-1 monoclonal antibodies. The steady-state C_{max} and $AUC_{0\text{-}tau}$, following SC administration of PF-06801591 at 130 mg Q4W in humans, were predicted to be approximately 8% and 43%, respectively, of the C_{max} and AUC of the no observed adverse effect level (NOAEL) determined from the nonclinical safety study of the PrCa VBIR in combination with PF-06801591 in cynomolgus monkeys. Also, the predicted steady state C_{max} and average concentration ($C_{average}$) of PF-06801591 at 130 mg Q4W are comparable or lower than those achieved by nivolumab or pembrolizumab at tolerated intravenous dose levels, either given alone or in combination with an anti-CTLA4 mAb (Keytruda [pembrolizumab] United States Package Insert (USPI) version 12/2015; Opdivo [nivolumab] USPI version 3/2015).

1.6.4.1. PF-06801591, an Anti-PD-1 Antibody: Clinical Experience in Study B8011001 (NCT02573259)

B8011001 is an ongoing Phase 1, open-label, multi-center, multiple-dose, dose escalation and expansion, safety, PK, and PD study of PF-06801591. The primary purpose of this study is to evaluate safety and early signs of efficacy. This clinical study was divided into a dose escalation (Part A) phase and a dose expansion (Part B) phase. One hundred forty-six participants have been dosed on the study. No dose limiting toxicity was observed and there was no maximum tolerated dose identified.

Part A Dose Escalation

Part A dose escalation evaluated 4 pre-specified IV dose levels (0.5, 1, 3, and 10 mg/kg administered every 3 weeks [Q3W]), and 1 subcutaneous (SC) dose level (300 mg administered every 4 weeks [Q4W]) in adult participants with locally advanced or metastatic melanoma, squamous cell cancer of head and neck, ovarian cancer, sarcoma, small cell lung cancer, adenocarcinoma of salivary gland, endometrial adenocarcinoma, malignant peritoneal neoplasm, esophageal adenocarcinoma or renal cell carcinoma. Participants had progressive disease on ≥1 prior line of therapy for locally advanced or metastatic disease or refused standard of care therapy; were not previously treated with an anti-PD-1/PD-L1 agent; and had adequate renal, bone marrow, liver, and cardiac function, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Forty participants were enrolled into Part A with 25 participants total enrolled into the IV dose cohorts and 15 participants enrolled into the SC dose cohort.

Part B Dose Expansion

The 300 mg SC dose was evaluated in an expanded population of 106 participants. This included 68 participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) and 38 participants with locally advanced or metastatic urothelial carcinoma who were anti-PD-1 or anti-PD-L1 treatment-naïve and who had progressive disease on or were intolerant to systemic therapy or for whom standard of care systemic therapy was refused or unavailable. Participants with NSCLC could have received up to 1 line of prior systemic

therapy for locally advanced or metastatic disease and if they had known epidermal growth factor receptor (EGFR) activating mutation or an anaplastic lymphoma kinase (ALK) rearrangement were required to have, in addition, at least 1 targeted therapy for their disease. Participants with UC could have received up to 2 lines of prior systemic therapies for locally advanced or metastatic disease. The selected participants had adequate renal, bone marrow, liver, and cardiac function, with ECOG performance status 0 or 1. All participants received 300 mg of PF-06801591 SC every 4 weeks.

Complete information for PrCa VBIR may be found in the single reference safety documents (SRSD). The SRSDs for this study are the PF-06753512 Investigator's Brochure for: AdC68 (PF-06755992), plasmid DNA (PF-06755990), PF-06801591, and tremelimumab.

The SRSD for the electroporation device is the Trigrid™ Delivery System electroporation device Investigator's Brochure.

Additional reference information can be found in the individual tremelimumab IB and the PF-06801591 IB.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Part A Objectives

Part A Primary Objective

- To assess safety and tolerability of increasing dose levels of the prostate cancer vaccine-based immunotherapy regimen (PrCa VBIR) components alone and in combination with increasing doses of PF-06801591.

- To characterize the dose limiting toxicities (DLTs), if any are observed, and overall safety profile of escalated doses of the PrCa VBIR components alone and in combination with increasing doses of PF-06801591.

- To determine the Part B Expansion Dose for the PrCa VBIR components and PF-06801591in combination.

Part A Secondary Objectives

- To evaluate the immune response elicited by the PrCa VBIR to the selected prostate cancer tumor-antigens.

- To evaluate the overall safety profile in prostate cancer participants.

- To evaluate the PK of tremelimumab after SC administration.

- To evaluate the PK of PF-06801591 after SC administration.

- To evaluate the anti-drug antibody (ADA) response of tremelimumab after SC administration with the other PrCa VBIR components.

- To evaluate the ADA response of PF-06801591 after SC administration with the other PrCa VBIR components.

Part A Exploratory Objectives

- To document any preliminary evidence of anti-tumor activity.

- [redacted]

- [redacted]

2.2. Part A Endpoints

Part A Primary Endpoint

- Incidence and grade of treatment-emergent adverse events including DLTs as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

Part A Secondary Endpoints

- Immune response including T cells specific to the three selected prostate cancer tumor-antigens.

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) and timing.

- Tremelimumab single-dose PK parameters, including the maximum concentration (C_{max}), time to maximum concentration (T_{max}), and area under the concentration versus time curve (AUC) from time zero to the last quantifiable time point prior to the second tremelimumab dose ($AUC_{last)}$ and if data permit, AUC from time zero extrapolated to infinity (AUC_{inf}); and trough concentrations after multiple dosing (C_{trough}).

- PF-06801591 single-dose PK parameters, including C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}; and C_{trough} after multiple dosing.

- Incidence and titers of ADA and neutralizing antibodies against tremelimumab.

- Incidence and titers of ADA and neutralizing antibodies against PF-06801591.

Part A Exploratory Endpoints

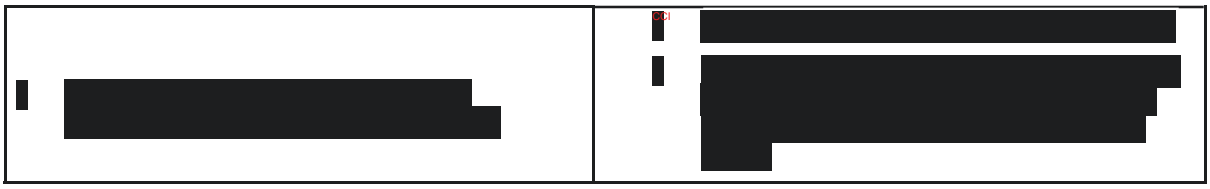
- Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 (Appendix 3) by calculating the Objective Response Rate (ORR) and Progression-Free Survival (PFS).

- Antitumor response and tumor control duration based on total measurable tumor burden as assessed by the Immune-Related Response Criteria Derived from RECIST 1.1 (irRECIST) (Appendix 4).

- Bone outcome according to Prostate Cancer Working Group 3 (PCWG3) criteria.[44] (Appendix 5)

2.3. Part B Objectives and Endpoints

Primary Objective(s):	Primary Endpoint(s):
• To evaluate the overall safety profile of the PrCa VBIR + PF-06801591 in prostate cancer participants.	• Incidence and grade of treatment-emergent adverse events including DLTs as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03). • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) and timing.
Secondary Objective(s):	**Secondary Endpoint(s):**
• For Cohort 3B: To evaluate the anti-tumor response induced by treatment in participants with mCRPC utilizing solid tumor response criteria. • For Cohort 3B: To evaluate the anti-tumor response induced by treatment utilizing immune related response criteria. • For Cohort 3B: to evaluate bone metastatic disease outcome in participants with mCRPC. • For Cohorts 3B: To estimate the duration of radiographic Progression-Free Survival (rPFS) in participants with mCRPC. • To evaluate response rate based on 50% reduction of prostate specific antigen (PSA). • To evaluate PSA kinetics. • To evaluate trough concentrations of tremelimumab after SC administration at selected doses. • To evaluate trough concentrations of PF-06801591 after SC administration at selected doses. • To evaluate the anti-drug antibody (ADA) response of tremelimumab after SC administration with the other PrCa VBIR components. • To evaluate the ADA response of PF-06801591 after SC administration with the other PrCa VBIR components.	• For Cohort 3B: Objective response rate (ORR) and duration of response, as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix 3). • For Cohort 3B: Antitumor response and tumor control duration based on total measurable tumor burden as assessed by the Immune-Related Response Criteria Derived from RECIST 1.1 (irRECIST) (Appendix 4). • For Cohort 3B: Bone outcome according to Prostate Cancer Working Group 3 (PCWG3) criteria (Appendix 5).[44] • For Cohort 3B: Radiographic Progression-Free Survival (rPFS) by RECIST 1.1, irRECIST and PCWG3 Criteria in participants with mCRPC. • PSA-50 response rate and duration of response. • Baseline and changes from baseline for PSA, PSA velocity, PSA slope and PSA doubling time (PSADT). • Trough concentrations after multiple dosing (C_{trough}). • C_{trough} after multiple dosing. • Incidence and titers of ADA and neutralizing antibodies against tremelimumab. • Incidence and titers of ADA and neutralizing antibodies against PF-06801591.
CCI [redacted]	[redacted]



3. STUDY DESIGN

3.1. Study Overview

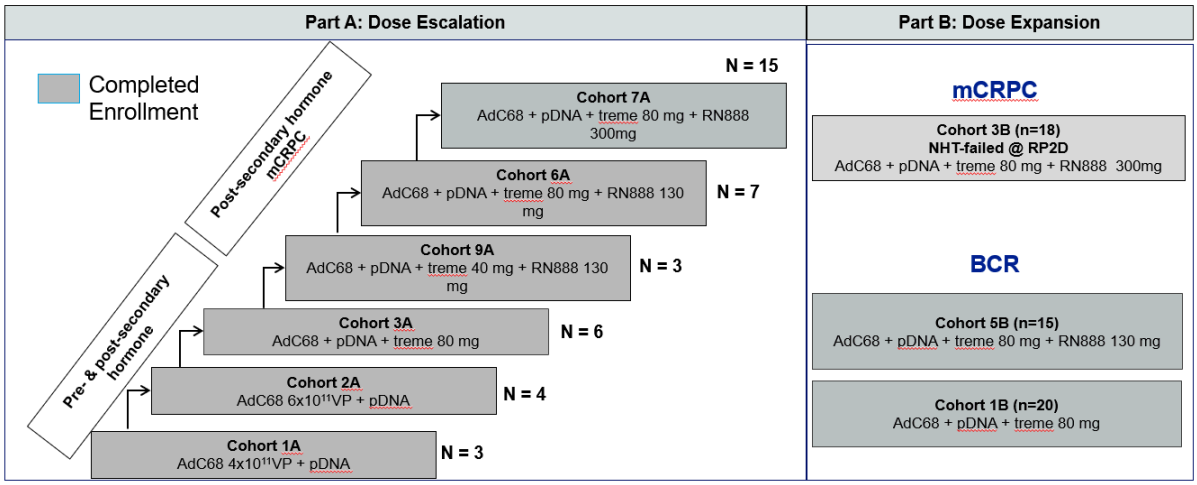
This is a Phase 1, open label, multi-center, multiple dose, safety, PK, CCI and immunogenicity study evaluating the components of a vaccine-based immunotherapy regimen for prostate cancer (PrCa VBIR). PrCa VBIR consists of the following components: Adenovirus (AdC68), pDNA and tremelimumab. In addition, cohorts will evaluate PrCa VBIR when given in combination with PF-06801591.

