A PHASE 1, OPEN-LABEL, DOSE ESCALATION AND EXPANSION STUDY OF PF-06801591 IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC MELANOMA, SQUAMOUS CELL HEAD AND NECK CANCER, OVARIAN CANCER, SARCOMA, NON-SMALL CELL LUNG CANCER, UROTHELIAL CARCINOMA OR OTHER SOLID TUMORS

Compound:	PF-06801591
Compound Name:	Not applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	125,681
European Clinical Trials Database (EudraCT) Number:	2016-003314-27
Protocol Number:	B8011001
Phase:	Phase 1

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	11 September 2015	N/A
Amendment 1	10 December 2015	Section 3.1.5 Modification of dose limiting toxicities by addition of the following criteria, as per a request of the FDA to define these toxicities: 1. Platelet transfusion requirement or a platelet count < 10,000/uL, 2. Concurrent AST or ALT >3X ULN and total bilirubin >2X ULN (potential Hy's law case).
		Sections 4.1, 4.2 and 4.3: Update the period to require contraception require that male patients who are able to father children and female patients of childbearing potential use two (2) effective methods of contraception throughout the study and for at least 5 months following the last dose of PF-06801591, as per a request of the FDA based on compartmental modeling and allometric scaling of monkey PK data.
		Schedule of Assessments: Added contraception check at days 63 and 120, to prolong monitoring of contraceptive use after last dose, during follow-up.
		Section 8.1: Update as per a request of the FDA to include that adverse events the investigator deems immune-related and whether an immunosuppressive therapy (eg, corticosteroids, other immunosuppressant drugs) is indicated, will be recorded on the CRF. For any adverse event, regardless of investigator determined causality, if the management requires administration of an immunosuppressive therapy, the use will be documented on a specific case report form that will record generic drug name, stop and start dates (duration), dose, units, route, frequency of administration, and response to medication.

Document	Version Date	Summary of Changes and Rationale
		Schedule of Assessments: Due to alignment with laboratory analyses, changes were made to blood volumes for collection of whole blood biomarkers and receptor occupancy samples. In addition, some editorial clarifications were made for the time collection of anti- PF-06801591 antibody measurement and PF-06801591 PK blood samples (ie, up to Cycle 10), and a specification (ie, PrepD1) was added for banked biospecimens, for the sake of clarification.
		Schedule of Assessments: Update for serious adverse events (SAEs) to include that the active reporting period to Pfizer or its designated representative is through and including 150 calendar days after the last administration of the investigational product or until administration of subsequent anti-cancer therapy whichever comes first, in order to align SAEs monitoring with contraception use period.
		Section 8.2: Update the reporting period for SAEs, ie, is through and including 150 days, after the last administration of the investigational product or until administration of subsequent anti-cancer therapy, whichever comes first, in order to align SAEs monitoring with contraception use period. Also, an update was made in this section to be consistent with the Schedule of Assessments, to mention that additional, immune-related AEs will be collected with a follow-up phone call at 63 and 120 days after last dose administration date to collect post-treatment related AE information.
Amendment 2	21 July 2016	Updated TOC, lists of tables, figures, and appendices.
		Schedule of Activities split into 2 schedules: one for IV administration and one for subcutaneous administration of study treatment.
		Schedule of Activities: Removal of Day 63 (Post-treatment) and update of assessments on Day 28 and Day 90 (Post-treatment).

Document	Version Date	Summary of Changes and Rationale
		Schedule of Activities for SC Administration, added a "Day 21 of Cycle 1" column for clinical assessments: abbreviated physical examination, vital signs, hematology & chemistry laboratory panels, adverse events, and concomitant and non-drug supportive interventions.
		Schedule of Activities, Vital Signs: added "X" to schedule for vital signs to be performed on Day 3 of Cycle 1, which had been inadvertently omitted.
		Schedules of Activities and Section 4.1. (Inclusion Criterion # 6) were updated to correct Appendix 6 to 7, to refer to the ECOG Performance Status.
		Schedules of Activities: Subsequent Cycles updated to clarify that free T3 (triiodothyronine), and free T4 (thyroxine) testing are included in the Blood Chemistry panel, as per Table 4 in the Laboratory Safety Assessment Section (7.1.3).
		Schedules of Activities: Footnote created to provide details on the blood collection for high sensitivity C-reactive protein.
		Schedules of Activities: Footnote created to provide details on the blood collection for TBNK (Whole Blood).
		Schedules of Activities: Footnote created to provide details on the blood collection for baseline cytokines.
		Schedule of Activities IV and SC Administration footnotes: updated to indicate that standard of care radiographic assessments performed within 28 days of C1D1 may not have to be repeated and used as the screening (baseline) tumor assessment.
		Schedule of Activities for IV and SC Administration footnotes: Second scan changed from required to preferred. Clarified "entire" study and defined end of entire study (2 years after LPFT).
		Schedules of Activities: updated to clarify which assessments must be performed on Day 8 and/or Day 15 after Cycle 2.

Document	Version Date	Summary of Changes and Rationale
		Schedules of Activities, footnote ee: Added "entire" study and defined end of entire study (2 years after LPFT). Wording on clinic visit during follow-up window can replace survival telephone call.
		Schedule of Activities and Section 3.1. (Study Overview): Updated length of PF-06801591 treatment (up to 2 years). Treatment until disease progression clarified as disease progression per irRECIST.
		Schedule of Activities and Section 3.1.5. (Dose-Limiting Toxicity Definition): Updates were made to include the SC cohort at a fixed dose of 300 mg administered over a cycle of 28 days.
		Schedule of Activities and Section 7.4. (Tumor Response Assessments): Extended tumor assessments beyond end of treatment if treatment did not end for disease progression, death, or consent withdrawal.
		Pharmacokinetic and Pharmacodynamic Schedule of Activities: updated and split into 2 schedules: PF-06801591 IV and subcutaneous administration.
		PK & Pharmacodynamic Schedules of Activities: Clarifications were added to footnotes for the PK sampling on Day 1 of Cycle 1, and a new footnote was created to clarify the (±2) window on Day 8 of Cycle 2.
		PK & Pharmacodynamic Schedules of Activities: Clarified archival or fresh tumor biopsy required at Screening only in Part 2.
		Section 1.2. (Background and Rationale): Updates were made as per recent publications.
		Section 1.2.4. (SC Dose Rationale): New text was added to explain the rationale for the fixed dose of 300 mg that is administered subcutaneously (SC) in the additional dose cohort.
		Section 1.2.5. (Rationale for Pre-treatment and On-treatment Biopsies and Expansion of Various Dose Level Cohorts): Language was added to clarify the rule for the decision to dose escalate (Part 1A) vs the MTD and RP2D determination.

Document	Version Date	Summary of Changes and Rationale
		Section 1.2.5. (Rationale for Pretreatment and On treatment Biopsies and Expansion of Various Dose Level Cohorts): Wording on each dose level to enroll up to 15 patients.
		Section 1.2.5. (Rationale for Pretreatment and On treatment Biopsies), and Section 3.1.1. (Study Overview Part 1): Part 1B to include 3 to 5 minimum patients with available pre- and on-treatment biopsies.
		Section 1.3. (Biomarker Rationale): Edits were made to clarify that potential effects of PF-06801591 on the PD-1 receptor and the PD-L1 ligand expression will not be assessed by flow cytometry. PD-1 receptor cannot be adequately assessed by flow cytometry because PF-06801591 competes for binding with the flow cytometry antibody for PD-1.
		Section 2.1.1. (Objectives for Part 1), & Section 2.1.2. (Objectives for Part 2): Updates were made for the additional dose cohort with a SC administration. Objective "To evaluate the phenotypes and quantity of TILS before and after PF-06801591 " has been moved from Secondary to Exploratory as TILs may not necessarily be evaluable.
		Sec 2.2. Exploratory Endpoints: Wording was added to expand and clarify endpoints.
		Section 3.1. (Study Overview): Added "or other solid tumors" to list of treated tumor types for the study in order to enable enrollment of other tumor types that have clinical evidence of response to anti PD-1 to PD-L1 agents at the discretion of the sponsor.
		Section 3.1. (Study Overview): Text was edited to clarify that up to 15 patients, instead of approximately 8 to 15 patients will be enrolled per dose level (except for the 0.5 mg/kg dose level), in Part 1. In addition, a paragraph was added to explain the enrollment of the additional SC cohort at a fixed dose of 300 mg. Text was deleted to remove the number of sites involved, allowing some flexibility.

Document	Version Date	Summary of Changes and Rationale
		Schedule of Activities for IV Administration, Section 3.1. (Study Overview), & Section 5.4. (Administration): A window for the infusion time of PF-06801591 was added to have 60 minutes ± 10 minutes.
		Section 3.1.1. (Study Overview, Part 1): Text was added to introduce the SC dosing cohort.
		Section 4.1. (Inclusion Criteria): Updated criterion #1a to allow for other tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents to be considered at the discretion of the sponsor. Updated criterion #1 to remove an upper limit on prior lines of therapy. Updated criterion #1c to clarify that a paraffin-embedded tumor block, freshly cut tissue slides, or a de novo (ie, fresh) tumor sample completed during the screening period, must be available for exploratory biomarker analysis. Clarified in Part 1A or 2 that fresh biopsy can be used if archival biopsy is unavailable. In Part 1B, archival sample encouraged, but waived if unavailable.
		Section 4.2. Exclusion Criteria: Added wording on prior allogeneic bone marrow or hematopoietic stem cell transplant.
		Section 5.4. (Administration) was divided into two (2) sections: 5.4.1. (IV Administration), and 5.4.2. (SC Administration) to provide updated information on the SC administration for the additional cohort. Study Treatment footnote in the Schedule of Activities was updated accordingly for the SC administration.
		Section 6.3. (Study Procedures/Follow-up Visit): Defined end of entire study as 2 years after last patient enrolled has been first treated and explained that clinic visit can replace telephone call for survival data

Document	Version Date	Summary of Changes and Rationale
		Section 7.1.1. (Pregnancy Testing) & Section 7.1.3. (Laboratory Safety Assessments, Table 4): FSH testing at Screening only was added to confirm the postmenopausal status for women who have not experienced their menses since at least 12 months. Confirmation of FSH level was already mentioned in inclusion criterion #15c, but it needed to be clarified in the above mentioned sections of the protocol. Schedule of Activities was updated accordingly.
		Section 7.1.6. (Local Site Injection Tolerability Assessment (SC Cohort Only): New text was added to include a site injection tolerability assessment for the additional SC dose level cohort. Footnote in the Schedule of Activities for subcutaneous drug administration was created accordingly to reflect this new procedure.
		Section 7.5. (CA-125 Tumor Marker Assessment - Ovarian Cancer Only): A new section was added to provide details on this test for ovarian cancer patients only. Schedule of Activities footnote created accordingly to reflect this new procedure.
		Section 9.1.3. (Per-protocol Analysis Set): Clarified that SC patients with major deviations will not be evaluated for DLTs.
		Section 9.3. (Sample Size Determination): Updated wording on sample size and number of patients for Parts 1A and 1B.
		References (Section 16): References added to Sec 1 Introduction: Tecentriq PI, web site links to other solid tumor types and mismatch repair. References by Rusin & DeVita were added for background on CA-125; References for Gillison and Ansell were added for updates on nivolumab.
		Appendix 10. (SC Injection Site Location Diagram): A new appendix was added to the document to provide detailed instructions for the SC administration of PF-06801591.

Document	Version Date	Summary of Changes and Rationale
Amendment 3	03 JUN 2017	Throughout document: removal of relapsed and refractory classic Hodgkin Lymphoma references in protocol title and protocol body. Removal of lymphoma response criteria.
		Schedule of activities: added for Part 2, and administrative edits made for schedule of activities for Part 1, including addition of preexisting Day 8 ECG, survival follow up visits, clarification of SAE collection up to 150 days after last treatment, and include information regarding collection tumor assessment information after end of treatment for patients who did not end treatment due to disease progression, death, or withdrawal of consent.
		Section 1. Introduction: Addition of background information for urothelial carcinoma, and updated section with emerging data on pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab in support of study rationale.
		Section 1.9: Addition of clinical experience information for PF-06801591. Addition of risk benefit assessment.
		Section 2. Objectives and Endpoints: Added objectives and endpoints specific for Part 2.
		Section 3. Study design: administrative edits made to clarify design of study. Details of Part 2 incorporated, including the enrollment of NSCLC patients in Arm 1, and Urothelial patients in Arm 2. Included information on dose selected for Part 2 expansion.
		Section 4. patient selection: added specific inclusion/ exclusion criteria for Part 2.
		Section 5.1.2. Allocation of treatment for dose expansion: Added interactive response technology (IRT) system for patient enrollment in Part 2.
		Section 5.4.2. Dose Delays: Added dose delay information.
		Section 6.3.2. Survival follow up: Added survival follow up section to align with information included in schedule of activities.
		Section 7.1.3. Laboratory assessments: Administrative edits made to align Table 4 with items included in schedule of activities.

Document	Version Date	Summary of Changes and Rationale
		Section 7.3. Biomarker assessments: Clarified that archival sample for Part 2 must be taken within two year of start of study treatment.
		Section 8.2. SAE reporting period: Clarified that death must be reported as an SAE if it occurs within 150 calendar days after last administration of the investigational product, irrespective of any intervening treatment.
		Section 9.2. Statistical methods and properties: Removed reference to optimal biological dose, and added statistical methods for Part 2.
		Section 9.3. Sample size determination: Added information for Part 2.
		Section 9.4. Efficacy information: Added information for Part 2.
		Section 9.8 Data safety monitoring committee: Added information on preliminary analysis for safety and efficacy.
		Section 13. Definition of end of trial: Clarified that end of trial will be 2 years after last patient first dose (LPFD), not last patient last visit (LPLV).
		Appendix 8 Management of irAEs: Updated appendix with initial and follow-up irAE management information.
Amendment 4	07 August 2018	Study overview and section 9.3: The number of enrolled subjects has been changed throughout the part 2 of protocol from approximately 60 NSCLC and 40 urothelial cancer patients to approximately 70 and 30, respectively, to more accurately reflect projected enrollment. Statistical justification for patient sample size in section 9.3 has also been adjusted accordingly.
		Schedule of Activities, Part 2 and Section 7.1.1, Pregnancy testing: Per Poland competent authority request, added the following paragraph for pregnancy tests in Poland: In Poland, pregnancy tests should be performed after end of treatment on days 28, 60, 90, 120, and 150. Pregnancy tests on days 60, 90, 120, and 150 may be collected at home by the patient.