The study is divided in to two parts, Dose Escalation (Part A) followed by Dose Expansion (Part B). The overall design is presented in Figure 1 below.

Participants will participate in the treatment period of the study for approximately 9 months. This includes a 28 day screening period followed by two cycles of treatment (each 4 months in duration for a total of 8 months). Participants will then enter the maintenance phase of the study where they will continue to receive their assigned components, at the frequencies outlined in the schedule of activities. Treatment will continue until: disease progression, participant refusal or unacceptable toxicity occurs. Participants who demonstrate clinical benefit with manageable toxicity and who are willing to continue receiving study treatment will be given the opportunity to continue treatment upon agreement between the investigator and sponsor. When the participant discontinues treatment, they will then enter a 6 month post-dose follow-up period. The end of the study is the last participant last visit.

A cycle of the PrCa VBIR includes at minimum an AdC68 priming dose given intramuscularly (IM) on Day 1, followed by a total of three doses of DNA, given IM using an electroporation device at 4-week intervals for another 12 weeks (16 weeks total). Beginning with Cohort 3A, the PrCa VBIR cycle will also include tremelimumab given as SC injections at close proximity to the vaccinated muscles and the vaccine draining lymph nodes every four weeks at the immunization time points. For participants enrolled in Cohorts 6A through 9A or Cohorts 3B or 5B, the PrCa VBIR cycle will also include PF-06801591 given as SC injections at close proximity to the vaccinated muscles and the vaccine draining lymph nodes every four weeks at the immunization time points. After completing two cycles of treatment (≈8 months treatment duration), the participants will then enter the maintenance phase of the study.

Figure 1. Overall Study Design



The dose of each component evaluated in subsequent cohorts was determined based on the safety data from previous cohorts.

The treatment effect of cancer immunotherapy can often be delayed. Therefore, participants should be encouraged to continue on study treatment for at least 24 weeks before an investigator considers removing the participant due to disease progression, as long as:

- Participant and investigator agree.
- Participant continues to meet all other study protocol eligibility criteria.
- Acceptable toxicity.
- No deterioration of participant performance status.

If a participant withdraws from the study before Day 29 for reasons other than investigational product-related toxicity, another participant may be enrolled to replace that participant at the current dose level. In principle, all participants must be evaluated for 28 days following the first AdC68 vaccination. However, if a participant discontinues close to Day 29 for reasons other than toxicity, but due to a clear drug unrelated event (eg, traffic accident, clear disease progression), the participant may be deemed evaluable for safety if the investigator and sponsor's medical monitor both agree that the participant is suitable for inclusion in the dose limiting toxicity (DLT) evaluation group.

3.1.1. Dose Escalation (Part A)

The principles of 3+3 design were utilized for the dose escalation portion of the study. The dose escalation could include an increase in the dose of one component of the regimen or could include the addition of the lowest dose of an additional component. Dose escalation followed the scheme presented in Figure 1, assuming dose levels were achieved with 0 out of the initial 3 or maximum 1 out of the initial 6 participants developing DLTs. For each

component the highest tested dose level was used for subsequent cohorts unless the highest dose level is not tolerated (>1 out of the initial 3 to 6 participants developing DLT). If DLT occurred in >1 out of the initial 3 to 6 participants at the higher dose level then the lower level will be administered to subsequent cohorts. Intrapatient dose escalation was not permitted.

Activation of each cohort occurred no sooner than 28 days after the first three participants (or 6 participants if a DLT is observed and the cohort is expanded) receive the first AdC68 vaccination, but may occur later if the sponsor and investigators determine additional safety data is needed. The Pfizer clinical team and investigators reviewed all available safety data from the previous and current cohorts prior to making a decision to dose escalate. If no safety issues that would prohibit dose escalating were observed, the next cohort of participants would be open for accrual.

Part A dose escalation started with the lowest dose of AdC68, followed by three plasmid DNA boosts (5 mg fixed dose) in 4 week intervals (Cycle 1), repeated for two cycles. Since no identified unacceptable toxicity was reported in the first 2 cohorts (1A and 2A), the AdC68 dose of 6×10^{11} VP was used for all subsequent cohorts. In Cohort 3A, tremelimumab was added at 80 mg. Starting with Cohort 6A, the dose escalation of PF-06801591 in combination with PrCa VBIR started with a low dose (130 mg) and was then escalated up to 300 mg.

Based on the emerging safety and PK data from Cohort 3A, enrollment of participants in Expansion Cohort 1B was initiated allowing for adequate evaluation of the safety of PrCa VBIR with tremelimumab 80 mg. Likewise, enrollment of participants in Expansion Cohort 5B was initiated allowing for adequate evaluation of the safety of PrCa VBIR in combination with 130 mg of PF-06801591 based on the safety data from Cohort 6A.

Based on safety data from Cohort 7A, the Part B Expansion Dose for participants with mCRPC whose disease progressed after novel hormone therapy was determined to be AdC68 6×10^{11} VP + plasmid DNA 5 mg + tremelimumab 80 mg + PF-06801591 300 mg. Enrollment in Expansion Cohort 3B was initiated at the Part B Expansion Dose, in order to further assess the safety, immune response, pharmacokinetics, and pharmacodynamics of PrCa VBIR of this dose level in the mCRPC population.

3.1.2. Dose Expansion (Part B)

In Part B, the selected doses of the PrCa VBIR in combinations with PF-06801591 were evaluated in two populations: (1) Participants with mCRPC whose disease has progressed despite novel hormone therapy (abiraterone or enzalutamide) to be treated with PrCa VBIR+ PF-06801591 alone; and (2) Participants with biochemical relapse of disease (BCR) to be treated with PrCa VBIR+ PF-06801591.

The study design has changed in two aspects: (1) in the removal of Cohort 10B, because studies of progression on novel-hormone therapy with abiraterone, with a switch to enzalutamide + Pr Ca VBIR, are no longer useful in defining Proof of Concept for this study; and (2) in no longer expanding cohort 3B, because sufficient sample size has been reached to make decisions about further development based upon safety and preliminary efficcacy.

The following listing identifies the Expansion Cohorts for Part B:

- Cohort 1B (20 participants treated): Twenty participants with BCR have been enrolled and treated in this expansion cohort, using PrCa VBIR and tremelimumab at a dose level of 80 mg. No PF-06801591 was included in this regimen. **No additional participants will be enrolled.**

- Cohort 5B (15 participants treated): Fifteen participants with BCR and no prior therapy have been treated with PrCa VBIR in combination with 130 mg PF-06801591. **No additional participants will be enrolled.**

- Cohort 3B (18 participants treated): Eighteen participants with mCRPC whose disease has progressed despite novel hormonal treatment (enzalutamide or abiraterone) have been treated with PrCaVBIR in combination with 300 mg PF-06801591. **No additional participants will be enrolled.**

Different cohorts of patients opened for enrollment in parallel. Cohorts are non-randomized; slot assignments were managed by the study team with sites notified in advance of cohort availability. Participants are not allowed to crossover between the different combinations evaluated in this study.

3.1.3. Maintenance Treatment Period

To mimic the immune response induced by the PrCa VBIR encoding tumor associated self-antigens in non-human primates, the response induced by the PrCa VBIR encoding a rhesus PSMA (rhPSMA) antigen was evaluated. Durable and high magnitude induction of polyfunctional IFNγ CD8 and CD4 T-cell titers recognizing rhPSMA were observed by 2 cycles of the PrCa VBIR with a 100% responder frequency. The immune response was maintained long term (3-4 month) after discontinuation of vaccination post completion of the second PrCa VBIR cycle. The IFNγ CD8 titers recognizing rhPSMA with cytolytic ability declined slightly approximately 2 months after discontinuation of vaccination. At Week 57, 26 weeks after the last of 8 vaccinations, re-administration of pDNA given concurrently with tremelimumab rapidly increased the magnitude of self-antigen specific polyfunctional and cytolytic T-cell responses. Based on these data, following 2 cycles of the PrCa VBIR, a maintenance boost cycle of 2 months with DNA delivered by electroporation and SC injections of tremelimumab is proposed as long as the participant derives clinical benefit. Participants will also continue to receive monthly PF-06801591 as received prior to the maintenance treatment period, where applicable.

3.2. DLT Definition

Severity of adverse events will be graded according to CTCAE version 4.03. For the purpose of dose escalation, any of the following adverse events occurring in the first 28 days following the first AdC68 vaccination that are not considered related to disease/progression will be classified as DLTs:

Hematologic:

The following DLT criteria apply to participants enrolled in Cohorts 1A through 4A and Cohorts 6A through 9A only:

- Grade 3 neutropenia lasting >7 days.
- Febrile neutropenia (febrile neutropenia is defined as an absolute neutrophil count $<1.0 \times 10^9$/L with a single temperature of >38.3°C, or 101°F, or a sustained temperature of ≥38°C, or 100.4°F, for more than one hour).
- Grade ≥3 neutropenic infection.
- Grade ≥3 thrombocytopenia.
- Grade ≥3 anemia lasting more than 7 days.
- Grade ≥3 lymphopenia lasting more than 14 days.

Non-hematologic:

The following criteria apply to all cohorts:

Non-hematologic laboratory abnormalities:

- Grade ≥3 laboratory abnormalities either associated with symptoms or associated with worsening of an existing condition or that suggests a new disease process or that requires additional active management (eg, discontinuation of the drug, close observation, more frequent follow-up assessments, further diagnostic investigation or specific treatment).
    - The following will not be considered DLTs: elevation of gamma-glutamyltransferase (GGT), elevation of alkaline phosphatase, hypo/hyperchloremia, hypo/hyperphosphoremia, hypoalbuminemia, hypomagnesemia, hypocalcemia of less than 15 days, amylase or lipase elevation not associated with clinical symptoms that spontaneously resolved within 7 days to Grade ≤1 or baseline, and Grade ≤3 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that spontaneously resolve within 7 days to Grade ≤1 or baseline.

Other non-hematologic events:

- Grade ≥3 toxicities, including toxicities of the major organs which include heart, kidney, liver, lung, colon, pancreas, brain and adrenal, hypophysis and thyroid glands.
- Those toxicities that have been adequately treated (eg, nausea, vomiting, diarrhea) are not considered DLTs.
- Grade 3 flu like symptoms lasting greater than 3 days with adequate treatment.
- Fever of >40.0°C, or 104.0°F, lasting for more than 3 days with adequate treatment.

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

3.3. MTD Definition for Part A

An MTD may not be identified, as DLTs are not frequently observed with cancer vaccines. However, since PrCa VBIR includes non-vaccine components, the potential for DLTs has to be taken into account. In practice, according to the 3+3 design, the MTD estimate, for each component being escalated, is the dose level at which 0/3 or 1/6 evaluable participants experience a DLT within 28 days after the first AdC68 vaccination with the next higher dose having at least 2 of the initial 3 to 6 participants experiencing DLTs.

Adverse events occurring in Part B that meet the same grading criteria as the DLT criteria in Part A will be discussed with the Principal Investigators. During this discussion, a review of the details of the toxic effects and their clinical impact will be undertaken. Following this discussion with the Principal Investigators, a decision will be made by the Sponsor as to whether any action needs to be taken related to changing the dosing in any specific cohort of participants.