Document	Version Date	Summary of Changes and Rationale
		Schedule of Activities, Footnote O: Removed language: "No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date." Screening UA is not required within 72 hours of C1D1.
		Schedule of Activities For Part 1 Subcutaneous Administration of PF-06801591 – Changed Cycle 1 Day 22 to Cycle 1 Day 21 to accommodate calendar scheduling for this visit.
		Section 1.2. Background and Rationale: updates from recent clinical trials provided in NSCLC and urothelial cancer sections.
		Section 4.1.2. Part 2 Inclusion Criterion 5 for urothelial cancer patients, sub-bullet point e: Added the following sentence: If patients are treatment naïve and eligible for platinum-containing systemic therapy but are refusing platinum chemotherapy, they must also be documented to have previous PD-L1 high status. Rationale: Two ongoing clinical studies (KEYNOTE-361 and IMVIGOR-130) evaluating either single agent pembrolizumab or atezolizumab versus platinum chemotherapy in previously untreated metastatic urothelial carcinoma eligible for platinum-based chemotherapy treatment found that patients with PD-L1 low tumors in the monotherapy pembrolizumab or atezolizumab arms had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy.
		Section 4.2.2. Part 2 Exclusion Criterion 3: Added the following clarification: For example, patients with HBV surface antigen positive or HCV RNA positive will be excluded. Rationale: This provides examples of what constitutes "active" HBV or HCV infections.
		Section 4.2.1. Part1 Exclusion Criterion 12 and Section 4.2.2. Part2 Exclusion Criterion 12: Corrected definition of bifascicular block.

Document	Version Date	Summary of Changes and Rationale
		Section 4.2.2. Exclusion Criterion 17 added per South Korea competent authority request: For South Korea, vaccination except inactivated vaccine within 4 weeks prior to the enrolment of the study or during the study.
		Section 4.2.2. Exclusion Criterion 18 added per South Korea competent authority request: For South Korea, patients with active infection requiring systemic therapy will be excluded.
		Section 7.1.1. Pregnancy testing or postmenopausal status: Removed requirements to collect pregnany test within 5 days of menses and added "If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy is positive." to ensure consistency with newer Pfizer pregnancy testing language.
		Section 7.4. Tumor response assessments: The phrase "and bone scans" has been removed and the phrase "Bone scans should be performed at baseline and on-study for patients with known or suspected bone metastases not well-visualized on other imaging or if disease is suspected or has been previously documented as appropriate to follow disease." has been added for clarification.
		Section 7.7.1. Markers of drug response: Third paragraph has been modified to clarify collection of blood for DNA analysis will be collected at the screening and Cycle 2 Day 8 visits (Part 1 only) and Cycle 1 Day 1 visits (Part 2 only). Rationale: To differentiate collections in part 1 vs. part 2.
		Minor editorial changes throughout the protocol and schedule of changes.

This amendment incorporates all revisions to date, including amendments made at the request of the FDA.

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PROTOCOL SUMMARY

Background

Binding of the programmed cell death protein-1 ligands, PD-L1 and PD-L2, to the programmed cell death protein-1 (PD-1) receptor found on T cells inhibits T-cell proliferation, cytokine production, and its cytotoxic functions. Upregulation of PD-1 ligands occurs in certain tumor types, and signaling through this pathway can contribute to the inhibition of active T-cell immune surveillance of tumors.[1] In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Approval of nivolumab/Opdivo® (a fully human immunoglobulin G4 [IgG4] anti-PD-1 antibody [Ab]), pembrolizumab/Keytruda® (a humanized IgG4 anti-PD-1 Ab), atezolizumab/Tecentriq® (a humanized IgG1 anti-PD-L1 Ab), durvalumab/Imfizi® (a humanize IgG1 anti-PD-1 antibody), and avelumab/Bavencio® (a fully human IgG1 anti-PDL-1 Ab) for the treatment of multiple tumor indications provide compelling evidence that blockage of the PD-1 pathway is a validated immunotherapeutic approach.[2,3,4,5,6]

PF-06801591 is a humanized, immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to the PD-1 receptor. By blocking its interaction with PD-L1 and PD-L2, PD-1 pathway-mediated inhibition of the immune response is released, leading to an anti-tumor immune response. In this clinical study, intravenous (IV) and subcutaneous (SC) administration of PF-06801591 will be evaluated for the treatment of adult patients with locally advanced or metastatic solid tumor types with clinical evidence of response to anti-PD-1 or PD-L1 agents.

Study Overview

This is a Phase 1, open-label, multi-center, multiple-dose, dose escalation and expansion, safety, pharmacokinetics (PK), and pharmacodynamic study of PF-06801591. The primary purpose of this study is to evaluate safety and early signs of efficacy of PF-06801591. This clinical study will be divided into a dose escalation (Part 1) phase, and a dose expansion (Part 2) phase. Approximately 140 patients are expected to be enrolled into the study.

Part 1 Dose Escalation

Part 1 dose escalation will evaluate 4 pre-specified IV dose levels (0.5, 1, 3, and 10 mg/kg), and 1 SC dose level (300 mg) in adult patients with locally advanced or metastatic melanoma, squamous cell cancer of head and neck (SCCHN), ovarian cancer, sarcoma, non-small cell lung cancer (NSCLC), urothelial carcinoma, or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents, who are unresponsive to currently available therapies or for whom no standard therapy is available. Approximately 40 patients will be enrolled into Part 1. The actual number of patients enrolled in Part 1 will depend on the observed safety and tolerability profile of PF-06801591, and the number of dose levels required to identify the maximum tolerated dose (MTD).

For the IV administration portion, a cycle is definied as 1 dose of PF-06801591 administered every 3 weeks (q3w). The IV dose-limiting toxicity (DLT) observation period is defined as starting on Day 1 of study drug administration through Day 21 of the treatment cycle. For the SC administration portion, a cycle is defined as 1 dose of PF-06801591 administered every 4 weeks (q4w). The SC administration DLT observation period is defined as starting on Day 1 of study drug administration through Day 28 of the treatment cycle. A staggered start will be employed for both IV and SC administration portions: a single patient will be dosed and observed for 48 hours. If no safety concerns arise during this 48-hour period, additional patients may be enrolled into the same dose level.

The 300 mg SC administration cohort will enroll patients concurrently with the IV administration portion, following evaluation of the 3 mg/kg IV administration dose level. If the 300 mg dose administered by SC is deemed intolerable, a lower dose level of 150 mg maybe evaluated.

Part 1 will be further divided into Part 1A (safety cohort) and Part 1B (pharmacodynamic cohort). For both IV and SC administration portions, each safety cohort will enroll 2-4 patients per dose level. A modified toxicity probability interval (mTPI) method,[7] targeting a DLT rate of 27.5% will be utilized for dose escalation. In the IV administration portion, if based on Part 1A information the dose level is deemed safe and well- tolerated, an additional 2 to 5 patients will enroll into the same dose level in Part 1B. In the SC administration portion, if based on Part 1A information the 300 mg dose level is deemed safe and well- tolerated, an additional 11 (approximate) patients will be enrolled into Part 1B. Up to approximately 9 patients may be enrolled into each dose level in the IV administration portion, and up to approximately 15 patients may be enrolled into the 300 mg SC administration portion (Part 1A and Part 1B combined). The mTPI approach would be applied across Parts 1A and 1B to ensure that the administered doses do not surpass the toxicity boundaries. Safety data from all patients in Parts 1A (safety cohort) and available data at cutoff from Parts 1B (pharmacodynamic cohort) will be used to determine the MTD. Tumor biopsies collected at pre and post treatment time points (screening and Cycle 2 Day 8 [C2D8]) are mandatory for all Part 1B patients.

Part 2 Dose Expansion

Part 2 will enroll approximately 70 patients with anti-PD-1 or anti-PD-L1 treatment naïve NSCLC and approximately 30 patients with anti-PD-1 or anti-PD-L1 treatment naïve urothelial carcinoma who progressed on, or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable. All patients will receive 300 mg of PF-06801591 SC q4w. When the first tumor assessment has been completed for the first 30 NSCLC patients, an interim analysis may be performed to evaluate safety and efficacy.

In this study, all patients in Part 1 and Part 2 will:

1. Undergo up to 4 weeks of screening prior to study entry.

2. Receive treatment with investigational product for up to 2 years, or until one of the following:

    a. Disease progression by immune-related Response Evaluation Criteria in Solid Tumors (irRECIST, confirmed progressive disease [PD] or initial PD followed by rapid clinical deterioration); or

    b. Unacceptable toxicity occurs; or

    c. Withdrawal of consent; or

    d. Patient no longer willing to participate in trial; or

    e. Study termination.

    Any additional treatment beyond 2 years shall be discussed and approved by the sponsor. Patients will be allowed to stay on treatment in the case of initial radiological disease progression, if the investigator feels that it is in the patient's best interest. For example, if a patient does not have rapid clinical deterioration, after initial assessment demonstrating unconfirmed PD. If a patient has a confirmed CR (ie, 2 consecutive CR assessments at least 4 weeks apart) by irRECIST, patient may also discontinue treatment at the discretion of the investigator and continue follow-up assessments.

3. Will complete a 1 month follow-up visit after the last dose for adverse event (AE) collection and serious adverse event (SAE) follow-up if necessary.

4. Will undergo assessment for late immune related AEs (irAEs) up to 120 days after completion of PF-06801591 administration(see Section 3.1.5.1 Late Immune-Related Dose-Limiting Toxicities). Subsequent anti-cancer therapy will also be recorded during these follow up visits.

5. Will be contacted by telephone every 8 weeks for survival data collection after the 120-day follow-up visit, until the end of the trial (defined as 2 years after last patient first dose [LPFD], see Section 13.2). Subsequent anti-cancer therapy will also be documented during survival follow-up visits.

Study Objectives and Endpoints

Part 1 Dose Escalation

Primary Objective(s):	Primary Endpoint(s):
• To assess safety and tolerability of increasing dose levels of PF-06801591 administered IV in patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents to establish the MTD. • To assess safety and tolerability of PF-06801591 administered SC in patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents.	• Dose Limiting Toxicities (DLTs) at escalated doses of PF-06801591. • AEs as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), timing, seriousness, and relationship to study therapy PF-06801591. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To characterize the single dose and multiple dose PK of PF-06801591 following IV or SC administration.	• PK parameters of PF-06801591: Cycle 1 and Cycle 4 maximum drug concentration (Cmax), area under the concentration versus time curve (AUC) from time zero to the last quantifiable time point prior to the next dose (AUClast), and if data permit, clearance (CL), volume of distribution (Vd)/ volume of distribution at steady state (Vss), accumulation ratio (Rac) when feasible, and terminal elimination half-life (t1/2).
• To evaluate the immunogenicity of PF-06801591 following repeated administration.	• Incidence of anti-drug antibody (ADA) and neutralizing antibodies (NAb) against PF-06801591.
• To characterize PD-1 Receptor Occupancy (RO) in peripheral blood T cells following IV or SC PF-06801591 administration at each dose level.	• PD-1 RO by PF-06801591, as assessed by measuring the levels of unbound (free) cell surface PD-1 on circulating T cells over time following PF-06801591 administration.
• To evaluate preliminary anti-tumor activity of PF-06801591.	• Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 and immune related RECIST (irRECIST) and proportion of patients with partial response (PR) and immune related partial response (irPR), as appropriate >80%. • Time to event endpoints based on RECIST and irRECIST, and progression free survival (PFS), duration of stable disease (DOSD), and DOR (duration of response).
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[redacted]	[redacted]
[redacted]	[redacted]

Part 2 Dose Expansion

Primary Objective(s):	**Primary Endpoint(s):**
• To further characterize the safety and tolerability of PF-06801591 following SC administration in NSCLC and urothelial carcinoma.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy PF-06801591 administered by SC administration. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
• To estimate clinical efficacy by overall response rate (ORR) of PF-06801591 following SC administration in NSCLC and urothelial carcinoma.	• Overall response rate (ORR) as assessed using RECIST version 1.1 and irRECIST.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To further evaluate preliminary anti-tumor activity of PF-06801591 following SC administration.	• Time to event endpoints by PF-06801591 administered by SC based on RECIST and irRECIST, including time to response (TTR) and time to progression (TTP) as well as PFS (and irPFS as appropriate), DOSD (and irDOSD as appropriate), and DOR (and irDOR as appropriate).
• To evaluate overall survival (OS).	• Median time to death, proportion of patients alive at 6 months, 1 year, and 2 years.
• To collect PF-06801591 drug concentration data in patients following SC administration for evaluation of population PK.	• Trough PF-06801591 concentrations for selected cycles.
• To evaluate the immunogenicity of PF-06801591 following repeated SC administration.	• Incidence of ADA and NAb against PF-06801591 administered by SC.

SCHEDULE OF ACTIVITIES FOR PART 1 INTRAVENOUS ADMINISTRATION

The Schedule of Activities tables provide an overview of the protocol visits and procedures. Refer to the Assessments Section 7 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 patient.

Schedule of Activities for Part 1 Intravenous Administration of PF-06801591		**Treatment Period**											**Post-Treatment**			
		Cycle 1 Only (Days 1 to 21)					**Cycle 2 (Days 1 to 21)**			**Subsequent Cycles (Days 1 to 21)[cc]**		**EOT[dd]**	**1 Month and Late irAE Follow up[ee]**			**Survival Follow up[ff]**
	Screening[a] (≤28 days prior to study entry)	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8 (C3 Only)**		**Days after last dose**			**Every 2 months after 120 day follow up visit**
													28 days	**90 days**	**120 days**	
Visit Window (days)					**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		+7	**±7**	**±7**	±7
Informed Consent[b]	X															
Tumor History[c]	X															
Medical History[d]	X															
Complete Physical Examination	X	X										X	X			
Abbreviated Physical Examination[e]			X	X	X	X	X	X	X	X						
Baseline Signs and Symptoms[f]		X														
Height	X															
Weight[g]	X	X					X			X		X				
Vital Signs (BP/Pulse Rate/PO/Temp)[h]	X	X	X	X	X	X	X	X	X	X		X	X			
ECOG Performance Status[i]	X	X					X			X		X	X			
Triplicate 12-Lead ECG[j]	X (single ECG only)	X			X		X	X		X	X	X				

Schedule of Activities for Part 1 Intravenous Administration of PF-06801591		Treatment Period											Post-Treatment			
		Cycle 1 Only (Days 1 to 21)					Cycle 2 (Days 1 to 21)			Subsequent Cycles (Days 1 to 21)[cc]		EOT[dd]	1 Month and Late irAE Follow up[ee]			Survival Follow up[ff]
	Screening[a] (≤28 days prior to study entry)	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8 (C3 Only)		Days after last dose			Every 2 months after 120 day follow up visit
													28 days	90 days	120 days	
Visit Window (days)					±1	±2	±2	±2	±2	±2	±2		+7	±7	±7	±7
Laboratory																
Hematology[k]	X	X			X	X	X		X	X		X	X			
Blood Chemistry[l]	X	X			X	X	X		X	X		X	X			
Coagulation[m]	X	X			X	X	X		X	X		X	X			
CA-125 (Ovarian Cancer Only)[n]	X	X					X			X		X	X			
Urinalysis[o]	X					X	X			X		X	X			
Pregnancy Test or FSH Level[p]	X	X					X			X		X	X			
C-Reactive Protein (CRP or hsCRP)[q]		X				X		X	X			X				
TBNK (whole blood)[r]		X				X		X	X			X				
Cytokines[s]		X	Optional collection as clinically indicated													
Hepatitis B, C, and HIV tests[t]	X															
Registration and Treatment																
Registration[u]		X														
Study Treatment[v]		X					X			X						
Tumor Assessments																
CT or MRI Scan[w]	X	Every 6 weeks (±5 days) up to 24 wks, and every 6 or 12 weeks (±5 days) thereafter according to calendar, regardless of treatment delays										X	X (Every 12 weeks as necessary)			
Other Clinical Assessments																
Adverse Events[x]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Schedule of Activities for Part 1 Intravenous Administration of PF-06801591		Treatment Period											Post-Treatment			
		Cycle 1 Only (Days 1 to 21)					Cycle 2 (Days 1 to 21)			Subsequent Cycles (Days 1 to 21)[cc]		EOT[dd]	1 Month and Late irAE Follow up[ee]			Survival Follow up[ff]
	Screening[a] (≤28 days prior to study entry)	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8 (C3 Only)		Days after last dose			Every 2 months after 120 day follow up visit
													28 days	90 days	120 days	
Visit Window (days)					±1	±2	±2	±2	±2	±2	±2		+7	±7	±7	±7
Serious Adverse Events[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Up to 150 days after last treatment
Concomitant Medication and non-drug supportive interventions[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subsequent anti-cancer therapy[aa]													X	X	X	X
Survival follow-up[ff]																X
Contraception check[bb]	X	X					X			X		X	X	X	X	

BP = blood pressure; C3 = cycle 3; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; Hs CRP = high sensitivity C-reactive protein; IV = intravenous; MRI = magnetic resonance imaging; NAb = neutralizing antibodies; PO = pulse oximetry; TBNK = T cell/B cell/natural killer cell; wks = weeks.