3.4. Part B Expansion Dose

The Part B Expansion Dose for each component is the dose chosen for further study based on Phase 1 study results.

3.4.1. Part B Expansion Dose: Participants with mCRPC (Cohort 3B)

1. AdC68: $6x10^{11}$ VP administered IM.
2. pDNA: 5 mg administered IM with electroporation device.
3. Tremelimumab: 80 mg administered SC:

   3a. Tremelimumab dose may be decreased to 40 mg SC depending upon emerging safety data.

4. PF-06801591: 300 mg administered SC:

4a. PF-06801591 dose may be decreased to 130 mg SC depending upon emerging safety data.

3.4.2. Part B Expansion Dose: Participants with Rising PSA at High Risk for Recurrence After Definitive Local Therapy (Biochemical Relapse or BCR)

1. AdC68: $6x10^{11}$ VP administered IM.
2. pDNA: 5 mg administered IM with electroporation device.
3. Tremelimumab: 80 mg administered SC:

   3a. Tremelimumab dose may be decreased to 40 mg SC depending upon emerging safety data.
4. PF-06801591: 130 mg administered SC:

Dosing for tremelimumab and PF-06801591 will be explored as follows: Dosing may start with tremelimumab at 80 mg + PF-06801591 130 mg in an initial group of 3 to 6 patients. A decision will be made whether to continue tremelimumab at 80 mg with an increase of PF-06801591 to 300 mg, if the starting dose level is tolerated; or to decrease tremelimumab to 40 mg keeping PF-06801591 at 130 mg or increasing PF-06801591 to 300 mg based upon emerging safety data. The final dose level for this population will then be selected to complete this cohort.

3.5. Declaration of RP2D

At the conclusion of the Part B, Dose Expansion, a RP2D will be declared for the mCRPC and BCR cohorts. The RP2D declaration will be based upon the totality of the clinical evidence, including safety, efficacy, PK/PD, and any other information relevant to this decision.

4. PARTICIPANT SELECTION

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

4.1. Inclusion Criteria for All Participants

Participant eligibility should be reviewed and documented by an appropriate member of the investigator's study team before participants are included in the study.

Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Histological or cytological diagnosis of adenocarcinoma of the prostate.

2. Men age ≥18 years.

3. Adequate Bone Marrow Function, including:

   a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;

   b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;

   c. Hemoglobin ≥9 g/dL.

4. Adequate Renal Function, including:

   a. 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.

5. Adequate Liver Function, including:

   a. Total serum bilirubin ≤1.5 x ULN unless the participant has documented Gilbert syndrome;

   b. Aspartate aminotransferase and Alanine aminotransferase (AST and ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement secondary to tumor;

   c. Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in case of bone metastasis).

6. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgement. Post-surgical pain will not be considered a basis for exclusion.

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

8. Participants who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

4.1.1. Additional Inclusion Criteria for Participants with Rising PSA at High Risk for Recurrence After Definitive Local Therapy (Biochemical Relapse)

9. Definitive loco-regional therapy for primary diagnosis including one of the following:

   a. External radiotherapy or any salvage therapy including but not limited to brachytherapy, cryotherapy or salvage therapy;

   b. Radical prostatectomy and radiotherapy therapy, such as external radiotherapy or brachytherapy;

c. Prostatectomy only for participants who are not candidates for salvage therapy. Salvage therapy includes but is not limited to any of the following: any radiation therapy (such as external beam therapy, brachytherapy) or any other salvage therapy such as cryotherapy.

10. Hormone sensitive (androgen dependent) relapsing prostate cancer post definitive local therapy. Relapse is defined as a subsequent detectable PSA (≥0.2 ng/ml) that increases on 2 or more determinations after radical prostectomy. The values must be separated by at least 2 weeks.

11. High risk of development of metastatic disease defined as PSA doubling time less than or equal to 10 months (calculated at least 3 months before treatment administration). The PSADT calculation must include all available PSA values available over the past 6 months prior to registration using the Memorial Sloan Kettering Cancer Center (MSKCC) PSA Doubling Time Prediction Tool available at the following website: http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx.

12. Male participants able to father children must agree to use one highly effective method of contraception throughout the study and for at least 90 days after the last dose of assigned treatment.

13. No concurrent use of ADT or orchiectomy. Prior use of ADT in the neoadjuvant or adjuvant setting with radiotherapy is allowed as long as it was completed at least 6 months prior to registration.

14. No evidence by imaging (of any type) of metastatic involvement as follows: loco-regional or distant lymph nodes; loco-regional or distant soft tissues; or any organ involvement, including bone.

15. Testosterone level ≥150 ng/dL.

4.1.2. Additional Inclusion Criteria for Participants in Part B Expansion Cohort 3B - After Novel Hormone Treatment (enzalutamide or abiraterone)

16. Prior therapy with a novel hormone therapy (enzalutamide or abiraterone) .

17. Testosterone levels <50 ng/dL.

18. Documented progressive disease and/or local recurrence defined by the following modified PCWG3[44] criteria:

a. PSA progression defined as a minimum of 2 consecutive rising levels, with an interval of ≥1 week between each determination. For Part B only, the last determination must have a minimal value of ≥0.2 ng/mL and be determined within two weeks prior to screening.

OR

b. Measurable disease defined as showing new or progressive metastatic lymph node and/or local recurrence or visceral metastatic disease (with the exception of metastases to the liver) on CT or MRI scans.

OR

c. Radionuclide bone scan with at least 2 new bone lesions.

For Part B, at least approximately 40% of the participants to be enrolled must have at least 1 measurable lesion as defined by RECIST v1.1.

19. Currently using a GnRH agonist or antagonist (unless surgically castrated).

20. Currently using a GnRH agonist or antagonist (unless surgically castrated).

21. No concurrent treatment with novel hormone therapy.

4.2. Exclusion Criteria for all Participants

Participants with any of the following characteristics/conditions will not be included in the study:

1. Diagnosis of neuroendocrine prostate tumor or neuroendocrine tumor component.

2. Metastases to the brain or liver.

3. ECOG performance status (PS) ≥2.

4. History of prior malignancy other than prostate cancer within the past 3 years excluding successfully resected treated basal cell carcinoma or squamous cell carcinoma of the skin.

5. Major surgery within 4 weeks of first dose.

6. Radiation therapy within 4 weeks of starting study treatment, except: palliative or focal/limited radiotherapy to a limited field is allowed after consultation with the sponsor's medical monitor at any time during study participation, including during screening.

7. Systemic anti-cancer therapy (including immunotherapy and chemotherapy) within 4 weeks or 5 half-lives, whichever is shorter, prior to first dose.

8. Sepuleucel-t and Prostvac within 12 months of first dose.

9. Receipt of an investigational agent within 30 days, prior to first dose.

10. Receipt of an immunosuppressive dose of corticosteroids or other immunosuppressive medication (eg, methotrexate, rapamycin) within 30 days of first dose. (Exceptions: Participants with adrenal insufficiency may take up to 5 mg of prednisone or equivalent daily. Topical, nasal and inhaled corticosteroids are allowed).

11. History of or active autoimmune disorders (including but not limited to: myasthenia gravis, thyroiditis, pneumonitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, scleroderma.

12. Acetylcholine receptor binding antibody ≥0.5 nmol/L and/or abnormal neurologic examination at screening indicating possible underlying myasthenia gravis.

13. History of inflammatory bowel disease (eg, Crohn's disease or ulcerative colitis), celiac disease, acute or chronic colitis, or other chronic gastrointestinal conditions associated with diarrhea.

14. Active and clinically significant bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness. In equivocal cases AIDS related-illness, subjects may be eligible if their viral load is negative. HIV seropositive subjects who are healthy and low-risk for AIDS-related outcomes could be considered eligible. Eligibility criteria for HIV-positive subjects should be evaluated and discussed with the sponsor's medical monitor and will be based on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions (eg, opportunistic infections), and status of HIV treatment. Also the potential for drug-drug interactions will be taken into consideration.

15. Any of the following in the previous 12 months or currently: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism, as well as ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, or QTc interval >470 msec at screening.

16. Individuals in whom a skin-fold measurement of the cutaneous and subcutaneous tissue exceeds 40 millimeters (mm) for three or more designated electroporation of IM injection sites (ie, right or left deltoid or vastus lateralis muscles).

17. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate IM injection.

18. Current use of any implanted electronic stimulation device, including but not limited to cardiac pacemakers, automatic implantable cardiac defibrillator, nerve stimulators, or deep brain stimulators.

19. Syncopal episode within 12 months of registration.

20. Presence of any surgical or traumatic metal implants at all designated sites of administration.

21. Blood pressure >160/100 mmHg despite medical treatment.

22. Participation or plans to enroll in other studies involving investigational drug(s) within 4 weeks prior to first dose. Participants may only continue to participate in the follow-up activities of another study if no interventional drug(s), blood collection, or treatment of any kind is involved.

23. Known or suspected hypersensitivity to any components of the PrCa VBIR regimen.

24. Other severe 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 participant inappropriate for entry into this study.

25. COVID-19/SARS-CoV2: SARS-CoV2 testing is not mandated for entry into this protocol. However, testing should follow local clinical practice standards and requirements. A positive result on an approved test, even if the participant is asymptomatic, excludes a participant from this trial.

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

4.3. Lifestyle Guidelines

All male participants who are able to father children and are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 90 days after the last dose of investigational product. The investigator or his/her designee, in consultation with the participant, will confirm the most appropriate method of contraception for the individual participant from the permitted list of contraception methods (see below) and instruct the participant in its consistent and correct use. Participants need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly and document such conversation in the participant's chart. In addition, the investigator or his/her designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant's 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. Female partner with an established use of oral, inserted, injected, or implanted hormonal methods of contraception is allowed provided the 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. Female partner with a correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository).

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

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

6. Female partner who meets the criteria for non-childbearing potential, defined as:

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

    - Have medically confirmed ovarian failure; or

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

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 Study Manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, participant study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigational 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 investigational site and the study team are not available. It is therefore intended to augment,

but not replace, the established communication pathways between the investigational 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 participant directly, and if a participant calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference 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).

5.1. Allocation to Treatment

Eligible participants will be enrolled to receive components of the PrCa VBIR in an open-labeled, unblinded manner. In Part A, participants will be successively assigned to the next available treatment slot at a dose level decided on after the previous cohort's safety evaluation and ongoing observations of earlier enrolled participants.

Dose level allocation will be performed by the sponsor after participants have given their written informed consent and have completed the necessary baseline assessments. The site staff will email a completed Registration Form to the designated sponsor study team member. The sponsor will assign a participant identification number documenting participant enrollment.

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

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

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

5.2. Participant Compliance

All doses of adenovirus, pDNA, tremelimumab and PF-06801591 will be administered by the appropriately designated study staff at the investigational site. The site will complete the required dosage Preparation Record located in the Study Manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Pfizer monitor.

5.3. Investigational Product Supplies

All components of PrCa VBIR (PF-06753512) will be supplied by Pfizer. The PrCa VBIR consists of the following components: Adenovirus (AdC68), plasmid DNA (pDNA), tremelimumab. Sites will be provided with the following supplies:

- PF-06755992 Adenovirus Solution for Injection 2 x 10^{11} VP/mL (AdC68).
- PF-06755990 Plasmid Solution for Injection 2.50 mg/mL (pDNA).
- PF-06753388 Tremelimumab Solution for Injection 100 mg/mL.
- TDS-IM electroporation device and associated supplies (eg, cartridges) for pDNA administration.
- PF-06801591 Solution for Injection 50 mg/mL.