Footnotes for Schedule of Activities for Part 1 Intravenous Administration

a. **Screening:** To be performed within 28 days prior to study entry.
b. **Informed Consent:** Must be obtained prior to undergoing any study specific procedures.
c. **Tumor History:** Will be collected within 28 days during screening prior to study entry. Includes history of disease under study including details of primary diagnosis and treatment history. Record tumor human papilloma virus (HPV) status for those patients with squamous cell cancer of head and neck (SCCHN) whenever available.
d. **Medical History:** Includes history of disease process (eg, staging) other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
e. **Abbreviated Physical Examination (PE):** Abbreviated PEs should be performed as appropriate at each visit where complete PEs are not required.
f. **Baseline Signs & Symptoms:** On Day 1 prior to the start of study treatment, patients will be asked about any signs and symptoms experienced within the past 14 days prior to study entry. Baseline signs and symptoms will be recorded on the Medical History CRF page. During the study, any new or worsening conditions since baseline will be recorded on the Adverse Events (AE) CRF page.

g. **Weight:** Patient's body weight will be measured at Day 1 of each treatment cycle or within 72 hours before dosing to check for weight gain/loss >10% from the prior weight used for PF-06801591 IV dose calculations. The decision to recalculate PF-06801591 dose based on the weight obtained at each cycle can be in accordance with institutional practice; however if the patient experienced either a weight loss or gain of >10% compared to the weight used to calculate the most recent dose, the amount of PF-06801591 required for study drug preparation and administration for the current cycle must be recalculated using this most recent weight.
h. **Vital Signs:** includes temperature, sitting blood pressure (BP), pulse rate (to be recorded in the sitting position after 5 minutes of rest), and pulse oximetry (PO, at rest and after exertion). On Day 1 of each cycle, vital signs should be measured prior to infusion start (pre-dose), BP, and pulse rate will be repeated 1 hour (±10 minutes) after the start of the infusion.
i. **Performance Status:** Per Eastern Cooperative Oncology Group (ECOG) performance scale in Appendix 6.
j. **Triplicate 12-Lead Electrocardiogram (ECG):** See Assessment Section 7.1.5. ECGs will be collected at times specified in the Schedule Of Activities. The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) will be performed approximately 2 minutes apart to determine mean QTcF interval. All 12-lead ECGs should be confirmed by a qualified person at the institution and will be reviewed by a central laboratory. ECGs on Day 1 of each cycle will be collected both prior to dosing and at the end of infusion (approximately 1 hour) following administration of each dose of PF-06801591. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥45 msec from the pre-dose baseline, or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
k. **Hematology:** See Assessments Section 7.1.3 for Laboratory Tests list. Assessments and physician's evaluation must be performed prior to dosing. No need to repeat on Cycle 1 Day 1 (C1D1) if baseline assessment performed within 72 hours prior to that date. Assessments performed on Cycle 2 Day 1 (C2D1) and each subsequent cycle should be performed within 48 hours prior to dosing.
l. **Blood Chemistry:** See Assessments Section 7.1.3 for Laboratory Tests list. No need to repeat on C1D1 if screening assessment performed within 72 hours prior to that date. Assessments and physician's evaluation should be performed prior to dosing. Assessments performed on C2D1 and Day 1 of each subsequent cycle must be performed within 48 hours prior to dosing.
m. **Coagulation assays:** See Assessments Section 7.1.3 for Laboratory Tests list. No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing.
n. **CA-125 (Ovarian Cancer Only):** The first measurement for CA-125 must be collected within 2 weeks before treatment is started, during the screening period. Subsequent CA-125 levels will be measured on Day 1 of each cycle before treatment, at End of Treatment, and at Follow-up visit 28 days after last dose administration. There is no need to repeat on C1D1, if the baseline (screening) assessment was performed within 72 hours prior to that day.
o. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if clinically indicated (eg, only after the second positive dipstick result for heme). If ≥2+ protein on urine dipstick, then collect spot urine sample to calculate urine protein to creatinine ratio (UPCR) or collect 24hr urine. See Section 7.1.3 for Laboratory Tests list.
p. **Pregnancy Test (Serum/Urine) or FSH Level (Serum):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Pregnancy tests will also be routinely repeated at Day 1 of every treatment cycle during the active treatment period, at the End of Treatment visit, at the 28-day Follow-Up Visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations. Patients with confrmed positive pregnanct test(s) should not be dosed. For female patients who achieved postmenopausal status and have not experienced their menses for at least 12 consecutive months, a serum FSH test must be conducted at screening only to confirm a FSH level within the laboratory's reference ranges.
q. **High Sensitivity C-Reactive Protein (hsCRP) or C-Reactve Protein (CRP):** One 5 mL blood sample will be collected per schedule of activities to measure hsCRP or CRP**.**
r. **TBNK (Whole Blood):** Whole blood absolute immune cell counts (T-cell/B-cell/Natural Killer cells [TBNK]) will be measured by collecting a 5 mL blood sample per schedule of activities. Sample collected on C1D1 should be completed pre-dose.
s. **Cytokines:** One 2.5 mL blood sample will be collected to isolate serum on Day 1 of Cycle 1 (pre-dose), in order to have a baseline for cytokine measurement should cytokine release syndrome occurs. Optional samples will be collected throughout the study, as clinically indicated.
t. **Hepatitis B, C and HIV Tests:** Conduct tests for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody (HCV Ab), and human immunodeficiency virus (HIV) serology. In the case of apparent ongoing HBV or HCV infection, reflex serum viral load testing will be performed.
u. **Registration:** Patient number and dose level allocation operated by Pfizer Inc. Treatment should begin no longer than 3 days from registration.

v. **Study Treatment:** PF-06801591 will be administered once every 21 days as an intravenous (IV) infusion over 60 minutes ±10 minutes. Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation and administration rate. Since processing of samples at the central laboratory has to be completed within 24 hours of collection, please try to accommodate the administration of study treatment on either: A **Monday to Wednesday schedule** for samples collected on **Day 1 of Cycle 1**; or, a **Monday to Friday schedule** for all subsequent new cycles of treatment (ie, **Day 1 of Cycle 2 +**).

w. **Tumor Assessments:** See Section 7.4 Tumor Response Assessments. CT or MRI scans to be done every 6 weeks (±5 days) from the start of study entry until disease progression by immune-related RECIST (irRECIST), death, withdraw consent, or subsequent administration of an anti-chemotherapy agent. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C1D1, (2) performed using the method requirements (ie, RECIST v. 1.1), (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. CT or MRI scans may be assessed every 12 weeks (±5 days) for patients who 1) have remained on treatment for ≥24 weeks, and 2) have no confirmed progression by irRECIST within the last 6 months, and 3) have demonstrated stability of disease. Confirmation of response (complete response [CR]/partial response [PR]) with a second consecutive scan at least 4 weeks later is preferred. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. CT or MRI scans should be completed before tumor biopsy samples are collected. If a patient is classified as having progressive disease (PD) during an on treatment tumor assessment, then confirmation of PD by a second consecutive scan at least 4 weeks later in the absence of rapid clinical deterioration is required. After End of Treatment for patients who did not end treatment due to disease progression, death, or withdrawal of consent, a tumor assessment will be performed every 12 weeks (±1 week), until disease progression by irRECIST, or initiation of a new anti-cancer treatment, or end of the trial (2 years after last patient first dose [LPFD], see Section 13.2 End of Trial in All Other Participating Countries), whichever is first.

x. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. 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. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. Additional, immune related AEs (irAEs) will be collected with a follow up phone call at 90 and 120 days after last dose administration date to collect post treatment related AE information.

y. **Serious Adverse Event (SAE) Assessments:** For serious adverse events (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 150 calendar days after the last administration of the investigational product or until administration of subsequent anti-cancer therapy whichever comes first. 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.

z. **Concomitant Medications and Non Drug Supportive Interventions:** all concomitant medications should be recorded in the CRF including supportive care drugs (eg, Anti-emetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

aa. **Subsequent anticancer therapy**: After the completion of the EOT visit subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in 120 day safety follow-up, and subsequently during survival follow-up.

bb. **Contraceptive Check (frequency to match that of pregnancy tests):** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

cc. **Subsequent Cycles:** Day 8 and 15 visits are not required after Cycle 2. **Note**: For ECG, refer to footnote "j" that mentions an assessment scheduled on Day 8 of Cycle 3. For Blood PK samples for PF-06801591, refer to the separate PK & Pharmacodynamic Schedule of Activities that mentions blood collection scheduled on both Day 8 and Day 15 of Cycle 4. For PD-1 Receptor Occupancy samples (whole blood), refer to the separate PK & Pharmacodynamic Schedule of Activities and footnote "c" that mention blood collection scheduled on Day 15 of Cycle 4.

dd. **End-of-treatment Visit:** conducted at the visit that the patient is discontinued from the trial and no longer than 1 week after the patient has been discontinued. Complete tumor assessments if not completed in the last 6 weeks.

ee. **1-Month and Late irAE Follow-up:** At least 28 days and no more than 35 days after discontinuation of treatment or last dose of study drug whichever is later, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. To collect additional late irAE information, all patients will have a follow- up phone call 90 and 120 days (±7 days) after last dose administration date to collect post-treatment related AE information. Subsequent anti-cancer therapies information will also be collected during these follow up visits. If any concern arises, the patient will be called in for an inpatient follow-up visit within 5 calendar days of the initial phone call (assessments will be the same as the assessments performed at the 1-month follow up visit completed after end of treatment [EOT]).

ff. **Survival Follow-up:** Subsequent to the 120-day follow-up period, overall survival (OS) follow-up will be conducted by telephone every 8 weeks (±7 days) until end of the entire trial (2 years after LPFD, see Section 13.2 End of Trial in All Other Participating Countries). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call. Subsequent anti-cancer therapies information will also be collected.

PHARMACOKINETIC AND PHARMACODYNAMIC SCHEDULE OF ACTIVITIES: PART 1 INTRAVENOUS ADMINISTRATION OF PF-06801591

Pharmacokinetic and Pharmacodynamic Schedule of Activities for Part 1 Intravenous Administration of PF-06801591																		
	Screen	**Cycle 1 (Days 1 to 21)**						**Cycle 2 Days 1 to 21)**			**Cycle 3 (Days 1 to 21)**	**Cycle 4 (Days 1 to 21)**				**Cycle 5 (Days 1 to 21)**	**Further Cycles**	**End of Treat-ment**
Visit Identifier		**Day 1**			**Day 3 (±8 hrs)**	**Day 8 (±1)**	**Day 15 (±2)**	**Day 1**		**Day 8 (±2)*** or (±5 for fresh tumor biopsy only)[e]**	**Day 1**	**Day 1**		**Day 8 (±1)**	**Day 15 (±2)**	**Day 1**	**Day 1**	
		Pre-dose*	**1 hr***	**24 hr****				**Pre-dose***	**1 hr***		**Pre- dose***	**Pre- dose***	**1 hr***			**Pre-dose***	**Pre-dose***	
Blood PK Sample for PF-06801591[a]		X	X	X	X	X	X	X	X		X	X	X	X	X		X (Cycles 6,8,10)	X
Blood Sample for Anti-PF-06801591-antibody[b]		X						X				X					X (Cycles 6,8,10)	X
Target engagement (TE) biomarkers																		
PD-1 Receptor Occupancy (whole blood)[c]		X		X		X	X	X			X	X			X	X		X
Pharmacodynamic and immune monitoring biomarkers																		
Archived Tumor Tissue Sample[d, f]	X																	
Mandatory Fresh Tumor Biopsy[e, f]	X									X								
Optional Fresh tumor Biopsy[e]																		X
Whole blood biomarkers[g]	X	X								X		X				X		X
Cytokines /Chemokines/Soluble PD-L1 (plasma)[h]	X	X	X				X			X	X	X					X (Cycle 6 & 8)	X
Banked Biospecimen[i]	X									X								

PK = pharmacokinetics; ADA = anti-drug antibody; SOA = Schedule of Activities; IHC = immunohistochemistry; NAb = neutralizing antibody.
* The 1-hr samples should be collected within 1 hr after the end of infusion and pre-dose samples should be collected within 6 hrs before the start of infusion. **Note:** No day window is allowed for PK/Pharmacodynamic sampling on Day 1 of Cycle 1 and subsequent cycles as applicable.
**The 24-hr samples should be collected ±2 hours based on the 24-hr period after the end of the infusion.
***The ±2 day's window applies only to the following procedures performed on Day 8 of Cycle 2: Whole blood biomarkers, Cytokines/Chemokines/Soluble PD-L1 (plasma), and Banked Biospecimen.