Study centers will receive a supply of clinical trial materials upon site activation with instructions on how to confirm drug receipt. Resupplies will be made during the course of the study based on need. Study centers will supply commonly available sterile syringes and needs for IM and SC administration. The details on drug supply will be provided in the Investigational Product Manual (IP Manual). The study monitor should be contacted for any issues related to drug supplies.

5.3.1. Dosage Form(s) and Packaging

PF-06755992 Adenovirus Solution for Injection is presented as a sterile solution for intramuscular administration. Each vial contains AdC68 at 2 x 10^{11} VP/mL in an aqueous buffered solution. Each vial is filled with an adequate volume to eject 1 mL from a syringe with an IM needle attached. The vial is sealed with a stopper and an overseal and labeled according to local regulatory requirements.

PF-06755990 Plasmid Solution for Injection is presented as a sterile solution for intramuscular administration. Each vial contains pDNA at 2.5 mg/mL in aqueous buffered solution. The vial is filled with an adequate volume to eject 1 mL from the identified syringe and IM needle. The vial is sealed with a coated stopper and an overseal and labeled according to local regulatory requirements.

Each TDS-IM cartridge, for unique use, for administration of the pDNA plasmid solution will be supplied in sterile pouch (one cartridge/pouch) labeled according to local regulatory requirements.

PF-06753388 Tremelimumab Solution for Injection is presented as a sterile solution. Each vial contains tremelimumab at 100 mg/mL in aqueous buffered solution. The vial is filled with an adequate volume to eject 0.75 mL from a syringe with a SC needle attached. The vial is sealed with a coated stopper and an overseal and labeled according to local regulatory requirements.

PF-06801591 50 mg/mL injection is presented as a sterile solution. Each vial contains 100 mg of PF-06801591 in 2 mL of aqueous buffered solution, with a nominal volume of 2.25 mL. Each vial is sealed with a coated stopper and an overseal, and labeled according to local regulatory requirements.

5.3.2. Preparation and Dispensing

Adenovirus, pDNA, tremelimumab and PF-06801591 are provided as single use vials, and will be packaged and dispensed in cartons with tamper evident seals. The cartons should not be opened until the drug is to be administered. For the adenovirus, pDNA, tremelimumab and PF-06801591, see the Investigational Product (IP) manual for instructions on how to prepare the investigational products for administration.

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

5.4. Administration

All AdC68 intramuscular injections are given bilaterally. AdC68 will be administered on Day 1 of Cycles 1 and 2. Please refer to the IP manual for full instructions on the dosage and administration.

pDNA intramuscular injections are given bilaterally. pDNA will be administered beginning on Day 29 of Cycles 1 and 2 and will then be given at 4 week intervals. After Cycle 2, pDNA will continue to be administered every 2 months in the Maintenance Treatment Period. Please refer to the IP manual for full instructions on the dosage and administration of the pDNA and to the TDS-IM Instructions for Use document for the set up and use of the electroporation device. The TDS-IM device should be operated by clinical personnel that have completed the necessary training on device operation.

All IM injections (AdC68 and pDNA) will be given bilaterally in the deltoid muscles or in the vastus lateralis muscles of the quadriceps. Preference should be given to the vastus lateralis muscles when possible.

Tremelimumab will be administered bilaterally subcutaneously at 4 week intervals during Cycles 1 and 2 on the same day as the AdC68 or pDNA dosing beginning with Cohort 3A as described in the STUDY DESIGN section. After Cycle 2, tremelimumab will continue to be administered every 2 months in the Maintenance Treatment Period. Both AdC68 or pDNA injections should be given prior to tremelimumab administration. Please refer to the IP manual for full instructions on the dosage and administration of tremelimumab. Tremelimumab is to be administered in close proximity to the vaccination site. If the vaccination is administered in the vastus lateralis, the tremelimumab is to administered subcutaneously in either the lower quadrants of the abdomen or the quadriceps. If the vaccination is administered in the deltoid, the tremelimumab is to be administered subcutaneously bilaterally in the outer triceps.

PF-06801591 will be administered bilaterally subcutaneously at 4 week intervals on the same day as the AdC68 or pDNA and tremelimumab during Cycles 1 and 2 beginning with Cohort 6A as described in the STUDY DESIGN section. The AdC68 or pDNA as well as the tremelimumab doses should be given prior to PF-06801591 administration. During the Maintenance Treatment Period, participants in a cohort assigned to receive PF-06801591 will continue to be dosed with PF-06801591 at 4 week intervals. Please refer to the IP manual for full instructions on the dosage and administration of PF-06801591. PF-06801591 is to be administered in close proximity to the vaccination site. If the vaccination is administered in the vastus lateralis, the PF-06801591 is to be administered subcutaneously bilaterally in the lower quadrants of the abdomen. If the vaccination is administered in the deltoid, the PF-06801591 is to be administered subcutaneously bilaterally in the outer triceps.

5.4.1. Recommended Dose Modifications

Every effort should be made to administer investigational product on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, 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.

5.4.2. Dosing Interruptions/Delays

Participants experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment with all of the components interrupted/delayed. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

Re-treatment following treatment interruption for treatment related toxicity may not occur until all of the following parameters have been met:

- ANC $\geq$1,000/mm^3.
- Platelets count $\geq$50,000/mm^3.

- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator 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 2 weeks of treatment interruption or cycle delay, investigational product(s) may be resumed. Refer to Section 5.4.4 for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 2 weeks of dosing interruption or 2 weeks of new cycle delay, permanent discontinuation of treatment should be considered. Treatment resumption for participants recovering from treatment-related toxicity after >2 weeks of treatment interruption or cycle delay may be considered only if the participant is deemed to be deriving obvious clinical benefit per the investigator's best medical judgment and needs to be agreed between the investigator and the sponsor.

5.4.3. Dosing Interruptions/Delays due to Non-Related Events

If participants require treatment interruption for reasons other than treatment-related toxicity (eg, surgery) lasting >4weeks, treatment resumption should be decided in consultation with the Sponsor.

In the event of active SARS-CoV2 infection confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion), the following criteria apply:

- For symptomatic patients with active SARS-CoV2 infection, investigational treatment should be delayed for at least 14 days from start of symptoms.
- This delay is intended to allow 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.
- Inform the Sponsor prior to restarting treatment.
- Consider potential drug-drug interactions (as described per study protocol) for any concomitant medication administered for treatment of SARS-CoV2 infection.

5.4.4. Dose Reductions

Following dose interruption or cycle delay due to toxicity, the investigational product(s) may need to be reduced when treatment is resumed.

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

5.4.4.1. AdC68 Dose Reductions

Changes in the dose levels for AdC68 will be discussed with the sponsor. Dose reduction of adenovirus by 1 dose level may be allowed depending on the type and severity of toxicity encountered. In addition, an intermediate dose may be considered. Participants requiring a dose level lower than the starting dose will be discontinued from treatment and enter into the follow-up phase unless otherwise agreed between the investigator and sponsor. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Table 1. Adenovirus Available Dose Levels

Dose Level	Adenovirus*
Starting	4×10^{11} VP
+1	6×10^{11} VP

* Intermediate doses may also be considered upon discussion with the sponsor.

Table 2. Dose Modifications for Adenovirus Related Toxicity

Toxicity	Grade 1/2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator*.	Discontinue treatment.
Hematologic	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level.	Discontinue treatment.

* Nausea, vomiting, or diarrhea must persist at Grade 3 despite maximal medical therapy to require dose modification.

5.4.4.2. Tremelimumab Dose Reductions

Changes in the dose levels for tremelimumab will be discussed with the sponsor. For cohorts where PrCa VBIR will be administered alone, dose reduction of tremelimumab by 1 dose level may be allowed depending on the type and severity of toxicity encountered. For cohorts where PrCa VBIR will be given in combination with PF-06801591, dose reductions of tremelimumab by 1 dose level will be allowed. In addition, an intermediate dose may be considered. Participants requiring a dose level lower than 40 mg will be discontinued from treatment and enter into the follow-up phase unless otherwise agreed between the investigator and sponsor. Algorithms for the management of suspected pulmonary, GI, liver, endocrine, skin, neurological and renal toxicities have been developed (See Appendix 7). All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

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

If a participant experiences a Grade ≥3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to Grade ≤2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.

Table 3. Tremelimumab Available Dose Levels

Dose Level	Tremelimumab*
-1	40 mg
Starting	80 mg**

* Intermediate doses may also be considered upon discussion with the sponsor.
** Dose lower than 80 mg may be evaluated based on emerging safety data.

Table 4. Dose Modifications for Tremelimumab Related Toxicity When Given in Combination with AdC68 or pDNA

Toxicity	Grade 1/2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator*.	Discontinue treatment.
Hematologic	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level.	Discontinue treatment.

* Nausea, vomiting, or diarrhea must persist at Grade 3 despite maximal medical therapy to require dose modification.

5.4.4.3. PF-06801591 Dose Reductions

Events including, but not limited to, pneumonitis, colitis, creatinine and liver function test (LFT) elevation should be monitored carefully with this class of agents. Changes in the dose levels for PF-06801591 may be allowed depending on the type and severity of toxicity encountered. Dose reductions may be required for PF-06801591, tremelimumab or potentially both compounds depending on the event and the severity. After a dose interruption, it is acceptable to resume dosing with the PrCa VBIR alone, and PF-06801591 treatment to resume at the next planned dosing. Dose reductions of PF-06801591 by 1 dose level may be allowed, including dose reductions below the starting dose. In addition an intermediate dose may be considered. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Table 5. PF-06801591 Available Dose Levels

Cohort	Starting Dose*	Level -1**
3B	300 mg	130 mg
5B	130 mg	75 mg

* The starting dose may be modified based on emerging safety data. See Section Clinical PF-06801591 Dosing for additional details.
** Intermediate doses may also be considered upon discussion with the sponsor.

Table 5 describes the recommended dose modification for PF-06801591 treatment-associated toxicity. Algorithms for the management of suspected pulmonary, GI, liver, endocrine, skin, neurological and renal toxicities have been developed (See Appendix 7).

Participants requiring >2 weeks of dose interruption should be considered for discontinuation of treatment with PF-06801591. Participants may be allowed to resume dosing with the PrCa VBIR alone rather than in combination with PF-06801591 for one dose with plans to resume dosing with PF-06801591 at the next dosing timepoint if agreed upon by the investigator and sponsor. This would result in more than 2 weeks of dose interruption. Participants who discontinue PF-06801591 due to toxicity will be allowed to remain in the study and continue treatment with the other components.

The following serves as demonstrating general rules. Action may differ in specific cases based on evaluation by the investigator and the sponsor.

Table 6. Dose Modifications for PF 06801591 and/or Tremelimumab (When Given in Combination With PF 06801591) Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	For pneumonitis, endocrinopathy, colitis, creatinine, AST, ALT, or total bilirubin elevations, withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume at the same dose level or reduce by 1 level (considering each compound separately) at the discretion of the investigator. For all other events, continue at the same dose level.	For pneumonitis, colitis, endocrinopathy, creatinine, AST, ALT or total bilirubin elevations, or pruritus discontinue treatment.** For all other events withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level (considering each compound separately) at the discretion of the investigator.* Treatment may resume with the PrCa VBIR with an interruption of PF-06801591 for one dose at the discretion of the investigator.	Discontinue treatment.**
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, then resume treatment at the same dose level.	Discontinue treatment.**

* Nausea, vomiting, or diarrhea must persist at Grade 3 despite maximal medical therapy to require dose modification.