Footnotes for Pharmacokinetics and Pharmacodynamic Schedule of Activities for Part 1 Intravenous Administration of PF-06801591

a. **Blood samples for determination of PF-06801591 concentration:** Blood samples will be collected at each time point for PK analysis of PF-06801591. After cycle 4, pre-dose PK samples will be collected only on every 2nd cycle (cycles 6, 8, and 10, etc.). An additional PK sample should also be taken at the end of treatment.

b. **Blood sample for Anti-PF-06801591 Antibody Measurement:** Blood samples (approx. 10 mL each) will be collected at each time point for anti drug antibody (ADA)/ neutralizing antibodies (Nab) assessment. After cycle 4, pre-dose ADA/NAb will be collected only on every 2nd cycle (cycles 6, 8, and 10, etc.). An additional ADA/NAb sample should also be taken at the end of treatment.

c. **Receptor Occupancy:** A 4 mL whole blood sample will be collected at the time points indicated in the PK/Pharmacodynamic SOA. PD-1 occupancy by PF-06801591 on T cells will be measured using flow cytometry.

d. **Archived Tumor Tissue Sample (Mandatory Biomarker Sample Collection):** All patients will provide an archival biopsy sample. This sample will not be required from patients if a de novo (ie, fresh) tumor sample is obtained at screening (within 28 days of 1st dose of PF-06801591) in accordance with local institutional practice for tumor biopsies.

e. Fresh Tumor Tissue Samples

- Mandatory tumor biopsies will be obtained at screening (within 28 days of 1st dose of PF-06801591) and on Cycle 2 Day 8 +/- 5 days (C2D8), for Part 1B expansion cohort patients.
- **Biomarker Sample collection:** Fresh biopsy is optional for the first 2 to 4 patients (Part 1A) at each dose level of the dose cohorts. Additional optional biopsy collection as clinically indicated and/or at EOT visit is optional may be obtained for all patients.
- If biopsy is to be completed the same day as CT scan, it must be completed after the CT scan. Details for handling of these samples including processing, storage, and shipment will be provided in the Central Lab Manual.

f. **Tumor Biopsy Biomarkers:** A portion of the archival and fresh tumor biopsy samples collected as detailed in footnotes d and e and at the time points indicated in the PK/Pharmacodynamic SOA will be submitted to the following analysis: Immune cell phenotypes and immune-related markers will be evaluated by IHC; expression of immune- and disease-related ribonucleic acid (RNA) transcripts will be evaluated by tumor RNA sequencing; T cell repertoire and tumor antigen profile will be evaluated by tumor DNA sequencing.

g. **Whole Blood Biomarkers:** The following samples will be collected at the indicated time points as detailed in the PK/Pharmacodynamic SOA: A 6 mL sample will be drawn for immune cell phenotyping by flow cytometry; a 2.5 mL sample will be collected into a tube for evaluation of immune-related transcripts by RNA sequencing. A 6 mL sample will be collected for T cell repertoire analysis.

h. **Plasma Biomarkers**: One 3.5 mL blood sample will be collected into a tube optimized for plasma separation at the indicated time points to measure levels of cytokines, chemokines, and soluble PD-L1.

i. **Banked Biospecimen:** A 4 mL blood sample (Prep D1) will be collected at the screening and Cycle 2, Day 8 visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. Specimens will be retained as whole blood in a biobank for exploratory biomarker assessments, unless prohibited by local regulation or by decision of the Institutional Review Board or Ethics Committee. Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to PF-06801591, or the identification of those patients who might preferentially benefit from treatment with PF-06801591.

SCHEDULE OF ACTIVITIES FOR PART 1 SUBCUTANEOUS ADMINISTRATION OF PF-06801591

The Schedule of Activities tables provide an overview of the protocol visits and procedures. Refer to the Assessments Section 7 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 patient.

Schedule of Activities for Part 1 Subcutaneous Administration of PF-06801591		**Treatment Period**											**EOT[ee]**	**Post-Treatment**			
		Cycle 1 (Days 1 to 28)						**Cycle 2 (Days 1 to 28)**			**Sub-sequent Cycles (Days 1 to 28)[dd]**			**1 Month and Late irAE Follow up[ff]**			**Survival Follow Up[gg]**
	Screening (≤28 days prior to study entry)[a]	**D1**	**D2**	**D3**	**D8**	**D15**	**D21**	**D1**	**D8**	**D15**	**D1**	**D8** C3 only		**Days after last dose**			**Every 2 months after 120 day follow up visit**
														28 days	**90 days**	**120 days**	
Visit Window					**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**+7**	**±7**	**±7**	**±7**
Informed Consent [b]	X																
Tumor History[c]	X																
Medical History[d]	X																
Complete Physical Examination	X	X											X	X			
Abbreviated Physical Examination[e]			X	X	X	X	X	X	X	X	X						
Baseline Signs and Symptoms[f]		X															
Height	X																
Weight[g]	X	X						X			X		X				
Vital Signs (BP/Pulse Rate/PO/Temp)[h]	X	X	X	X	X	X	X	X	X	X	X		X	X			
ECOG Performance Status[i]	X	X						X			X		X	X			
Triplicate 12-Lead ECG[j]	X (single ECG only)	X			X			X	X		X	X	X				

Schedule of Activities for Part 1 Subcutaneous Administration of PF-06801591		Treatment Period											EOT[ee]	Post-Treatment			
		Cycle 1 (Days 1 to 28)						Cycle 2 (Days 1 to 28)			Sub-sequent Cycles (Days 1 to 28)[dd]			1 Month and Late irAE Follow up[ff]			Survival Follow Up[gg]
	Screening (≤28 days prior to study entry)[a]	D1	D2	D3	D8	D15	D21	D1	D8	D15	D1	D8 C3 only		Days after last dose 28 days	90 days	120 days	Every 2 months after 120 day follow up visit
Visit Window					±1	±2	±2	±2	±2	±2	±2	±2		+7	±7	±7	±7
Laboratory																	
Hematology[k]	X	X			X	X	X	X		X	X		X	X			
Blood Chemistry[l]	X	X			X	X	X	X		X	X		X	X			
Coagulation [l]	X	X			X	X	X	X		X	X		X	X			
CA-125 (Ovarian Cancer Only)[n]	X	X						X			X		X	X			
Urinalysis[o]	X					X		X			X		X	X			
Pregnancy Test or FSH Level[p]	X	X						X			X		X	X			
C-Reactive Protein (CRP or hsCRP)[p]		X				X	X		X	X			X				
TBNK (whole blood)[r]		X				X	X		X	X			X				
Cytokines[s]		X	Optional collection as clinically indicated														
Hepatitis B, C, and HIV tests[t]	X																
Registration and Treatment																	
Registration[u]		X															
Study Treatment[v]		X						X			X						
Local Site Injection Tolerability Assessment[w]		X						X			X						

Schedule of Activities for Part 1 Subcutaneous Administration of PF-06801591	**Treatment Period**												**EOT[ee]**	**Post-Treatment**			
		Cycle 1 (Days 1 to 28)						**Cycle 2 (Days 1 to 28)**			**Sub-sequent Cycles (Days 1 to 28)[dd]**			**1 Month and Late irAE Follow up[ff]**			**Survival Follow Up[gg]**
	Screening (≤28 days prior to study entry)[a]	**D1**	**D2**	**D3**	**D8**	**D15**	**D21**	**D1**	**D8**	**D15**	**D1**	**D8** C3 only		**Days after last dose**			**Every 2 months after 120 day follow up visit**
														28 days	**90 days**	**120 days**	
Visit Window					**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**+7**	**±7**	**±7**	**±7**
Tumor Assessments																	
CT or MRI Scan[w]	X	Every 8 weeks (±5 days) up to 24 wks, and every 8 or 12 weeks (±5 days) thereafter according to calendar, regardless of treatment delays											X	X (Every 12 weeks)			
Other Clinical Assessments																	
Adverse Events[x]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Up to 150 days after last treatment
Concomitant Medication and non-drug supportive interventions[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subsequent anti-cancer therapy[bb]														X	X	X	X
Survival follow up[gg]																	X
Contraception check[cc]	X	X						X			X		X	X	X	X	

BP = blood pressure; C = cycle; CRP = C-reactive protein CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; Hs-CRP = high sensitivity C-reactive protein; MRI = magnetic resonance imaging; PK = pharmacokinetics; PO = pulse oximetry; SC = Subcutaneous; TBNK = T cell/B cell/natural killer cell; wks = weeks

Footnotes for Schedule of Activities for Part 1 Subcutaneous Administration

a. **Screening:** To be performed within 28 days prior to study entry.
b. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.

c. **Tumor History:** Will be collected within 28 days during screening prior to study entry. Includes history of disease under study including details of primary diagnosis and treatment history. Record tumor HPV status for those patients with SCCHN whenever available.
d. **Medical History:** Includes history of disease process (eg, staging) other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
e. **Abbreviated Physical Examination (PE):** Abbreviated PEs should be performed as appropriate at each visit where complete PEs are not required.
f. **Baseline Signs & Symptoms:** On Day 1 prior to the start of study treatment, patients will be asked about any signs and symptoms experienced within the past 14 days prior to study entry. Baseline signs and symptoms will be recorded on the Medical History CRF page. During the study, any new or worsening conditions since baseline will be recorded on the Adverse Events (AE) CRF page.
g. **Weight:** Patient's body weight will be measured at Day 1 of each treatment cycle.
h. **Vital Signs:** includes temperature, sitting BP, pulse rate (to be recorded in the sitting position after 5 minutes of rest), and PO (at rest and after exertion). On Day 1 of each cycle, vital signs should be measured prior to SC injection (pre-dose), BP, and pulse rate will be repeated 1 hour (±10 minutes) after the administration of the SC injection.
i. **Performance Status:** Per ECOG performance scale in Appendix 6.
j. **Triplicate ECG:** See Assessment Section 7.1.5. ECGs will be collected at times specified in the Schedule Of Activities. The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) will be performed approximately 2 minutes apart to determine mean QTcF interval. All 12-lead ECGs should be confirmed by a qualified person at the institution and will be reviewed by a central laboratory. ECGs on Day 1 of each cycle will be collected prior to dosing, and at the end of infusion (approximately 1 hour) following administration of each dose of PF-06801591. When coinciding with blood sample draws for PK, ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥45 msec from the pre-dose baseline, or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
k. **Hematology:** See Assessments Section 7.1.3 for Laboratory Tests list. Assessments and physician's evaluation must be performed prior to dosing. No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. Assessments performed on C2D1 and each subsequent cycle should be performed within 48 hours prior to dosing.
l. **Blood Chemistry:** See Assessments Section 7.1.3 for Laboratory Tests list. No need to repeat on C1D1 if screening assessment performed within 72 hours prior to that date. Assessments and physician's evaluation should be performed prior to dosing. Assessments performed on C2D1 and Day 1 of each subsequent cycle must be performed within 48 hours prior to dosing.
m. **Coagulation assays:** See Assessments Section 7.1.3 for Laboratory Tests list. No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing.
n. **CA-125 (Ovarian Cancer Only):** The first measurement for CA-125 must be collected within 2 weeks before treatment is started, during the screening period. Subsequent CA-125 levels will be measured on Day 1 of each cycle before treatment, at End of Treatment, and at Follow-up visit 28 days after last dose administration. There is no need to repeat on C1D1, if the baseline (screening) assessment was performed within 72 hours prior to that day.
o. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if clinically indicated (eg, only after the second positive dipstick result for heme). If ≥ 2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24hr urine.
p. **Pregnancy Test (Serum/Urine) or FSH Level (Serum):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Pregnancy tests will also be routinely repeated at Day 1 of every treatment cycle during the active treatment period, at the End of Treatment visit, at the 28-day Follow-Up Visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations. Patients with confirmed positive pregnancy test(s) should not be dosed. For female patients who achieved postmenopausal status and have not experienced their menses for at least 12 consecutive months, a serum FSH test must be conducted at screening only to confirm a FSH level within the laboratory's reference ranges.
q. **CRP or hsCRP:** One 5 mL blood sample will be collected per schedule of activities to measure C-reactive protein (CRP) or high sensitivity C-reactive protein (hsCRP) to monitor for potential immune activation or inflammation. Sample for C1D1 must be collected prior to dosing.
r. **TBNK (Whole Blood):** Whole blood absolute immune cell counts (TBNK) will be measured by collecting a 5 mL blood sample per schedule of activities. Sample collected on C1D1 should be completed pre-dose.

s. **Cytokines:** One 2.5 mL blood sample will be collected to isolate serum on C1D1 (pre-dose), in order to have a baseline for cytokine measurement should cytokine release syndrome occurs. Optional samples will be collected throughout the study, as clinically indicated.
t. **Hepatitis B, C and HIV Tests:** See Assessments Section 7.1.3 for Laboratory Tests list. In the case of apparent ongoing HBV or HCV infection, reflex serum viral load testing will be performed.
u. **Registration:** Patient number and dose level allocation operated by Pfizer Inc. Treatment should begin no longer than 3 days from registration.
v. **Study Treatment:** PF-06801591 will be administered 300 mg once every 28 days as a subcutaneous (SC) injection. Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation and administration rate. Since processing of samples at the central laboratory has to be completed within 24 hours of collection, please try to accommodate the administration of study treatment on either: A **Monday to Wednesday schedule** for samples collected on **C1D1**; or, a **Monday to Friday schedule** for all subsequent new cycles of treatment (ie, **C2D1** +).
w. **Local Site Injection Tolerability Assessment (SC Administration Cohort Only):** Assessment of each injection should be conducted for at least 1 hour following treatment administration on Day 1 of each cycle. Site tolerability assessments should continue after each dosing visit, only if injection site pain or injection site reaction (ISR) characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve.
x. **Tumor Assessments:** See Section 7.4 Tumor Response Assessments. CT or MRI scans to be done every 8 weeks (±5 days), from the start of study entry until disease progression by irRECIST, death, withdrawal of consent, or subsequent administration of an anti-chemotherapy agent. Bone scans should be performed at baseline and on-study for patients with known or suspected bone metastases not well-visualized on other imaging or if disease is suspected or has been previously documented as appropriate to follow disease. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C1D1, (2) performed using the method requirements (ie, RECIST v. 1.1), (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. CT or MRI scans may be assessed every 12 weeks (±5 days) for patients who 1) have remained on treatment for ≥24 weeks, and 2) have no confirmed progression by irRECIST within the last 6 months, and 3) have demonstrated stability of disease. Confirmation of response (CRPR) with a second consecutive scan at least 4 weeks later is preferred. Tumor assessments should be repeated at the End of Treatment visit if more than 8 weeks have passed since the last evaluation. CT or MRI scans should be completed before tumor biopsy samples are collected. If a patient is classified as having PD during an on-treatment tumor assessment, then confirmation of PD by a second consecutive scan at least 4 weeks later in the absence of rapid clinical deterioration is required. After End of Treatment for patients who did not end treatment due to disease progression, death, or withdrawal of consent, a tumor assessment will be performed every 12 weeks (±1 week), until disease progression by irRECIST, or initiation of a new anti-cancer treatment, or end of trial (2 years after last patient first dose, see Section 13.2 End of Trial in All Other Participating Countries), whichever is first.
y. **AE Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. 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. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. Additional, immune related AEs (irAEs) will be collected with a follow up phone call at 90 and 120 days after last dose administration date to collect post treatment related AE information.
z. **SAE Assessments:** 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 150 calendar days after the last administration of the investigational product or until administration of subsequent anti-cancer therapy whichever comes first. 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.
aa. **Concomitant Medications and Non Drug Supportive Interventions:** all concomitant medications should be recorded in the CRF including supportive care drugs (eg, Anti-emetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
bb. **Subsequent anticancer therapy**: After the completion of the EOT visit subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in 120 day safety follow-up, and subsequently during survival follow-up.

cc. **Contraceptive Check (frequency to match that of pregnancy tests):** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception throughout the study and continue for at least 5 months after the last dose. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

dd. **Subsequent Cycles:** Day 8 (except C3D8) and Day 15 visits are not required after Cycle 2. **Note**: For ECG, refer to footnote "j" that mentions an assessment scheduled on Day 8 of Cycle 3. For Blood PK samples for PF-06801591 and for PD-1 Receptor Occupancy samples (whole blood), refer to the separate PK & Pharmacodynamic Schedule of Activities.

ee. **End-of-treatment Visit:** conducted at the visit that the patient is discontinued from the trial and no longer than 1 week after the patient has been discontinued. Complete tumor assessments if not completed in the last 8 weeks.

ff. **1-Month and Late irAE Follow-up:** At least 28 days and no more than 35 days after discontinuation of treatment or last dose of study drug whichever is later, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. To collect additional late immune-related AE information, all patients will have a follow- up phone call 90 and 120 days (±7 days) after last dose administration date to collect post-treatment related AE information. If any concern arises, the patient will be called in for an inpatient follow-up visit within 5 calendar days of the initial phone call (assessments will be the same as the assessments performed 28 days (range 28-35 days) after EOT follow-up visit).

gg. **Survival Follow-up:** Subsequent to the 120-day follow-up period, overall survival (OS) follow-up will be conducted by telephone every 8 weeks (± 7 days) until end of the entire trial (2 years after last patient first dose, see Section 13.2 End of Trial in All Other Participating Countries). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call. After the completion of the EOT visit subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in 120 day safety follow-up, and subsequently during survival follow-up.

PHARMACOKINETIC AND PHARMACODYNAMIC SCHEDULE OF ACTIVITIES: PART 1 SUBCUTANEOUS ADMINISTRATION OF PF-06801591

Pharmacokinetic and Pharmacodynamic Schedule of Activities for Part 1 Subcutaneous Administration of PF-06801591																					
	Screen	**Cycle 1 (Days 1 to 28)**							**Cycle 2 (Days 1 to 28)**			**Cycle 3 (Days 1 to 28)**	**Cycle 4 (Days 1 to 28)**					**Cycle 5 (Days 1 to 28)**	**Further Cycles**	**End of Treat-ment**
Visit Identifier		**Day 1**			**Day 3 (±8 hrs)**	**Day 8 (±1)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1**		**Day 8 (±2)*** or (±5 for fresh tumor biopsy only)[e]**	**Day 1**	**Day 1**		**Day 8 (±1)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1**	**Day 1**	
		Pre-dose*	**1 hr***	**24 hr****					**Pre-dose***	**1 hr***		**Pre- dose***	**Pre- dose***	**1 hr***				**Pre-dose***	**Pre-dose***	
Blood PK Sample for PF-06801591[a]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X (Cycles 6,8, 10)	X
Blood Sample for Anti-PF-06801591-antibody[b]		X							X				X						X (Cycles 6,8, 10)	X
Target engagement (TE) biomarkers																				
PD-1 Receptor Occupancy (whole blood)[a]		X		X		X	X	X	X			X	X			X	X	X		X
Pharmacodynamic and immune monitoring biomarkers																				
Archived Tumor Tissue Sample[d,f]	X																			
Mandatory Fresh Tumor Biopsy[e,f]	X										X									
Optional Fresh tumor Biopsy[e,f]		Optional biopsy as clinically indicated																		X
Whole blood biomarkers[g]	X	X									X		X					X		X

Pharmacokinetic and Pharmacodynamic Schedule of Activities for Part 1 Subcutaneous Administration of PF-06801591																				
	Screen	**Cycle 1 (Days 1 to 28)**							**Cycle 2 (Days 1 to 28)**			**Cycle 3 (Days 1 to 28)**	**Cycle 4 (Days 1 to 28)**					**Cycle 5 (Days 1 to 28)**	**Further Cycles**	**End of Treat-ment**
Visit Identifier		**Day 1**			**Day 3 (±8 hrs)**	**Day 8 (±1)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1**		**Day 8 (±2)[***] or (±5 for fresh tumor biopsy only)[e]**	**Day 1**	**Day 1**		**Day 8 (±1)**	**Day 15 (±2)**	**Day 21 (±2)**	**Day 1**	**Day 1**	
		Pre-dose*	**1 hr***	**24 hr****					**Pre-dose***	**1 hr***		**Pre-dose***	**Pre-dose***	**1 hr***				**Pre-dose***	**Pre-dose***	
Cytokines /Chemokines /Soluble PD-L1 (plasma)[h]	X	X	X				X				X	X	X						X (Cycle 6 & 8)	X
Banked Biospecimen[i]	X										X									

PK = pharmacokinetics; ADA = anti-drug antibody; SOA = Schedule of Activities; IHC = immunohistochemistry; NAb = neutralizing antibody; SC = Subcutaneous.
* The 1-hr samples should be collected within 1 hr after the end of SC injection and pre-dose samples should be collected within 6 hrs before the administration of the SC injection. **Note:** No day window is allowed for PK/Pharmacodynamic sampling on Day 1 of Cycle 1 and subsequent cycles as applicable.
**The 24-hr samples should be collected ±2 hours based on the 24-hr period after the end of the SC injection.
***The ±2 days window applies only to the following procedures performed on Day 8 of Cycle 2: Whole blood biomarkers, Cytokines/Chemokines/Soluble PD-L1 (plasma), and Banked Biospecimen.

Footnotes for Pharmacokinetics and Pharmacodynamic Schedule of Activities for Part 1 Subcutaneous Administration of PF-06801591

a. **Blood samples for determination of PF-06801591 concentration:** Blood samples will be collected at each time point for PK analysis of PF-06801591. After cycle 4, pre-dose PK samples will be collected only on every 2nd cycle (cycles 6, 8, and 10, etc.). An additional PK sample should also be taken at the end of treatment.

b. **Blood sample for Anti-PF-06801591 Antibody Measurement:** Blood samples (approx. 10 mL each) will be collected at each time point for ADA/NAb assessment. After cycle 4, pre-dose ADA/NAb will be collected only on every 2nd cycle (cycles 6, 8, and 10, etc.). An additional ADA/NAb sample should also be taken at the end of treatment.

c. **Receptor Occupancy:** A 4 mL whole blood sample will be collected at the time points indicated in the PK/Pharmacodynamic SOA. PD-1 occupancy by PF-06801591 on T cells will be measured using flow cytometry.

d. **Archived Tumor Tissue Sample (Mandatory Biomarker Sample Collection):** All patients will provide an archival biopsy sample. This sample will not be required from patients if a de novo (ie, fresh) tumor sample is obtained at screening (within 28 days of 1st dose of PF-06801591) in accordance with local institutional practice for tumor biopsies.

e. Fresh Tumor Tissue Samples

- Mandatory tumor biopsies will be obtained at screening (within 28 days of 1st dose of PF-06801591) and on Cycle 2 Day 8 +/- 5 days (C2D8), for Part 1B pharmacodynamic cohort patients.
- **Biomarker Sample collection:** Fresh biopsy is optional for the first 2 to 4 patients (Part 1A) at each dose level of the dose cohorts. Additional optional biopsy collection as clinically indicated and/or at EOT visit is may be obtained for all patients.

- If biopsy is to be completed the same day as CT scan, it must be completed after the CT scan. Details for handling of these samples including processing, storage, and shipment will be provided in the Central Lab Manual.

f. **Tumor Biopsy Biomarkers:** A portion of the archival and fresh tumor biopsy samples collected as detailed in footnotes d and e and at the time points indicated in the PK/Pharmacodynamic SOA will be submitted to the following analysis: Immune cell phenotypes and immune-related markers will be evaluated by IHC; expression of immune- and disease-related RNA transcripts will be evaluated by tumor RNA sequencing; T cell repertoire and tumor antigen profile will be evaluated by tumor DNA sequencing.

g. **Whole Blood Biomarkers:** The following samples will be collected at the indicated time points as detailed in the PK/Pharmacodynamic SOA: A 6 mL sample will be drawn for immune cell phenotyping by flow cytometry; a 2.5 mL sample will be collected into a tube for evaluation of immune-related transcripts by RNA sequencing. A 6 mL sample will be collected for T cell repertoire analysis.

h. **Plasma Biomarkers**: One 3.5 mL blood sample will be collected into a tube optimized for plasma separation at the indicated time points to measure levels of cytokines, chemokines, soluble PD-L1 and autoantibodies by immunoassay.

i. **Banked Biospecimen:** A 4 mL blood sample (Prep D1) will be collected at the screening and Cycle 2, Day 8 visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. Specimens will be retained as whole blood in a biobank for exploratory biomarker assessments, unless prohibited by local regulation or by decision of the Institutional Review Board or Ethics Committee. Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to PF-06801591, or the identification of those patients who might preferentially benefit from treatment with PF-06801591.

SCHEDULE OF ACTIVITIES FOR PART 2: SUBCUTANEOUS ADMINISTRATION OF PF-06801591

The Schedule of Activities tables provide an overview of the protocol visits and procedures. Refer to the Assessments Section 7 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 patient.

Schedule of Activities for Part 2 SC Administration of PF-06801591		**Treatment Period**						**EOT[bb]**	**Post-Treatment**			
		Cycle 1 Only (Days 1 to 28)				**Cycle 2 (Days 1 to 28)**	**Subsequent Cycles (Days 1 to 28)[aa]**		**1-Month and Late irAE Follow up[cc]**			**Survival Follow Up[dd]**
Protocol Activity	**Screening[a] (≤28 days prior to study entry)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**		**28 days**	**90 days**	**120 days**	**Every 2 months after 120 day follow up visit**
Visit Window			**±1**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	**±7**
Informed Consent[b]	X											
Tumor History[c]	X											
Medical History[d]	X											
Complete Physical Examination	X	X						X	X			
Abbreviated Physical Examination[e]			X	X	X	X	X					
Baseline Signs and Symptoms[f]		X										
Height	X											
Weight[g]	X	X				X	X	X				
Vital Signs (BP/pulse rate/PO/Temp)[h]	X	X	X	X	X	X	X	X	X			
ECOG Performance Status[i]	X	X				X	X	X	X			
Triplicate 12-Lead ECG[j]	X (single ECG only)	X	X			X	X	X				

Schedule of Activities for Part 2 SC Administration of PF-06801591		Treatment Period						EOT[bb]	Post-Treatment			
		Cycle 1 Only (Days 1 to 28)				Cycle 2 (Days 1 to 28)	Subsequent Cycles (Days 1 to 28)[aa]		1-Month and Late irAE Follow up[cc]			Survival Follow Up[dd]
Protocol Activity	**Screening[a] (≤28 days prior to study entry)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**		**28 days**	**90 days**	**120 days**	**Every 2 months after 120 day follow up visit**
Laboratory												
Hematology[k]	X	X	X	X	X	X	X	X	X			
Blood Chemistry[l]	X	X	X	X	X	X	X	X	X			
Coagulation[m]	X	X	X	X	X	X	X	X	X			
Urinalysis[n]	X			X		X	X	X	X			
Pregnancy Test or FSH Level[o]	X	X				X	X	X	X			
Pregnancy Test or FSH Level in Post-Treatment Follow-up (Specific for Poland only)[o]									(Days)			
									28	60	90	120	150	
									X	X	X	X	X	
Cytokines[p]		X	Optional collection as clinically indicated									
Hepatitis B, C, and HIV tests[q]	X											
Registration and Treatment												
Registration[r]		X										
Study Treatment[s]		X				X	X					
Local Site Injection Tolerability Assessment[t]		X				X	X					
Tumor Assessments												
CT or MRI Scan[u]	X	Every 8 weeks (±5 days) up to 24 wks, and every 8 or 12 weeks (±5 days) thereafter according to calendar, regardless of treatment delays						X	X (Every 12 weeks)			

Schedule of Activities for Part 2 SC Administration of PF-06801591		Treatment Period						EOT[bb]	Post-Treatment			
		Cycle 1 Only (Days 1 to 28)				Cycle 2 (Days 1 to 28)	Subsequent Cycles (Days 1 to 28)[aa]		1-Month and Late irAE Follow up[cc]			Survival Follow Up[dd]
Protocol Activity	**Screening[a] (≤28 days prior to study entry)**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 1**		**28 days**	**90 days**	**120 days**	**Every 2 months after 120 day follow up visit**
Other Clinical Assessments												
Adverse Events[v]		X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events[w]	X	X	X	X	X	X	X	X	X	X	X	X Up to 150 days after last treatment
Concomitant Medication and non-drug supportive interventions[x]	X	X	X	X	X	X	X	X	X	X	X	
Subsequent anti-cancer therapy[y]									X	X	X	X
Survival follow up[dd]												X
Contraception check[z]	X	X				X	X	X	X	X	X	

BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PK = pharmacokinetics; PO = pulse oximetry; TBNK = T cell/B cell/natural killer cell; wks = weeks.