** For Grade >3 colitis or pneumonitis, discontinue treatment permanently. For any grade of myocarditis discontinue treatment permanently. For all other conditions participants may remain in the study and resume therapy once toxicity has returned to Grade ≤1 or baseline, after discussion with the Sponsor.

5.5. Investigational Product Storage

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

Upon receipt at the site, all drug product should be immediately transferred, in its original container, to the appropriate monitored storage area. Current storage conditions for AdC68 vials are frozen (-20°C±5°C). The current storage conditions for the pDNA, tremelimumab and PF-06801591 are refrigerated (2-8°C). Storage conditions stated in the single reference safety document (eg, Investigator's Brochure) will be superseded by the

storage conditions stated in the labeling. Please see the Instructions for Use for details on storage of the TDS-IM device.

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 daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.6. Investigational Product Accountability

All investigational product must be kept in a locked, limited access room. The investigational product and electroporation device must not be used outside of the context of this protocol. The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. To ensure adequate records, all components of PrCa VBIR as well as PF-06801591 will be accounted for in the drug accountability inventory forms as instructed by the sponsor.

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 study 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 participant's well-being may be given at the discretion of the treating physician.

Prophylactic antipyretics and other pain medications to prevent symptoms associated with investigational vaccine administration are not permitted.

All concomitant treatments, blood products, as well as non-drug interventions received by participants from screening until the end of study visit will be recorded on the Case Report Form (CRF).

5.7.1. Prohibited Concomitant Vaccines

No vaccines (licensed or investigational) other than study vaccine, influenza and pneumococcal vaccines should be given during the study within 30 days prior to or after dosing. Other vaccines may be administered only if medically necessary (eg, tetanus post exposure prophylaxis).

For participants who receive tremelimumab, live attenuated vaccines should not be administered within 30 days prior to or after dosing with tremelimumab. The administration of inactivated vaccines is allowed.

5.7.2. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. Additionally, the concurrent use of vitamins or herbal supplements for an anticancer treatment is not permitted.

Participants currently being treated with a GnRH agonist or antagonist may continue treatment while participating in this study as long as the GnRH agonist treatment has been well tolerated for at least three months prior to study entry.

5.7.3. Participants on beta blockers

Per the TDS-IM Investigator's Brochure (28-Jun-2019), two cases of syncope have been reported in association with the device in a total of over 800 subjects receiving up to 5 administrations. Caution should be undertaken during injections in participant taking beta blockers. Strong consideration should be given to placing the participant in prone position depending on the participant's medical condition.

5.7.4. 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.

Participants currently being treated with denosumab or bisphosphonates (eg, zoledronate) for bone disease may continue treatment while participating in this study. However, initiation of treatment with these types of compounds should be avoided while participating in the study.

5.7.5. Anti-Diarrhea and Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is not permitted prior to the first dose of adenovirus, tremelimumab and/or PF-06801591. Primary prophylaxis on subsequent dosing days is at the investigator's discretion. The choice of the prophylactic drug is up to the investigator with sponsor approval and assuming the drug is not included in the Concomitant Treatment(s) section, as well as the duration of treatment assuming there is no known or expected drug-drug interaction. If so, then it must be approved by the sponsor.

5.7.6. Anti-inflammatory Therapy

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

5.7.7. Therapy for Treatment of Pyrexia and Flu-like Symptoms

Primary prophylaxis of fever or flu-like symptoms is not permitted prior to dosing of adenovirus. Following receipt of adenovirus, medications used to treat fever or flu-like symptoms (eg, acetaminophen, ibuprofen) should be administered at the first sign of either event.

5.7.8. Corticosteroids

Chronic, systemic corticosteroid use for palliative or supportive purpose is not permitted. The short term use of corticosteroids for medically indicated conditions is allowed and should be discussed with the sponsor. Topical, nasal and inhaled corticosteroids are allowed.

5.7.9. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and administration of the PrCa VBIR components or combination agents required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping all components of PrCa VBIR, PF-06801591 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate 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 Schedule of Activities and ASSESSMENTS section.

6.2. Study Period

For treatment period and maintenance treatment period procedures, see Schedule of Activities and ASSESSMENTS section.

6.3. Follow-up Period

Patients who have permanently discontinued treatment with the study drugs will complete the assessments required for the End of Treatment visit and then enter the follow-up period which includes 6 months of additional evaluations. For follow-up procedures see Schedule of Activities and ASSESSMENTS section.

6.4. Patient Withdrawal

Participant withdrawal may include either: (a) withdrawal from treatment with continued follow up, or (b) withdrawal from treatment and no further follow up.

6.4.1. Withdrawal from Treatment

Participants may withdraw from treatment at any time at their own request, or they may be withdrawn from treatment at the discretion of the Investigator or Sponsor for the following reasons: (a) safety, (b) lack of efficacy, (c) behavioral reasons, or (d) the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given study site. Reasons for withdrawal of study treatment may include:

- Objective disease progression by irRECIST (see Appendix 4). Disease progression will be confirmed with two consecutive timepoints at least 4 weeks (or at least 6 weeks for progressing disease on bone scan) apart in the absence of rapid clinical deterioration;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity, including treatment-related DLT;
- Significant protocol violation;
- Lost to follow-up (defined as: If a participant repeatedly fails to return for scheduled visits and repeated attempts to contact the patient have been unsuccessful);
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

6.4.2. Wtihdrawal from Study

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up (defined as: If a participant repeatedly fails to return for scheduled visits and repeated attempts to contact the patient have been unsuccessful);
- Refused further follow-up;
- Death.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts should be documented in the participant's medical record. In any circumstance, every effort should be made to document participant outcome, if possible. The investigator should request that the participant return for a final visit, if applicable, and follow-up with the participant regarding any unresolved AEs.

If the participant refuses further visits, 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. Publicly available information may be used to determine follow up information as appropriately directed in accordance with local law.

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, which 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 participant. 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 fashion.

7.1. Safety Assessments

Safety assessments will include collection of adverse events (AEs), serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG (12 lead)), laboratory assessments, and verification of concomitant treatments.

7.1.1. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study will be recorded on the adverse events CRF page.

7.1.2. Laboratory Safety Assessment

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

Hematology	Chemistry	Coagulation	Urinalysis
Hemoglobin	ALT	PT or INR	Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)
Platelets	AST	PTT	
WBC	Alk Phos		
Absolute Neutrophils	Sodium		
Absolute Lymphocytes	Potassium		
Absolute Monocytes	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)
Absolute Eosinophils	Chloride		
Absolute Basophils	Total Calcium		
	Total Bilirubin[1]		
	BUN or Urea		
	Creatinine		
	Uric Acid		
	Glucose (non-fasted)		
	Albumin		

Hematology	Chemistry	Coagulation	Urinalysis
	Phosphorous or Phosphate		
	Lactate dehydrogenase		
	Lipase		
	Amylase		
	Bicarbonate or carbon dioxide		
	Total protein		
	TSH (if abnormal, reflex free T4 and free T3 tests)[2]		

1. For Hy's law potential 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.
2. For participants in Cohorts 6A through 9A and Cohorts 3B and 5B.

7.1.3. Vital Signs, Physical Examination and Skin Assessment

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

A complete physical examination (PE) will be performed at Screening and at the End of Treatment visit for each participant and will include an assessment of all body systems (genitourinary examination is optional). A neurologic examination must be conducted at Screening to look for potential signs suggestive of autoimmune disorders. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an adverse event in the CRF.

Abbreviated PEs should be performed as appropriate per the Schedule of Activities (SOA), and on an as needed basis for assessment of adverse events. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care. However, a neurologic examination must be performed during each exam conducted during Cycle 1.

Weight and body surface area (BSA) do not need to be performed at each visit; however participants should be monitored throughout the study for significant weight change.

Vital signs will include measurements of blood pressure and temperature (oral, temporal, tympanic or axillary). On dosing days, vital signs should be measured prior to administration of any of the study treatments. Sitting blood pressure (BP) will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mmHg sufficient. The same arm (preferably the dominant arm) should preferably be used throughout the trial. A blood pressure cuff, which has been properly sized and calibrated, should be used to measure blood pressure. The use of automated devices for measuring BP is acceptable.

Assessment of the skin and subcutaneous tissue thickness at the eligible administration sites will be performed at screening as described in the TDS-IM Instructions for Use. The assessment procedure does not need to be repeated during the course of the study unless the participant experiences a greater than 10% change in body mass relative to screening.

7.1.4. (12-Lead) ECG

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all 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), three consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. 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 500 msec. If QTcF interval reverts to less than 500 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. Participants will then re-start 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 participant has a QTcF interval >515 msec or becomes symptomatic, the participant 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 participant clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

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

7.1.5. Monitoring for Potential Immune Mediated Endocrinopathies

Participants will be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including Addisonian crisis), and hyper- or hypothyroidism. Laboratory evaluation will be performed as clinically indicated based on symptoms. For example, the development of symptoms of adrenal insufficiency, such as unexplained nausea, vomiting and hypotension, would trigger prompt evaluation (Cosyntropin Stimulation Testing) and treatment (systemic glucocorticoids). Symptoms suggestive of an inflammatory pituitary process with mass effect, such as diplopia, visual field abnormalities and severe headache, call for urgent pituitary imaging and evaluation for hypopituitarism, with specific attention to the pituitary-adrenal axis. Symptoms of disordered thyroid metabolism, such as changes in bowel frequency, fatigue, unexplained weight loss or gain should prompt evaluation of

thyroid function tests, with a focus on free thyroid hormone levels (T3 and T4) given the possibility that thyroid stimulating hormone levels may be unreliable due to immune-mediated pituitary dysfunction.

7.1.6. Acetylcholine Receptor Testing

A blood sample will be collected at screening for central evaluation of AChR antibodies. CCI [redacted] Treatment decisions will be made based on the clinical diagnosis.

7.1.7. Cardiac Safety Monitoring

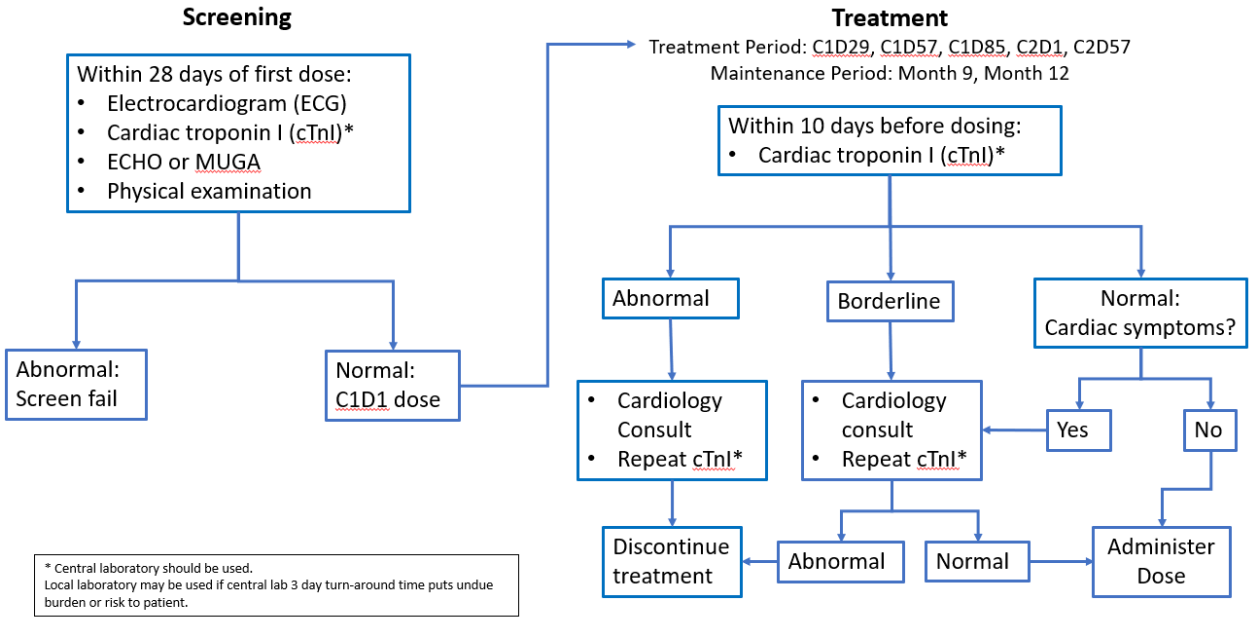
The algorithm for cardiac Safety Monitoring is shown in Figure 2 below.

For participants undergoing screening, circulating levels of cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range within 28 days before study entry, preferably using the central laboratory kits provided. Dosing should not proceed until results within the normal reference range have been received by the Investigator. For any results above of the normal reference range (even if borderline), the participant should be referred to a cardiologist by the Investigator for complete cardiac workup and repeat cardiac troponin. The participant can only enter the study after cardiac evaluation, troponin findings within the normal reference range, cardiac clearance and with approval of the Sponsor.

For participants ongoing in the study, circulating levels of cardiac Troponin-I (cTnI) must be measured within 10 days of dosing on the days shown in the SOA (ie, C1D29, C1D57, C1D85, C2D1, C2D57, month 9 and month 12) and found to be within the normal reference range. No dosing of participants can occur unless the cTnI is within the normal reference range. For any results above the normal reference range (even if borderline) the participant must be referred by the Investigator to a cardiologist for complete work-up and repeat cTnI. Dosing can only occur after cardiac evaluation, cTnI findings within the normal reference range, cardiac clearance and with approval of the Sponsor.

While central laboratory testing for cTnI is preferred, it requires a minimum of 3 days to return results. Therefore, local laboratory testing of cTnI may be used, but only if the timing of measuring cTnI by the central laboratory test (minimum 3 day turnaround time) puts an undue burden or risk on the participant. The use of cardiac troponin-T is strongly discouraged, but could be used in place of cTnI if the central laboratory test puts an undue burden or risk on the participant.

Figure 2. Cardiac Safety Monitoring Algorithm



7.2. Pharmacokinetics Assessments

7.2.1. Serum for Assessment of Tremelimumab Pharmacokinetics

Blood samples (approximately 3 mL whole blood) to provide at least 1 mL of serum for measurement of serum tremelimumab concentrations will be collected from participants enrolled into Cohorts 3A or later at the time points specified in the SOA. PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample for determination of tremelimumab PK should be collected from participants experiencing unexpected and/or serious AE's and the date and time of blood sample collection and of last dosing prior to PK collection documented in the CRF.

All efforts will be made to obtain the tremelimumab PK samples at the scheduled nominal time relative to dosing. However, samples obtained within the protocol specified time window will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, participant and sponsor.

Details regarding the collection, processing, storage and shipping of tremelimumab PK samples will be provided in the study manual.

Tremelimumab PK samples will be assayed using a validated analytical method in compliance with Pfizer standard operating procedures.

As part of the understanding of the PK of the investigational product, tremelimumab samples may be used for evaluation of the bioanalytical methods of tremelimumab. CCI [redacted]

7.2.2. Serum for Assessment of PF-06801591 Pharmacokinetics

Blood samples (approximately 5 mL) to provide serum for the analysis of PF-06801591 concentrations will be collected from participants enrolled into Cohorts 6A through 9A or Dose Expansion Cohorts 3B and 5B at the time points specified in the SOA. 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 participants experiencing unexpected and/or serious AE's and the date and time of blood sample collection and of last dosing prior to PK collection documented in the CRF.

All efforts will be made to obtain PK samples at the scheduled nominal time relative to dosing. However, samples obtained within the protocol-specified time window will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, 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, participant, and sponsor.

Sample for PK analysis will be assayed for PF-06801591 using a validated analytical method in compliance with Pfizer standard operating procedures. CCI [redacted] These data will not be included in the clinical study report. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

CCI [redacted]

7.3.1. Cellular Immune Assays

Blood samples of approximately 50 mL whole blood from all time points specified in the SOA will be collected in appropriate blood collection tubes to provide approximately 50 million peripheral blood mononuclear cells (PBMC) for the assessment of tumor-antigen specific cellular immune responses from all participants from the study. The whole blood in the appropriate collection tube will be transferred to a qualified local laboratory for the separation and cryopreservation of PBMC on Ficoll™ gradients within 6 hours of blood draw. Cryopreserved PBMC will be stored at the local laboratory prior to shipment to Pfizer for subsequent evaluation of cellular immune responses. In addition, these samples may be used for evaluation of T cell receptor sequences or other exploratory assays.

Details regarding the collection, processing, storage and shipping of the PBMC samples will be provided in the study manual. The PBMC processing laboratory will be qualified to separate and store PBMC samples in accordance with Pfizer standard operating procedures.

PBMC samples will be assayed for cellular immune responses against PSMA, PSCA and PSA antigens using qualified analytical methods in compliance with Pfizer standard operating procedures. Other antigens from potential epitope spreading or antigen cascading may also be analyzed.

CCI [redacted]

CCI

[redacted]

Assessment of response will be made using RECIST version 1.1 (Appendix 3) and irRECIST (Appendix 4) and PCWG3 criteria (Appendix 5) for bone disease.

All participants' files and radiologic images must be available for source verification and for potential peer review. In addition, historical images (collected up to one year prior to study entry) may be requested for potential peer review.

7.5. Immunogenicity Evaluations

7.5.1. Tremelimumab Immunogenicity Evaluations

Blood samples (approximately 5 mL) to provide at least 2 mL of serum to detect ADA and neutralizing antibody (Nab) against tremelimumab (~1 mL each of ADA and Nab) will be collected from participants enrolled in to Cohorts 3A to 9A and Cohorts 1B to 5B at the times specified in the SOA.

Details regarding the collection, progressing, storage and shipping of the blood samples will be provided in the Study Manual.

The tremelimumab ADA and Nab samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. The ADA sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Only those samples tested positive for ADA will be further tested for Nab.

CCI [redacted]

7.5.2. PF-06801591 Immunogenicity Evaluations

Blood samples (approximately 5 mL) to provide at least 2 mL of serum for detection of ADA and Nab against PF-06801591 (~1 mL each for ADA and Nab) will be collected from participants enrolled in Cohorts 6A to 9A and Cohorts 3B and 5B into appropriately labeled tubes at times specified in the SOA. Additional instructions for sample collection, processing, storage, and shipping will be provided in the lab manual.

The ADA samples will be analyzed using a validated assay in compliance with Pfizer standard operating procedures. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Samples tested positive for ADA will be further analyzed for Nab using a validated assay in compliance with Pfizer standard operating procedures.

CCI [redacted]

7.6. Banked Biospecimens

7.6.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. CCI [redacted]

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which case any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical study.

A 4-mL blood biospecimen Prep D1 (K_2 edetic acid (ethylenediaminetetraacetic acid)(EDTA)) whole blood collection optimized for DNA analysis) will be collected at the baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The banked biospecimens will be collected from all patients unless prohibited by local regulations or ethics committee decision. Detailed collection, processing, storage, and shipment instructions are provided in the study manual.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.6.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions.
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Markers of Drug Response Section will be used. Patients may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.7. Other Assessments

7.7.1. Tumor and Medical History

History of the patient's disease under study including details of the primary diagnosis and treatment history will be collected within 28 before the start of treatment. In addition, a history of disease process other than the cancer under study (active or resolved) and concurrent illnesses will be collected. This will also include prior treatments and any current medical treatments for any condition.

Also, the Gleason score at the time of the patient's initial diagnosis and/or the time of the most current recurrence should be collected if the information is available.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the

AE. The investigator is required to assess causality. 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.

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.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including the 6 month follow-up period. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor 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 are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation 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 symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported 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.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- 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.

Whether or not the medication error should be accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- 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 the protocol-stipulated 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 reporting as an AE.

8.6. 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;
- 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 safety reporting 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 safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE) grade 5 (see the section on Severity Assessment).

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, 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.

Medical device complaints may meet the SAE reporting requirement criteria (see the section on Medical Device Complaint Reporting Requirements). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a patient, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items.

Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization.

- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Liver Function Tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a patient, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

- For patients with preexisting AST or ALT baseline values above the normal range: AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational 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. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. 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 should be 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 persistent pre-treatment 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 AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 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 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.

8.9. 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 in the CRF, as appropriate, 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 (see the section on Reporting Requirements). 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, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. 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 women (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male participant 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 study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an 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) 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 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 the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure 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]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported 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 investigator. 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 study 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.

8.11. 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 the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Patient Withdrawal)

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

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or 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 or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be collected on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might have led to death or serious deterioration in health.

Significant medical device complaints are defined as those observations or incidences outside the expected normal operational ranges of the device (as detailed in the device specific training and instructions for use (IFU) documentation) that may have the potential to impact the correct operation of the device, administration of the drug or safety of the patient.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event. Complaints will be forwarded to the device manufacturer, Ichor Medical Systems ("Ichor") (San Diego, CA) in accordance with the Quality Agreement between Pfizer and Ichor.

8.14.4. 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.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis Sets

For safety evaluation, patients should have received at least one of the regimen components. For efficacy and pharmacodynamics evaluation, patients should have received at least one dose of all assigned components administered on Cycle 1 Day 1. For example, a patient would be included in the safety analyses if he is assigned to a cohort of AdC68 6 x 10^{11} VP in combination with tremelimumab but received only the AdC68 component. However, this patient would not be included in the efficacy CCI evaluation for that cohort. Patients who receive the designated investigational product of interest and have at least one post-dose drug concentration measurement will be included in the PK data analysis. Patients with major treatment deviations, defined as receiving <80% of their planned dose in the 28-day DLT observation period will not be evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation.

1. Safety analysis set.

The safety analysis set includes all enrolled patients who receive at least one dose of one of the components of the regimen.

2. Full analysis set.

The full analysis set includes all enrolled patients.

3. Per protocol analysis set.

The per protocol (PP) analysis set includes all enrolled patients (for each indication) who receive at least one dose of all assigned regimen components administered on Cycle 1 Day 1 of study medication and who do not have major protocol deviations during the 28 days after the first vaccination.

4. Modified Intention-to-Treat analysis set.

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5. PK analysis set.

The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest and who have no major protocol deviations influencing the PK assessment.

6. Immunogenicity analysis set.

The immunogenicity analysis set includes all enrolled patients who receive at least one dose of one of the components of the regimen.