Footnotes for Schedule of Activities for Part 2 Subcutaneous Administration

a. **Screening:** To be performed within 28 days prior to study entry.
b. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
c. **Tumor History:** Will be collected within 28 days during screening prior to study entry. Includes history of disease under study including details of primary diagnosis, treatment history and history of tumor diagnostics.
d. **Medical History:** Includes history of disease process (eg, staging) other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
e. **Abbreviated Physical Examination (PE):** Abbreviated PEs should be performed as appropriate at each visit where complete PEs are not required.
f. **Baseline Signs & Symptoms:** On Day 1 prior to the start of study treatment, patients will be asked about any signs and symptoms experienced within the past 14 days prior to study entry. Baseline signs and symptoms will be recorded on the Medical History CRF page. During the study, any new or worsening conditions since baseline will be recorded on the Adverse Events (AE) CRF page.
g. **Weight:** Patient's body weight will be measured at Day 1 of each treatment cycle.

h. **Vital Signs:** includes temperature, sitting BP, pulse rate (to be recorded in the sitting position after 5 minutes of rest), and pulse oximetry (PO, at rest and after exertion). On Day 1 of each cycle, vital signs should be measured prior to infusion start (pre-dose), BP, and pulse rate will be repeated 1 hour (±10 minutes) after the start of the infusion.
i. **Performance Status:** Per ECOG performance scale in Appendix 6.
j. **Triplicate 12-Lead Electrocardiogram (ECG):** See Assessment Section 7.1.5. ECGs will be collected at times specified in the Schedule Of Activities. The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) will be performed approximately 2 minutes apart to determine mean QTcF interval. All 12-lead ECGs should be confirmed by a qualified person at the institution and will be reviewed by a central laboratory. ECGs on Day 1 of each cycle will be collected prior to dosing, and at the end of infusion (approximately 1 hour) following administration of each dose of PF-06801591. When coinciding with blood sample draws for PK, ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥45 msec from the pre-dose baseline, or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
k. **Hematology:** See Assessments Section 7.1.3 for Laboratory Tests list. Assessments and physician's evaluation must be performed prior to dosing. No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. Assessments performed on C2D1 and each subsequent cycle should be performed within 48 hours prior to dosing.
l. **Blood Chemistry:** See Assessments Section 7.1.3 for Laboratory Tests list. No need to repeat on C1D1 if screening assessment performed within 72 hours prior to that date. Assessments and physician's evaluation should be performed prior to dosing. Assessments performed on C2D1 and Day 1 of each subsequent cycle must be performed within 48 hours prior to dosing.
m. **Coagulation assays:** See Assessments Section 7.1.3 for Laboratory Tests list. No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing.
n. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if clinically indicated (eg, only after the second positive dipstick result for heme). If ≥2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24hr urine.
o. **Pregnancy Test (Serum/Urine) or FSH Level (Serum):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Pregnancy tests will also be routinely repeated at Day 1 of every treatment cycle during the active treatment period, at the End of Treatment visit, at the 28-day Follow-Up Visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations. In Poland, pregnancy tests have to be performed after end of treatment on Days 28, 60, 90, 120 and 150. Pregnancy tests on Days 60, 90, 120 and 150 may be collected at home by the patient. Patients with confirmed positive pregnancy test(s) should not be dosed. For female patients who achieved postmenopausal status and have not experienced their menses for at least 12 consecutive months, a serum FSH test must be conducted at screening only to confirm a FSH level within the laboratory's reference ranges.
p. **Cytokines:** One 2.5 mL blood sample will be collected to isolate serum on Day 1 of Cycle 1 (pre-dose), in order to have a baseline for cytokine measurement should cytokine release syndrome occurs. Optional samples will be collected throughout the study, as clinically indicated.
q. **Hepatitis B, C and HIV Tests:** See Assessments Section 7.1.3 for Laboratory Tests list. In the case of apparent ongoing HBV or HCV infection, reflex serum viral load testing will be performed.
r. **Registration:** the patient enrollment number will be assigned through the use of an interactive response technology (IRT) system.
s. **Study Treatment:** PF-06801591 will be administered once every 28 days as either a flat dose SC injection of 300 mg. Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation and administration rate.
t. **Local Site Injection Tolerability Assessment:** Assessment of each injection should be conducted for at least 1 hour following treatment administration on Day 1 of each cycle. Site tolerability assessments should continue after each dosing visit, only if injection site pain or ISR characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve.

u. **Tumor Assessments:** See Section 7.4 Tumor Response Assessments. CT or MRI scans to be done every 8 weeks (±5 days), from the start of study entry until disease progression by irRECIST, death, withdrawal of consent, or subsequent administration of an anti-chemotherapy agent. Bone scans should be performed at baseline and on-study for patients with known or suspected bone metastases not well-visualized on other imaging or if disease is suspected or has been previously documented as appropriate to follow disease. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C1D1, (2) performed using the method requirements (ie, RECIST v. 1.1), (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. CT or MRI scans may be assessed every 12 weeks (±5 days) for patients who 1) have remained on treatment for ≥24 weeks, and 2) have no confirmed progression by irRECIST within the last 6 months, and 3) have demonstrated stability of disease. Confirmation of response (complete response [CR]/partial response [PR]) with a second consecutive scan at least 4 weeks later is preferred. Tumor assessments should be repeated at the End of Treatment visit if more than 8 weeks have passed since the last evaluation. CT or MRI scans should be completed before tumor biopsy samples are collected. If a patient is classified as having progressive disease (PD) during an on-treatment tumor assessment, then confirmation of PD by a second consecutive scan at least 4 weeks later in the absence of rapid clinical deterioration is required. After End of Treatment for patients who did not end treatment due to disease progression, death, or withdrawal of consent, a tumor assessment will be performed every 12 weeks (±1 week), until disease progression by irRECIST, or initiation of a new anti-cancer treatment, or end of trial (2 years after last patient first dose, see Section 13.2 End of Trial in All Other Participating Countries), whichever is first.

v. **AE Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. 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. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. Additional, irAEs will be collected with a follow up phone call at 90 and 120 days after last dose administration date to collect post treatment related AE information.

w. **SAE Assessments:** 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 150 calendar days after the last administration of the investigational product or until administration of subsequent anti-cancer therapy whichever comes first. 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.

x. **Concomitant Medications and Non Drug Supportive Interventions:** all concomitant medications should be recorded in the CRF including supportive care drugs (eg, Anti-emetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

y. **Subsequent anticancer therapy**: After the completion of the EOT visit subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in 120 day safety follow-up, and subsequently during survival follow-up.

z. **Contraceptive Check (frequency to match that of pregnancy tests):** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception throughout the study and continue for at least 5 months after the last dose. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

aa. **Subsequent Cycles:** For Blood PK samples for PF-06801591 and for PD-1 Receptor Occupancy samples (whole blood) refer to the separate PK & Pharmacodynamic Schedule of Activities.

bb. **End-of-Treatment Visit:** conducted at the visit that the patient is discontinued from the trial and no longer than 1 week after the patient has been discontinued. Complete tumor assessments if not completed in the last 8 weeks.

cc. **1-Month and Late irAE Follow-up:** At least 28 days and no more than 35 days after discontinuation of treatment or last dose of study drug whichever is later, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. To collect additional late immune-related AE information, all patients will have a follow- up phone call 90 and 120 days (±7 days) after last dose administration date to collect post-treatment related AE information. If any concern arises, the patient will be called in for an inpatient

follow-up visit within 5 calendar days of the initial phone call (assessments will be the same as the assessments performed 28 days (range 28-35 days) after EOT follow-up visit).

dd. **Survival Follow-up:** Subsequent to the 120-day follow-up period, overall survival (OS) follow-up will be conducted by telephone every 8 weeks (±7 days) until end of the trial (2 years after last patient first dose, see Section 13.2 End of Trial in All Other Participating Countries). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call. After the completion of the EOT visit subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in 120 day safety follow-up, and subsequently during survival follow-up.

PHARMACOKINETIC AND PHARMACODYNAMIC SCHEDULE OF ACTIVITIES: PART 2 SUBCUTANEOUS ADMINISTRATION OF PF-06801591

Pharmacokinetic and Pharmacodynamic Schedule of Activities for Subcutaneous Administration of PF-06801591												
	Screen	**Cycle 1 (Days 1 to 28)**				**Cycle 2 (Days 1 to 28)**	**Cycle 3 (Days 1 to 28)**	**Cycle 4 (Days 1 to 28)**	**Cycle 5 (Days 1 to 28)**	**Subsequent Cycles**	**End of Treatment**	**Post-Treatment**
Visit Identifier		**Day 1**	**Day 8 (±1)**	**Day 15 (±2)**	**Day 22 (±2)**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**		**28 day follow-up (±7)**
		Pre-dose*				**Pre-dose***	**Pre-dose***	**Pre-dose***	**Pre-dose***	**Pre-dose***		
Blood PK Sample for PF-06801591[a]		X	X			X	X	X	X	X (Every 3 Cycles eg, 6, 9, 12, etc.)		X
Blood Sample for Anti-PF-06801591-Antibody[b]		X				X		X		X (Every 3 Cycles eg, 6, 9, 12, etc.)		X
Pharmacodynamic and immune monitoring biomarkers												
Archived Tumor Tissue Sample[c,e]	X											
Optional fresh tumor Biopsy[d]		Optional biopsy as clinically indicated									X	
Whole blood biomarkers[f]		X	X	X	X	X		X		X (Cycle 7, 10 & 13)	X	
Soluble factors (plasma)[g]		X	X	X	X	X		X		X (Cycle 7, 10 & 13)	X	
Banked Biospecimen[h]		X										
Pharmacogenomics[i]		X										

PK = pharmacokinetics; ADA = anti-drug antibody; SOA = Schedule of Activities; IHC = immunohistochemistry; NAb = neutralizing antibody.
* The pre-dose samples should be collected within 6 hrs before the administration of SC injection. **Note:** No day window is allowed for PK/Pharmacodynamic sampling on Day 1 of Cycle 1 and subsequent cycles as applicable.

Footnotes for Pharmacokinetics and Pharmacodynamic Schedule of Activities for Part 2 Subcutaneous Administration of PF-06801591

a. **Blood samples for determination of PF-06801591 concentration:** Blood samples will be collected at each time point for PK analysis of PF-06801591. After cycle 6, pre-dose PK samples will be collected only on every 3rd cycle (cycles 9, 12, etc.). An additional PK sample should also be taken at the 28-day follow up visit post-treatment.

b. **Blood sample for Anti-PF-06801591 Antibody Measurement:** Blood samples (approx. 10 mL each) will be collected at each time point for ADA/NAb assessment. After Cycle 5, blood samples for ADA/NAb assessment should be collected pre-dose on Day 1 every 3 cycles (eg, Cycles 6, 9, 12, etc.) and at the 28-day follow up visit post-treatment. A companion blood sample for the determination of PF-06801591 concentration will be collected in conjunction with the ADA sample collection to facilitate immunogenicity assessment.

c. **Archived Tumor Tissue Sample (Mandatory Biomarker Sample Collection):** Patients must provide FFPE tissue from the most recent primary or metastatic tumor biopsy or resection prior to study entry, taken within two year of start of study treatment. The requirement for archival tissue may be waived if a de novo (ie, fresh) biopsy is obtained at screening (within 28 days of 1st dose of PF-06801591) in accordance with local institutional practice for tumor biopsies.

d. **Optional Fresh Tumor Tissue Samples**

- Biopsy collection as clinically indicated and/or at EOT visit is optional.
- If biopsy is to be completed the same day as CT scan, it must be completed after the CT scan. Details for handling of these samples including processing, storage, and shipment will be provided in the Central Lab Manual.

e. **Tumor Biopsy Biomarkers:** A portion of the archival and fresh tumor biopsy samples collected as detailed in footnotes c and d and at the time points indicated in the PK/Pharmacodynamic SOA will be submitted to the following analysis: Immune cell phenotypes and immune-related markers will be evaluated by IHC; expression of immune- and disease-related RNA transcripts will be evaluated by tumor RNA sequencing; T cell repertoire and tumor antigen profile will be evaluated by tumor DNA sequencing. Anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR) mutation status from NSCLC samples and PD-L1 testing in all patient samples will be obtained if not done previously.

f. **Whole Blood Biomarkers:** The following samples will be collected at the indicated time points as detailed in the PK/Pharmacodynamic SOA. Two 2.5 mL samples will be collected for evaluation of immune-related transcripts by RNA sequencing. A 6 mL sample will be collected for T cell repertoire analysis.

g. **Soluble Factors**: One 3.5 mL blood sample will be collected into a tube optimized for plasma separation at the indicated time points to measure levels of soluble factors (eg, cytokines, chemokines, soluble PD-L1).

h. **Banked Biopecimen:** A 4 mL blood sample (Prep D1) will be collected at the C1D1 visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. Specimens will be retained as whole blood in a biobank for exploratory biomarker assessments, unless prohibited by local regulation or by decision of the Institutional Review Board or Ethics Committee. Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to PF-06801591, or the identification of those patients who might preferentially benefit from treatment with PF-06801591.

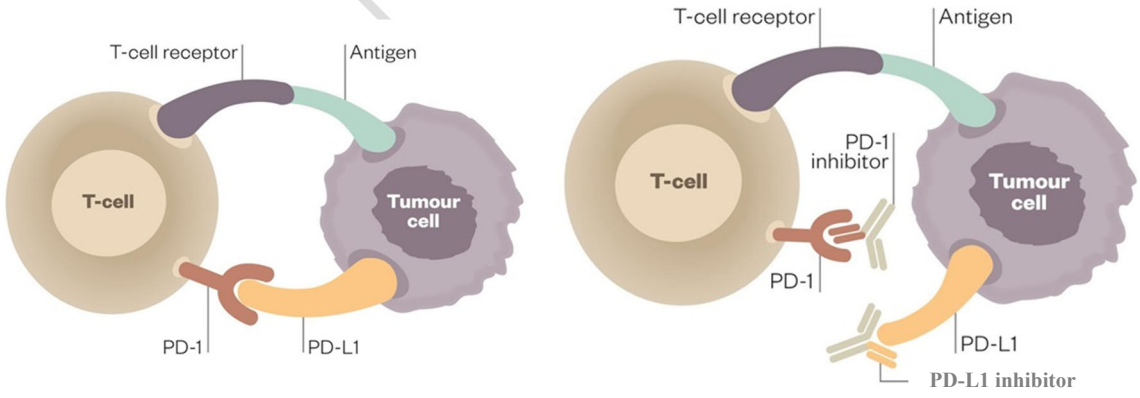
i. **Pharmacogenomics:** A 4 mL blood sample will be collected at the C1D1 visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response.

1. INTRODUCTION

Cancerous cells often evade detection by the immune system which normally attacks and kills abnormal cells.[8] The ability to escape immune recognition is a hallmark of cancer progression. While T cells specific to tumor antigens (Ags) can be readily isolated from patients, it is clear that T cell activation is not mediated by Ag stimulation alone.[9] Even in the presence of tumor Ags, T cells may exhibit exhaustion, rendering them unable to proliferate and hypo responsive to further Ag encounter. The T-cell response is regulated by immune checkpoints that include both co-stimulatory and co-inhibitory molecules. The positive signal delivered by co-stimulatory molecules is essential for an effective immune response, while the negative signal delivered by co-inhibitory molecules is essential for the prevention of autoimmunity and mediation of T-cell tolerance.[10]

Immune checkpoint inhibitors represent a novel class of antitumor agents which have demonstrated activity in certain types of cancers (eg, metastatic melanoma, non-small-cell lung cancer [NSCLC], squamous cell cancer of head and neck [SCCHN], renal cell carcinoma [RCC] and classical Hodgkin lymphoma [cHL]); these agents continue to be explored in broad set of malignancies, including ovarian cancers. One of the most studied checkpoints in the immune system is the human programmed cell death protein-1 (PD-1), a member of the cluster of differentiation (CD) 28 family of T-cell regulators that is highly expressed on activated effector tumor-infiltrating lymphocytes (TILs) and which interacts with 2 known ligands: programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2).[1] While PD-L2 is expressed primarily on macrophages and dendritic cells, PD-L1 is expressed on tumor cells, as well as diverse immune cells.[11] Upon interaction with either of its two ligands, PD-1 negatively regulates antigen receptor signaling, resulting in immune tolerance. Blocking PD-1 promotes therapeutic anti-tumor response in diverse preclinical tumor models (Figure 1).

Figure 1: Basis for Immune Therapy



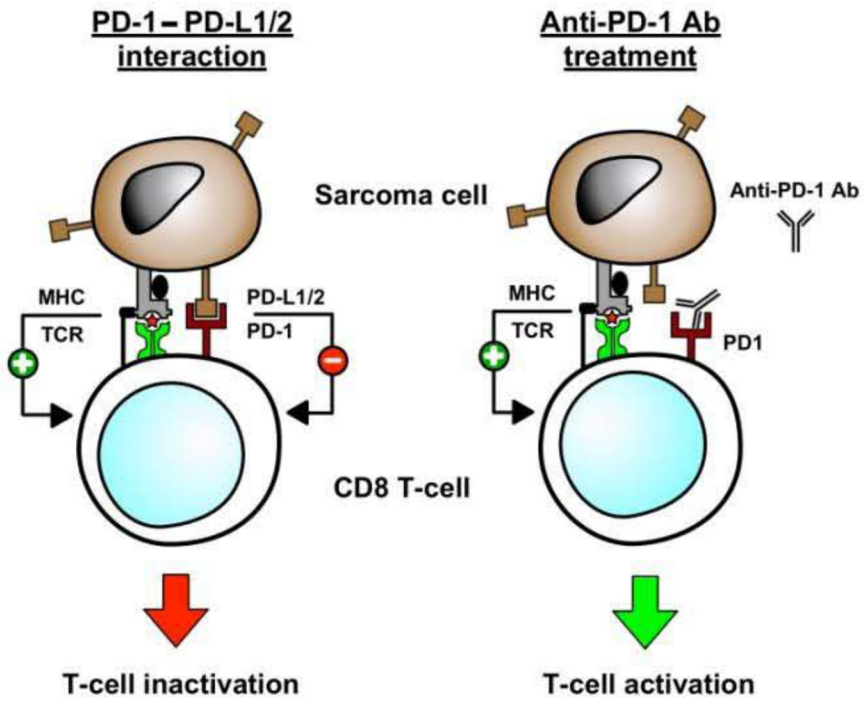
PD-1 = programmed cell death protein-1; PD-L1 = programmed death ligand-1.

Deactivated T cell: When PD-1 on the T cell binds to PD-L1 on the tumor cell, the T cell becomes deactivated, allowing the cancer cell to evade immune attack. Activated T cell: Inhibitors of PD-1 and PD-L1 can prevent the tumor cell from binding to PD-1, enabling the T cell to remain active and co-ordinate an attack.[12]

Receptors for PD-1 are expressed on several immune cells, in particular on cytotoxic T cells, and PD-1 expression has been found to be elevated in TILs isolated from patients with metastatic melanoma and SCCHN.[13,14,15] Although in resting immune cells PD-1 is minimally expressed, broad expression of this receptor is evident following immune activation.[16] Since PD-L1 is expressed on a wide variety of solid tumors including melanoma, SCCHN, NSCLC, ovarian, bladder, and renal cell carcinomas, it is hypothesized that high PD-L1 expression is the major mechanism of T-cell exhaustion in diverse malignancies.[17-19] Indeed, for some tumor types including RCC, ovarian, and urothelial cancers, high PD-1/PD-L1 expression is associated with poor prognosis and overall survival (OS).[18,20] These observations have led to development of potent inhibitors of the PD-1 pathway and form the basis for an immunotherapeutic approach to cancer.[10,21]

Sarcomas comprise a group of connective tissue neoplasms that are broadly classified as originating from soft tissues or bones. A recent sarcoma publication of tumor specimens from 105 cases showed that PD-1 positive lymphocytes and PD-L1 expression in tumor tissue were seen in 65% and 58%, respectively, of 105 soft tissue sarcomas. The degree of PD-1 positivity in TILs and PD-L1 overexpression in tumor specimens correlated with a poorer prognosis and more aggressive disease.[22] In a study of 38 human osteosarcoma samples, PD-L1 messenger ribonucleic acid (mRNA) gene expression ranged over 4 log (>5,000-fold difference). When absolute expression was normalized to that of housekeeping gene β-actin and categorized by log-transcript detection (low = 1 log; intermediate = 2 log; and high = 3 and 4 log), 9/38 samples (24%) showed high-level expression. A further 19 samples (50.0%) showed intermediate expression, 4 (10.5%) showed low-level expression, and 6 (15.8%) were negative.[23] Therefore, although anti-PD-1 therapy has not been widely tested in sarcoma patients, there is ample rationale for using anti-PD-1 treatment alone and possibly in combination with other checkpoint inhibitors in patients with advanced sarcoma.

Figure 2. PD-1 and PD-L1 in Soft Tissue Sarcomas



Programmed death ligand (PDL)-1 and PDL-2 molecules are expressed on the surface of sarcoma cells. Interaction between sarcoma associated PDL-1/2 and T cell PD-1 on the CD8 T cells leads to inactivation of tumor-directed CD8 T-cells, allowing the sarcoma to evade CD8 T-cell mediated killing. Use of anti-PD-1 antibodies blocks this T cell inactivation and allows the tumor-directed CD8 T-cells to remain active in destroying the sarcoma cells.[24]

The United States (US) Food and Drug Administration (FDA) has approved a number of anti-PD-1 and anti-PD-L1 molecules including:

1. Nivolumab/Opdivo® (a fully human immunoglobulin G4 [IgG4] anti-PD-1 Ab) for unresectable or metastatic melanoma, metastatic NSCLC, advanced renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), locally advanced or metastatic urothelial carcinoma, and recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).

2. Pembrolizumab/Keytruda® (a humanized IgG4 anti-PD-1 antibody) for unresectable or metastatic melanoma, metastatic NSCLC, cHL, and recurrent or metastatic SCCHN; approval of atezolizumab/Tecentriq® (a humanized IgG1 anti-PD-L1 antibody) for locally advanced or metastatic urothelial carcinoma, and metastatic NSCLC.

3. Durvalumab/Imfizi® (a humanize IgG1 anti-PD-1 antibody) for locally advanced or metastatic urothelial carcinoma.

4. Avelumab/Bavencio® (an anti-PD-L1 antibody), for the treatment of metastatic merkel cell carcinoma (MCC) and urothelial carcinoma.

These therapies have provided compelling evidence that blocking the PD-1 pathway is a viable immunotherapeutic approach for variety of tumor types.[1-6] Recently PD-1 antibodies in development (Table 1) have shown promising results in clinical trials with durable anti-tumor responses (ie, tumor shrinkage, extending OS time) seen early and continuing after treatment discontinuation, in other multiple tumor types including ovarian cancer, certain sarcomas, triple negative breast cancer, hepatocellular carcinoma, mismatch repair deficient cancers, small cell lung cancer, and gastric cancer[4-25] The PD-1/PD-L1 inhibitors also are less labor-intensive to administer than some other types of immunotherapies, and do not require personal preparation for each patient as do dendritic cell vaccines and chimeric antigen receptor (CAR) T-cell therapy.[12]

Table 1. Anti PD 1 Antibodies

Agent	Target	Description	[redacted]
PF-06801591	PD-1	Humanized IgG4 anti-PD-1	[redacted]
Nivolumab (Opdivo®) (BMS-936558, ONO-4538, MDX-1106)	PD-1	Fully human IgG4	[redacted]
Pembrolizumab (Keytruda®) (MK-3475, pembrolizumab)	PD-1	Humanized IgG4 kappa	[redacted]

Ig = immunoglobulin; L1 = ligand; NA = not available; PD-1 = programmed cell death protein-1; PD-L1 = programmed death ligand 1.
Source: Kim JW, Eder JP: Prospects for Targeting PD-1 and PD-L1 in Various Tumor Types. Oncology Cancer Network 2014.[13]

1.1. Mechanism of Action/Indication

PF-06801591 is a humanized, hinge region-stabilized IgG4 monoclonal antibody (mAb) specific for human PD-1 that can selectively binds to human PD-1 and block the interaction between PD-1 and PD-L1/PD-L2. PF-06801591 has been shown to induce T cell proliferation and interferon gamma (IFN-γ) and other proinflammatory cytokines secretion in human activated $CD8^+$ T cells [redacted].

PF-06801591 showed similar binding affinity to human PD-1 compared to pembrolizumab and nivolumab.[25]

The projected half-life ($t_{½}$) of approximately 3 weeks for PF-06801591 is similar to that of nivolumab and pembrolizumab.[2,4]

In this study, PF-06801591 will be used to assess safety and tolerability of increasing dose levels in patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents.

1.2. Background and Rationale

1.2.1. Melanoma

Melanoma is the most serious form of skin cancer and strikes adults of all ages. The 5-year prevalence of melanoma in the European Union (EU) is approximately 159,000 patients with an incidence of approximately 41,000 per year and approximately 11,000 deaths annually, as described in the World Health Organization (WHO) Europe region.[23] Melanoma accounts for approximately 5% of all new cases of cancer in the US. The incidence of melanoma continues to rise by almost 3% per year in the US. This translates to 76,000 new cases a year with 9,000 associated deaths. The male: female incidence ratio of melanoma is 1.4:1.[27] The 5-year survival rate is 15% for late-stage disease.[28] The activity of anti-PD-1 antibodies in melanoma is well-established, and anti-PD-1 antibodies are a standard of care in advanced melanoma.[2,4]

1.2.2. Head and Neck Cancer

Approximately 650,000 new cases of head and neck cancer are diagnosed globally each year with the most common form being SCCHN.[29, 30, 31] The SCCHN form represents an aggressive tumor type with a 10.1 month OS rate for patients with recurrent and/or metastatic disease.[32] In addition, SCCHN is considered to be an immunosuppressive tumor:[33] the circulating and tumor-infiltrating T cells of patients with SCCHN have signaling defects,[34] and immune effector cell anergy has been well described. Taken together with the ability of TILs to act against SCCHN tumor Ags, SCCHN tumors are suitable targets for immunotherapy. To date, the only FDA-approved immunotherapeutic agent for SCCHN is cetuximab; an anti-epidermal growth factor receptor (EGFR) Ab. EGFR antibody (Ab) is a tumor Ag expressed on >90% of all SCCHN tumors. In Phase 3 studies, recurrent and metastatic SCCHN patients treated with cetuximab plus concomitant chemotherapy had an increased OS rate of 7.4 months, compared to 10.1 months in SCCHN patients treated with chemotherapy alone.[30] Pembrolizumab has received accelerated approval from the FDA for recurrent or metastatic SCCHN with disease progression on or after platinum-containing chemotherapy based on the results of KEYNOTE-012, with an overall response rate (ORR) of 16% and complete response (CR) rate of 5%.[4] Nivolumab received FDA approval in the same setting based on the results of CheckMate 141 with ORR of 13.3% and CR rate of 2.5% and meaningful improvement in OS (hazard ratio [HR] 0.7, 95% confidence interval [CI] 0.52-0.92).[2]

1.2.3. Ovarian Cancer

In 2014 it was estimated that ovarian cancer resulted in the deaths of >14,000 women, more deaths than any other gynecologic cancers, making it the fifth leading cause of cancer-related death among women.[35] The incidence of ovarian cancer increases with age and is most prevalent during the eighth decade of life. In 2011, it was estimated that approximately 188,867 women living in the US had ovarian cancer. In a Phase II study with nivolumab in ovarian cancer, an ORR of 15% (3 of 20 patients) was seen with 1 partial response (PR) at 1 mg/kg and 2 CR at 3 mg/kg, and disease control rate (DCR) was 45%.[2,36] Median OS was 20 months, and median progression free survival (PFS) was 3.5 months. A study with pembrolizumab in PD-L1 positive ≥1% of tumor cells (51% of ovarian cancer patients) also had an ORR of 11.5% (3 of 26 patients) with 1 CR and DCR of 34.6%.[4]

1.2.4. Sarcomas

Sarcomas comprise a group of about 70 rare connective tissue neoplasms of mesenchymal origin that are broadly classified as originating from soft tissues or bones.[37] In 2014, an estimated 12,000 cases of soft tissue sarcoma and 3,000 cases of bone sarcomas were diagnosed in the US; approximately 4,700 and 1,500 people were expected to die from soft tissue and bone sarcomas, respectively.[38] Standard management is usually determined by multidisciplinary teams at sarcoma referral centers and from European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines. For metastatic disease and locally advanced tumors for which local control is not an option, chemotherapy and targeted agents are used.[39] Although multimodality treatments have improved outcomes for pediatric sarcomas, there is no treatment for metastatic refractory disease, and median OS for most metastatic adult sarcomas is only one year.[40] SARC028, a Phase II study of pembrolizumab in 86 patients with various sarcomas, demonstrated ORR of 0% (0 of 10) in leiomyosarcoma, 44% (4 of 9) in pleomorphic sarcoma, 22% (2 of 9) in liposarcoma, 11% (1 of 9) in synovial sarcoma, 17% (1 of 6) in chondrosarcoma, 0% (0 of 13) in Ewing's sarcoma, and 5% (1 of 19) in osteosarcoma. Median PFS was 18 weeks.[4, 11].

1.2.5. Non-Small Cell Lung Cancer (NSCLC)

There are extensive clinical data leading to the approval of nivolumab and pembrolizumab for the treatment of advanced or metastatic NSCLC.

Nivolumab

In the Phase 1 study, a maximum tolerated dose for nivolumab was not identified, and the safety profile was similar across tumor types and dose levels (0.1–10 mg/kg).[2] ORRs were similar across doses in melanoma and renal cell carcinoma (RCC), while higher ORRs were observed in NSCLC at 3 mg/kg and 10 mg/kg versus 1 mg/kg. Peripheral receptor occupancy was saturated at doses ≥0.3 mg/kg. In dose-response/exposure-response analyses, a positive dose-dependent objective response trend was observed for each tumor type, but appeared to plateau at nivolumab doses of ≥1 mg/kg for melanoma and RCC, and at ≥3 mg/kg for NSCLC. Although there was no apparent relationship between tumor shrinkage rate and exposure, tumor progression rate diminished with increasing exposure up to a dose of 3 mg/kg (every 2 weeks) in NSCLC.