9.2. Statistical Methods and Properties

The dose escalation phase will be governed by three 3+3 designs, one for each regimen component. The 3+3 design assumes that no more than 0 out of 3 (0/3) or 1 out of 6 (1/6) DLTs are observed at the highest tested dose level of a component and the highest dose is therefore taken forward for subsequent cohorts. However, if a lower dose level for one component is determined to be the maximum tolerated dose, the lower level will be administered to subsequent cohorts.

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.

Table 7. Probability of Escalating Dose

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

Probabilities of testing sequential doses can be calculated as the 3+3 escalation rules are predefined. For example the probability of escalating to a third dose level is 0.64 under the assumption that DLTs occur in 10% and 20% of patients respectively in the first dose and the second dose. The probability of escalating to a third dose is only 0.35 if DLTs occur in 20% and 30% of patients respectively in the first dose and the second dose tested.

9.2.1. Dose Escalation

Enrollment of patients into dose escalation cohorts will occur in a sequential manner starting with the lowest dose level, and escalation being permitted following evaluation of acceptable safety data by the investigator and Sponsor according to the principles of the 3+3 design. Patients will be assigned to dose cohorts on the basis of their order of entry into the study. Dose cohorts with an acceptable safety profile (0/3 or 1/6 patients with DLTs) may be expanded up to N=15 to further assess safety.

There is an assumption that higher doses of either AdC68, tremelimumab or PF-06801591 result in higher adverse event rates. However, due to the relatively low number of patients that may be potentially allocated to any dose combination, adverse event estimates may not follow this assumption and variable incidence of AEs can be observed.

For example, the dose AdC68 4 x 10^{11}VP in combination with tremelimumab 80 mg may have a higher proportion of observed adverse events than AdC68 4 x 10^{11}VP in combination with tremelimumab 80 mg and PF-06801591 300 mg, and this variability may be simply related to small cohort size alone. Clinical judgment will be exercised in taking forward combinations to the expansion cohort(s), in case no clear choice exists between more than 1 competing dose regimen.

9.3. Sample Size Determination

The exact sample size of the 3+3 designs in the Phase 1 Part A (Dose Escalation) cannot be pre-specified because of the dynamic feature of the design. The number of patients to be enrolled in the study will depend upon the observed safety profile, which will determine the number of patients at each dose level (eg, 3 or 6) and the number of dose levels explored.

Typically, at least 3 patients will be treated at each regimen dose level. Dose cohorts with an acceptable safety profile (0/3 or 1/6 patients with DLTs) may be expanded up to N=15 to further assess safety, immune response, pharmacokinetics, and pharmacodynamics. Decisions to enroll additional patients at dose levels already cleared for safety will be based on clinical judgment of the investigators and the sponsor considering all evaluable safety, immunoresponse, and/or pharmacodynamics data.

The estimated sample size for Part A would be 24-48 patients and will be dependent on the safety profile observed.

The sample size for Cohort 1B (AdC68 + pDNA + treme 80 mg SC for BCR patients who had no prior therapy) was determined clinically rather than statistically. Twenty patients were enrolled in that cohort to provide preliminary efficacy, safety, PK and biomarker data for this regimen.

For Cohort 3B (AdC + pDNC + treme 80 mg SC + PF-0689159 300 mg SC. for patients with mCRPC whose disease has progressed despite novel hormonal treatment), 18 patients were enrolled. The sample size was determined clinically rather than statistically. The smaller sample size was determined to be adequate for continued safety analysis. The main efficacy endpoint for this cohort will be objective response rate (ORR) based on RECIST version 1.1. There are no hypothesis tests for these endpoints. Bayesian approach with a non-informative

Jeffery's prior beta (0.5,0.5) will be used to calculate the posterior probability the ORR of the study treatment exceeds various ORR thresholds of interest in the end of the study. For example, if 6 responders were observed in the 18 patients, the posterior probability that the true ORR is greater than 25% would be about 80%.[9]

For Cohort 5B (AdC68 + pDNA + treme 80 mg SC + PF-0689159 130 mg SC. for BCR patients who had no prior therapy), the sample size was determined clinically rather than statistically. Fifteen patients were enrolled in that cohort to provide preliminary efficacy, safety, PK and biomarker data for the regimen.

9.4. Efficacy Analysis

CCI [redacted] The main analysis populations will be based on mITT and EP (see Section Analysis Sets).

Tumor response, using RECIST v1.1, irRECIST, and PCWG3 for bone disease, will be summarized and presented in the form of patient data listings. Traditional response measures in solid tumors, such as ORR and PFS were developed to evaluate chemotherapies and can be unreliable for tracking response to cancer vaccines. For example, apparent tumor burden may increase during the first few months of cancer vaccine treatment because of inflammation/T cell infiltration into tumors even in patients who go on to have durable responses. For these reasons time to progression and number of patients with progression could be calculated from first vaccination (Day 1), but also calculated excluding those progressions that happened before some specific timepoints (eg, Day 57, Day 113). Time to response will be calculated from first vaccination (Day 1) to time of first response (ie, CR or PR). When PFS is evaluated, the Kaplan-Meier approach will be used. Participants from Cohorts 7A and 3B may be combined for efficacy analyses as participants in those two cohorts have identical or similar eligibility criteria for study entry and are scheduled to receive the same regimen.

Additionally, total measurable tumor burden will be evaluated by the irRECIST criteria that include responses after disease progression that are not captured by RECIST evaluation criteria in solid tumors.

The Bayesian analyses as described in Section 9.3 will be carried out separately and may not be reported in the clinical study report.

9.5. Safety Analysis

The main analyses of DLTs will be based on the Per Protocol analysis set. Patients not meeting the criteria for inclusion in the Per Protocol Analysis set (ie, not evaluable for assessment of DLTs) will be replaced. Summaries and analyses of other safety parameters will include all patients in the Safety Analysis Set (see Section Analysis Sets).

9.5.1. Analysis of Primary Endpoint

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation (Part A). The occurrence of DLTs observed in the dosing cohorts will govern the dose escalation as described in Section 3.1.1 STUDY DESIGN. The properties of the statistical methods for the analyses of DLTs are described in section Statistical Methods and Properties. Adverse Events constituting DLTs will be listed per dose level. The per-protocol population will be used for the DLT evaluation. A patient who had a major protocol deviation may be excluded from the per-protocol population and hence will be replaced for the DLT evaluation but will still be included in the safety population for the general safety evaluation.

Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 4.03 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 by dose and by cycle.

9.5.2. Analysis of Secondary Safety Endpoints

Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab 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. ECG

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as the pre-dose ECG collected before the first dose of any component of the study treatment.

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, Frederica's). Data will be summarized and listed for QT, HR, PR, QRS, QTcF by cohort. Individual QT intervals will be listed by time and cohort. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by

cohort 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 using Maximum CTC AE 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).

If applicable, the effect of relevant 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. Analysis of Other Endpoints

9.6.1. Pharmacokinetic Analyses

9.6.1.1. Tremelimumab Pharmacokinetics

The concentration-time data of tremelimumab will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) according to dosing cohort and time.

For patients of Cohort 3A, the concentration-time data of tremelimumab after the first dose will be analyzed individually by non-compartmental methods to determine the PK parameters. The PK parameters to be estimated will include the C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, terminal elimination half-life ($t_{1/2}$), and apparent clearance (CL/F). In addition, the accumulation ratio (Rac) as calculated by the ratio of the trough concentration prior to the fifth tremelimumab dose (on Cycle 2 Day 1) to the concentration prior to the second tremelimumab dose (on Cycle 1, Day 29) will be determined individually if data permit. The PK parameters will be summarized using descriptive statistics according to dosing cohort.

9.6.1.2. PF-06801591 Pharmacokinetics

The concentration time data of PF-06801591 will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) according to dosing cohort and time.

For patients of Cohorts 6A through 9A, the concentration time data of PF-06801591 after the first dose will be analyzed individually by non-compartmental methods to determine the PK parameters. The PK parameters to be estimated will include the C_{max}, T_{max}, and AUC_{last}, and if data permit, AUC_{inf}, $t_{1/2}$, and CL/F. In addition, Rac as calculated by the ratio of the trough concentration prior to the fifth PF-06801591 dose (on Cycle 2 Day 1) to the concentration prior to the second PF-06801591 dose (on Cycle 1, Day 29) will be determined individually if data permit. The PK parameters will be summarized using descriptive statistics according to dosing cohort.

9.6.2. Immune Responses and Tremelimumab Immunogenicity

The time course data on immune response endpoints, including titers of antibodies against prostate cancer specific antigens and titers of antigen-specific T cells, will be summarized by descriptive statistics (n, median, minimum, and maximum) according to dosing cohort and time. If data permit, the time course data may also be analyzed by non-compartmental methods to estimate parameters including peak titers, time to peak titers, and area under the titer curve.

For patients receiving tremelimumab, the percentage of patients with positive ADA and neutralizing antibodies will be summarized by dosing cohort. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit.

For patients receiving PF-06801591, the percentage of patients with positive ADA and neutralizing antibodies will be summarized by dosing cohort. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit.

CCI [redacted]

CCI [redacted]

9.7. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

Surveillance for serious adverse events (SAEs) according to regulatory guidelines.

Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level in an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further 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 study site may be subject to review by the institutional review board (IRB)/ethics committee (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 study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. 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 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's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or 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.

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 (IRB)/Ethics Committee (EC)

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 legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study 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 applicable privacy laws.

The informed consent documents 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 must be reviewed and approved by the sponsor, 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 and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

12.5. 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 competent 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

End of trial is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

In the event of a Grade 4 or Grade 5 AE of Special Interest (meeting criteria for serious), such as cardiac or neurologic toxicity, enrollment and dosing in the study will pause, to allow for a thorough internal safety evaluation, possible external safety analysis and recommendations, and communication with the FDA. Enrollment and dosing will begin in the study only after agreement with the FDA.

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, investigational product problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PrCa VBIR at any time.If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a time period set by Pfizer. 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 for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date 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 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 primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients have 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 principal investigator of the results of the study based on information collected or generated by principal investigator, 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 they are 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 study sites, and that any subsequent publications by the principal investigator 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, 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. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AChR	Acetylcholine receptor
ADA	Anti-drug Antibody
ADT	Androgen Deprivation Therapy
AdC68	Adenovirus C68
ADR	Adverse Drug Reaction
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
AUC_{tau}	Area Under the Serum Concentration-time Curve Over the Dosing Interval
CCI	[redacted]
BP	Blood Pressure
BCR	Biochemical Relapse
CBC	Complete Blood Count
CD	Cluster of Differentiation
CI	Confidence Interval
CL/F	Apparent Clearance
CLss/F	Clearance at steady state
C_{max}	Maximum Drug Concentration
CR	Complete Response
CRF	Case Report Form
CRPC	Castrate Resistant Prostate Cancer
CT	Computed Tomography
CCI	[redacted]
CTLA4	Anti-cytotoxic T Lymphocyte-associated antigen 4
cTnI	Cardiac troponin I
C_{trough}	Trough Concentrations after Multiple Dosing
CYP450	Cytochrome P450 enzymes
DLT	Dose Limiting Toxicities
DMSO	Dimethyl-sulfoxide
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
FoxP3	Forkhead box P3

Abbreviation	Term
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GnRh	Gonadotropin-releasing Hormone
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigator's Brochure
ICAM-1	Intercellular Adhesion Molecule-1
ICOS	Inducible T-cell costimulator
IgG4	Immunoglobulin type G4
IHC	Immunohistochemistry
IFN	Interferon
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IV	Intravenous
LAG3	Lymphocyte activation gene 3
CCI	[redacted]
LFA-3	Lymphocyte Function-Associated Antigen 3
MAb	Monoclonal antibody
MDSC	Myeloid Derived Suppressor Cell
mCRPC	Metastatic Castrate Resistant Prostate Cancer
MHC	Major Histocompatibility Complex
MFD	Maximum Feasible Dose
MFS	Metastasis-free Survival
MG	Myasthenia gravis
mTPI	Modified Toxicity Probability Interval
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
MVA	Modified Vaccinia Virus Ankara
Nab	Neutralizing antibody
NHP	Non-Human Primates
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAC	New oral anticoagulant
NSCLC	Non-Small Cell Lung Cancer
CCI	[redacted]
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCWG3	Prostrate Cancer Working Group 3

Abbreviation	Term
CCI	[redacted]
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
pDNA	Plasmid DNA
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PrCa	Prostate Cancer
PSA	Prostate Specific Antigen
PSADT	Prostate Specific Antigen Doubling Time
PSCA	Prostate Stem Cell Antigen
PSMA	Prostate-Specific Membrane Antigen
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q3W	Every 3 Weeks
Q4W	Every 3 Weeks
QoL	Quality of Life
Rac	Accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
rPFS	Radiographic Progression-free Survival
SAE	Serious Adverse Event
SARS-CoV2	Severe Acute Respiratory Syndrome CoronaVirus 2
SC	Subcutaneous
SOA	Schedule of Assessments
SRE	Skeletal Related Event
SRSD	Single Reference Safety Document
$t_{1/2}$	Half-life
TCR	T cell receptor
TEAEs	Treatment Emergent Adverse Events
T_{max}	Time to Maximum Concentration
TDS-IM	TriGrid Delivery System
TTPP	Time to PSA progression
UTN	Universal trial number
VBIR	Vaccine-based immunotherapy regimen
Vd/F	Apparent Volume of Distribution
VP	Virus Particles
WBC	White Blood Cell

Appendix 2. ECOG Performance Status

Grade	ECOG Performance Status
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 3. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: 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 (based on PCWG3 criteria): Bone disease is defined as present or absent and will be followed as non-target lesions.
- Previous local treatment: A previously irradiated lesion (or lesion patiented 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 two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

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

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

- 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.

- [redacted]

- 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 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

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

Table 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

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

Appendix 4. Immune-Related Response Criteria Derived from RECIST 1.1 (irRECIST)

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

This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD-1/anti-PD-L1 antibodies which exert the antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects.[1,2] Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.[3,4]

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria.[3,4]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST v1.1 (irRECIST).[5]

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

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

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

irRECIST is defined as follows:

- Overall immune-related complete response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.
- Overall immune-related partial response (irPR): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.

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

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

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

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

Overall responses derived from changes in index, non-index, and new lesions are outlines in Table 8.

Table 8. Overall Response Derived from Changes in Index, Non-index and New Lesions

Measurable response	**Non-measurable Response**		**Overall response using irRECIST[b]**
Index and New Measurable Lesions (Tumor Burden)[a]	**Non-Index Lesions**	**New Non-Measurable Lesions**	
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

a. Decrease assessed relative to baseline.
b. Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

References:

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Appendix 5. Guidelines for Evaluation of Bone Scans

Based on Prostate Cancer Working Group 3.[38]

An international expert committee of prostate cancer clinical investigators (the Prostate Cancer Clinical Trials Working Group 3 [PCWG3]) was reconvened and expanded and met in 2012-2015 to formulate updated criteria on the basis of emerging trial data and validation studies of the Prostate Cancer Clinical Trials Working Group 2 recommendations.

Given the frequency of bone involvement in patients with progressive, castration-resistant disease, the decreased emphasis of early changes in PSA, and the increased availability of cytostatic agents, reliable methods to assess changes in bone are of increasing importance. PCWG3 recognizes that standards for using MRI and PET to assess bone metastases are under active investigation, so only radionuclide bone scans are considered here. PCWG3 also recognizes that there are no validated criteria for response on radionuclide bone scan.

For control/relieve/eliminate end points, the PCWG3 recommends that post-treatment changes be recorded "no new lesions," "new lesions" or "resolved bone lesion." However, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later, in the absence of clearly worsening disease or disease-related symptoms. In the event of visible lesions disappearing, this should also be confirmed at the next scheduled assessment.

For prevent/delay end points, progressing disease on bone scan is considered when at least two new lesions relative to the first post-treatment scan is confirmed on a subsequent scan. PCWG3 does not recommend performing a follow-up bone scan before 12 weeks of treatment unless clinically indicated. At the first 12-week reassessment, defining disease progression requires a confirmatory scan (which shows additional new lesions compared with the first follow-up scan) performed 6 or more weeks later, because lesions visible at the first 12-week assessment may represent disease that was not detected on the pretreatment scan. When further progression is documented on the confirmatory scan, the date of progression recorded for the trial, is the date of the first scan that shows the change.

Nonmetastatic to metastatic progression: Any new unequivocal bone lesion, except if that lesion appears in the first post-treatment scan; in that case, document the event, continue treatment until 2 additional new lesions appear, and record both events.

Appendix 6. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 4.03 dated June 14, 2010) has been placed in the Study Manual for this protocol. Alternatively, the NCI CTCAE may be reviewed on-line at the following NCI website: http://ctep.cancer/gov/reporting.ctc.html.

Appendix 7. Management of Immune-related Adverse Events (irAEs) including Myasthenia Gravis

Note: References to study treatment in the table below refer to PF-06801591 and/or tremelimumab.

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over Baseline. Colitis: asymptomatic.	-Continue study treatment. -Symptomatic treatment (eg, loperamide).	-Close monitoring for worsening symptoms. -Educate patient to report worsening immediately. -If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL. Colitis: abdominal pain; blood in stool.	-Withhold study treatment. - Symptomatic treatment.	-If improves to Grade ≤1: Resume study treatment. -If persists >5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL. Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs. Grade 4: life-threatening, perforation.	-Withhold for Grade 3. -Permanently discontinue study treatment for Grade 4 or recurrent Grade 3. -1.0 to 2.0 mg/kg/day prednisone IV or equivalent. -Add prophylactic antibiotics for opportunistic infections. -Consider lower endoscopy.	-If improves: -Continue steroids until Grade ≤1, then taper over at least 1 month; resume study treatment following steroids taper (for initial Grade 3). -If worsens, persists >3 to 5 days, or recurs after improvement: -Add infliximab 5 mg/kg (if no contraindication). -Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area.	-Continue study treatment. -Symptomatic therapy (for example, antihistamines, topical steroids).	-If persists >1 to 2 weeks or recurs: -Withhold study treatment. -Consider skin biopsy. -Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study treatment following steroids taper. -If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: Life threatening consequences.	-Withhold study treatment for Grade 3. -Permanently discontinue for Grade 4 or recurrent Grade 3. -Consider skin biopsy. -Dermatology consult. -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections.	-If improves to Grade ≤1: -Taper steroids over at least 1 month; resume study treatment following steroids taper (for initial Grade 3).

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only.	-Consider withholding study treatment. -Monitor for symptoms every 2 to 3 days. -Consider Pulmonary and Infectious Disease consults.	-Re-assess at least every 3 weeks -If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms.	-Withhold study treatment. -Pulmonary and Infectious Disease consults. -Monitor symptoms daily; consider hospitalization. -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections. -Consider bronchoscopy, lung biopsy.	-Re-assess every 1 to 3 days If improves: -When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume study treatment following steroids taper. -If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening.	-Permanently discontinue study treatment. -Hospitalize. -Pulmonary and Infectious Disease consults. -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections. -Consider bronchoscopy, lung biopsy.	-If improves to Grade ≤1: -Taper steroids over at least 1 month. -If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN.	-Continue study treatment.	-Continue liver function monitoring. -If worsens: Treat as Grade 2 or 3 – 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN.	-Withhold study treatment. -Increase frequency of monitoring to every 3 days.	-If returns to Grade ≤1: -Resume routine monitoring; resume study treatment. -If elevation persists >5 to 7 days or worsens: -Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN.	-Permanently discontinue study treatment. -Increase frequency of monitoring to every 1 to 2 days. -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections. -Consult gastroenterologist/ hepatologist. -Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	-If returns to Grade ≤1: -Taper steroids over at least 1 month. -If does not improve in >3 to 5 days, worsens or rebounds: -Add mycophenolate mofetil 1 gram (g) twice daily. -If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN.	-Continue study treatment.	-Continue renal function monitoring. -If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN.	-Withhold study treatment. -Increase frequency of monitoring to every 3 days. -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections. -Consider renal biopsy.	-If returns to Grade ≤1: -Taper steroids over at least 1 month, and resume study treatment following steroids taper. -If worsens: -Treat as Grade 4.
Grade 4 Creatinine increased >6 x ULN.	-Permanently discontinue study treatment. -Monitor creatinine daily. -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections Consider renal biopsy. -Nephrology consult.	-If returns to Grade ≤1: Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and/or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	-Withhold study treatment. - Hospitalize. -In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. -Consult cardiologist to establish etiology and rule-out immune-mediated myocarditis. -Guideline based supportive treatment as per cardiology consult.* -Consider myocardial biopsy if recommended per cardiology consult.	-If symptoms improve and immune-mediated etiology is ruled out, re-start study treatment. -If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis.	-Permanently discontinue study treatment. -Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections.	-Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).
*Local guidelines, or eg, ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus).	-Continue study treatment. -Endocrinology consult if needed. -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. -Rule-out secondary endocrinopathies (ie, hypopituitarism/hypophysitis).	-Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus).	-Withhold study treatment. -Consider hospitalization. -Endocrinology consult. -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. -Rule-out secondary endocrinopathies (ie, hypopituitarism/hypophysitis).	-Resume study treatment once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). -Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/ Hypophysitis (secondary endocrinopathies).	-If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): -Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women). -Hormone replacement/suppressive therapy as appropriate. -Perform pituitary MRI and visual field examination as indicated. **-If hypophysitis is confirmed:** -Continue study treatment if mild symptoms with normal MRI. Repeat the MRI in 1 month. -Withhold study treatment if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. -Add prophylactic antibiotics for opportunistic infections.	-Resume study treatment once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). -In addition, for hypophysitis with abnormal MRI, resume study treatment only once shrinkage of the pituitary gland on MRI/CT scan is documented. -Continue hormone replacement/suppression therapy as appropriate.

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE.	-Withhold study treatment pending clinical investigation.	-If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting study treatment. -If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE.	-Withhold study treatment. -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections. -Specialty consult as appropriate.	-If improves to Grade ≤1: -Taper steroids over at least 1 month and resume study treatment following steroids taper.
Recurrence of same Grade 3 irAEs.	-Permanently discontinue study treatment. -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections. -Specialty consult as appropriate.	-If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4.	-Permanently discontinue study treatment. -1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed. -Add prophylactic antibiotics for opportunistic infections. -Specialty consult.	-If improves to Grade ≤1: Taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency. Persistent Grade 2 or 3 irAE lasting 12 weeks or longer.	-Permanently discontinue study treatment. -Specialty consult.	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

Recommended Management Algorithim for Myasthenia Gravis