A clinical research trial enrolled 582 patients, randomized (1:1), to receive nivolumab 3 mg/kg every 2 weeks (n=292) or docetaxel 75 mg/m^2 q3w (n=290) until disease progression or unacceptable toxicity, excluding patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. The trial demonstrated OS improvement with a hazard ratio of 0.73 (95% CI: 0.60, 0.89); p <0.002, and a median OS of 12.2 months in patients on nivolumab and 9.4 months in patients on docetaxel. The trial also demonstrated significant improvement in ORR (19% vs 12%), with median response duration of 17 months for nivolumab and 6 months for the docetaxel, and no significant difference in progression-free survival (PFS).

The most common (≥20%) Grade 1-4 adverse reactions in the nivolumab arm included fatigue, musculoskeletal pain, cough, decreased appetite, and constipation. The most common (≥2%) Grade 3-4 adverse reactions were dyspnea, fatigue, pneumonia, pulmonary embolism, pleural effusion, hyperglycemia, respiratory failure, and pain. The most common (≥2%) Grade 3-4 laboratory abnormalities included lymphopenia, hyponatremia, anemia, increased aspartate aminotransferase (AST), and increased alanine aminotransferase (ALT). Serious adverse events (SAEs) were reported in 47 of patients receiving nivolumab. The most common SAEs were pneumonia, pulmonary embolism, dyspnea, and pleural effusion. Immune-mediated AEs that occurred in patients treated with nivolumab included hypothyroidism/thyroiditis, rash, pneumonitis, diarrhea/colitis, hyperthyroidism, hepatitis, nephritis, limbic encephalitis, and polymyalgia rheumatica.[2]

On October 9, 2015, the U. S. Food and Drug Administration (FDA) approved nivolumab at an intravenous dose of 3 mg/kg every 2 weeks, for the treatment of patients with metastatic NSCLC, including non-squamous histologies, with progression on or after treatment with platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have confirmed disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.

A phase 3 trial CheckMate-227 randomized 1739 NSCLC patients 1:1:1 to nivolumab combined with ipilimumab, nivolumab alone, or systemic chemotherapy as first line treatment. In all patients, the one year and median PFS was 30.9% and 4.9 months in patients treated with combination of nivolumab and ipilimumab vs 17.0% and 5.5 months in patients treated with chemotherapy alone (HR 0.83, 95% CI, 0.72 to 0.96). For patients whose tumor mutational burden was at least 10 mutations per megabase (n = 444), the one year and median PFS in patients who received combination therapy of nivolumab and ipilimumab was 42.6% and 7.2 months versus 13.2% and 5.5 months for patients who received chemotherapy (HR 0.58, 97.5% CI, 0.41 to 0.81 P‹0.001). PFS benefit in the high tumor mutation burden population was seen in patients with tumor PD-L1 expression <1% and ≥1% as well as non-squamous and squamous histologies. In patients with less than 10 mutations per megabase, the median PFS was 3.2 months in the nivolumab with ipilimumab arm and 5.5 months in the chemotherapy arm with HR 1.07(95% CI, 0.84 to 1.35). The rate of grade 3 and higher adverse events in nivolumab and ipilimumab was similar to that of the chemotherapy group.[41]

Pembrolizumab

In a three-arm trial of 1033 patients who were previously treated for metastatic NSCLC with PD-L1 expression on greater than or equal to 1% of tumor cells, those randomized to pembrolizumab (2 mg/kg q3w) (HR 0.71 (95% CI: 0.58, 0.88]; p<0.001) or pembrolizumab (10 mg/kg q3w) (HR 0.61 [95% CI: 0.49, 0.75]; p<0.001) had an improved OS compared with patients receiving docetaxel.[4] Median survival was 10.4 months in the pembrolizumab 2 mg/kg arm, 12.7 months in the pembrolizumab 10 mg/kg arm, and 8.5 months in the docetaxel arm. ORR was also significantly improved at 29-30% for pembrolizumab vs 8% for docetaxel.

The most common side effects of treatment with pembrolizumab included decreased appetite, fatigue, nausea, dyspnea, cough, and constipation. Rare but serious adverse events included immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.

On October 2, 2015, the U.S. FDA approved pembrolizumab for the treatment of metastatic NSCLC with expression of PD-L1 on ≥1% of tumor cells with disease progression on or after platinum-based chemotherapy. Disease with ALK or EGFR mutations should have progressed on FDA-approved targeted therapy for these mutations prior to receiving pembrolizumab.

In a clinical research trial of 305 patients with no prior treatment for metastatic NSCLC with PD-L1 expression on greater than or equal to 50% of tumor cells, those who received pembrolizumab (200 mg q3w) had a significant improvement in PFS (HR 0.50 [95% CI: 0.37, 0.68]; p<0.001) with a median PFS of 10.3 months versus 6.0 months for those receiving platinum-based chemotherapy. A pre-specified interim analysis demonstrated a statistically significant improvement in OS for patients randomized to pembrolizumab as compared with chemotherapy (HR 0.60 [95% CI: 0.41, 0.89]; p<0.005). ORR was also significantly improved at 45% to 28%.

On October 24, 2016, the U.S. FDA approved pembrolizumab at a dose of 200 mg administered intravenously q3w for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 on ≥50% of tumor cells as determined by an FDA-approved test.

In KEYNOTE-042, pembrolizumab was compared with platinum-containing chemotherapy (carboplatin + paclitaxel or carboplatin + pemetrexed) in 1274 first line metastatic NSCLC patients, randomized 1:1 and analyzed in 3 different subgroups with 1-19%, ≥20% and ≥50% PD-L1 tumor proportion score (TPS). In the pembrolizumab arm subgroups, median survival in months were 16.7 (HR 0.81, 95% CI, 13.9 to 19.7), 17.7 (HR 0.77, 95% CI, 15.3 to 22.1) and 20.0 (HR 0.69, 95% CI, 15.4 to 24.9), respectively, whereas in the chemotherapy arm subgroups they were 12.1 (95% CI, 11.3 to 13.3), 13.0 (95% CI, 11.6 to 15.3) and 12.2 (95% CI, 10.4 to 14.2), respectively. Further exploratory analysis of this data revealed that dividing the patients in two groups with ≥1-49% TPS revealed median OS of 13.4 months vs 12.1 months with HR of 0.92 (95% CI, 0.77 to 1.11) suggesting that survival benefit may be largely driven by the ≥50% TPS group. As expected, pembrolizumab had better safety profile than chemotherapy except for immune-mediated adverse events experienced.[42]

Recently, in May 2017, FDA also granted approval of pembrolizumab in combination with pemetrexed and carboplatin as first line treatment for metastatic non-squamous NSCLC following results from the KEYNOTE-021 study. In this study, 123 locally advanced or metastatic non-squamous NSCLC patients with no prior systemic treatment for metastatic disease, regardless of PD-L1 expression, were randomized to the pembrolizumab arm (60 patients) or to the chemotherapy only arm (63 patients). In this study, a statistically significant improvement in ORR was observed; an ORR of 55% was reported in patients treated with pembrolizumab plus pemetrexed and carboplatin, whereas an ORR of 29% was reported in patients treated with pemetrexed and carboplatin only. Greater than 93% of patient treated with pembrolizumab experienced response duration of ≥6 months.

KEYNOTE-189 subsequently compared use of pembrolizumab or placebo in combination with pemetrexed and a platinum-based systemic chemotherapy in 616 metastatic non-squamous NSCLC patients randomized (2:1) in the first line setting. At the time of the published analysis, the median OS was not reached in the pembrolizumab combination arm and was 11.3 months for the placebo combination arm. The 12-month OS rate was 73.0% in pembrolizumab arm and 48.1% in the placebo arm. The median PFS was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab arm and 4.9 months (95% CI, 4.7 to 5.5) in the placebo arm. Grade 3 or higher adverse events occurred in 67.2% of patients in the pembrolizumab arm and 65% in the placebo arm. Improvement in OS was seen across all levels of tumor PD-L1 expression. Discontinuation of treatment due to all drugs occurred in 13.8% of the patients treated with the combination arm and 7.9% in patients in the placebo arm.[43]

In KEYNOTE407, 559 patients with metastatic squamous NSCLC were randomized (1:1) to receive either chemotherapy (carboplatin + paclitaxel or nab-paclitaxel) combined with pembrolizumab or chemotherapy with placebo drug in the first line setting. In the pembrolizumab combination arm, median OS was 15.9 months (HR 0.64, 95% CI, 13.2 to not evaluable) whereas in the chemotherapy arm median OS was 11.3 months (95% CI, 9.5 to 14.8). PFS was 6.4 months (HR 0.56, 95% CI, 6.2 to 8.3) in the pembrolizumab combination arm and 4.8 months (95% CI, 4.3 to 5.7) in chemotherapy arm. As expected safety profiles were consistent with chemotherapy and pembrolizumab with no additional safety signals identified.[44]

1.2.6. Urothelial Carcinoma

For urothelial carcinoma, tumor infiltration of CD3+ and CD8+ T cells has been associated with better overall survival.[45,46] Urothelial cancer was the first indication with an FDA approved immunotherapy, and vaccination using weakened, live bacterium bacillus calmette-guérin (BCG) first took place in the 1970s.[45] Worldwide, it is estimated that 386,000 new cases of bladder cancer will occur each year, with approximately 105,000 deaths.[29] Approximately 75% of cases of bladder cancer are non- muscle invasive bladder cancer (NMIBC). Whilst treatment with BCG has been shown to reduce the risk of tumor recurrence,[47] approximately 40% of patient with NMIBC will fail BCG therapy.[48] Thus, other immunotherapeutic approaches for urothelial cancer were evaluated, and studies with pembrolizumab, nivolumab, atezolizumab, durvalumab and alemtuzumab are summarized below.

Pembrolizumab

Pembrolizumab received approval from the FDA in May 2017 for the treatment of locally advanced or metastatic urothelial carcinoma not eligible for cisplatin containing chemotherapy or with disease progression following platinum-containing chemotherapy or within 1 year of neo-adjuvant or adjuvant therapy with platinum-containing chemotherapy. In a Phase 3 study of 543 urothelial cancer patients who have progressed on platinum-based chemotherapy, treatment with pembrolizumab prolonged overall survival of patients to 8 months, as compared to 5.2 months in the chemotherapy group.[4, 49] As of data cutoff date, median duration of response in the pembrolizumab group was not reached, but approximately 68% of patients had duration of response (DOR) of at least 12 months. This is in comparison to DOR for chemotherapy, which was 4.3 months. The ORR also increased significantly in patients treated with pembrolizumab, with 21.1% versus 11.4% in the chemotherapy group. Grade 3 or greater adverse events was also significantly reduced, with 15% observed in the pembrolizumab group versus 49.4% observed in the chemotherapy group.

In patients who were treated with pembrolizumab, 0.4% experienced sepsis that led to death, and 0.8% of patients experienced pneumonia that led to death. The most common serious adverse reactions experienced by ≥2% of patients were urinary tract infection, hematuria, acute kidney injury, pneumonia and urosepsis.[4]

In May 2018, FDA issued a general public alert that in KEYNOTE-361 evaluating either single agent pembrolizumab versus platinum chemotherapy in previously untreated metastatic urothelial carcinoma eligible for platinum-based chemotherapy treatment, an interim analysis found that patients with PD-L1 low status had worse survival with pembrolizumab versus platinum-based chemotherapy. The pembrolizumab label in urothelial carcinoma has subsequently been updated to limit treatment in patients not previously treated with platinum containing therapy to those with PD-L1 combined positive score ≥10 who are not eligible for cisplatin-containing chemotherapy, or patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[4]

Nivolumab

In February 2017, nivolumab was granted accelerated approval for patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy or within 1 year of neo-adjuvant or adjuvant therapy with platinum-containing chemotherapy. In a Phase 2 study Checkmate 275 of nivolumab in 270 patients with locally advanced urothelial carcinoma in patients who progressed following treatment with at least one line of platinum-based chemotherapy, 19.6% of patients achieved a sustained and confirmed clinical response.[2, 50] Of these, 2% had a CR, and 19% had a PR. Confirmed objective response was highest in the patients who had ≥5% PD-L1 expression, with 28.4% achieving objective response. This is compared to only 16.1% of patients with ≤1% PD-L1 expression who achieved objective response. Overall survival for patients with ≥1% PD-L1 expression was 11.3 months, compared to 5.95 months for patients with ≤1% PD-L1 expression.

In this study, 1.5% of patients died from treatment related pneumonitis or cardiovascular failure. Serious adverse reactions occurred in 54% of patients, and the most common serious adverse reactions experienced by ≥2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration.[4]

Atezolizumab

In the IMvigor 210 Phase 2 clinical trial of 310 patient study of atezolizumab in locally advanced or metastatic urothelial carcinoma whose disease had progressed after previous platinum-based chemotherapy, confirmed ORR by independent review was 14.8% and patients with ≥5% PD-L1 expression had an ORR of 27%.[3, 51] This is compared to historical control of 10%. Median DOR was not reached and response duration ranged from 2.1+ to 13.8+ months. Of the 46 responders, 37 patients had an ongoing response for greater than or equal to 6 months and 6 for greater than or equal to 12 months. Atezolizumab was well tolerated, with Grade 3–4 immune-mediated adverse events observed in 5% of patients. The IMvigor 210 Phase 2 clinical trial also included a cohort of 123 cisplatin-ineligible patients. In this cohort, Balar et al[52] reported median overall survival of 15.9 months, ORR of 23% and CR rate of 9% in patients treated with atezolizumab, regardless of PD-L1 status. When the results were further evaluated based on PD-L1 expression, 28% ORR was observed in patients with ≥5% PD-L1 expression, whilst 10% ORR was observed for patients with ≥1% but <5% PD-L1 expression. Atezolizumab subsequently received accelerated approval for second-line treatment of urothelial carcinoma in May 2016, and first-line treatment for platinum-ineligible urothelial carcinoma in April 2017. However, the confirmatory Phase 3 IMvigor211 trial comparing atezolizumab versus chemotherapy in a second-line or greater setting for urothelial carcinoma failed to meet a primary endpoint of overall survival improvement in May 2017.

It has been reported that 0.9% of patients who received atezolumab experienced sepsis, pneumonitis or intestinal obstruction that led to death. Serious adverse reactions occurred in 45% of patients. The most frequent (>2%) serious adverse reactions were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis and confusional state.[3]

In May 2018, the FDA issued a general public alert that in an ongoing clinical study IMVIGOR-130 evaluating either single agent atezolizumab versus platinum chemotherapy in previously untreated metastatic urothelial carcinoma eligible for platinum-based chemotherapy treatment, an interim analysis found that patients with PD-L1 low status had worse survival with atezolizumab compared to patients who received platinum-based chemotherapy. The atezolizumab label in urothelial carcinoma has subsequently been updated to limit treatment in patients not previously treated with platinum containing therapy to those with PD-L1 tumor-infiltrating immune cells covering ≥5% of the tumor area who are not eligible for cisplatin-containing chemotherapy, or patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[3]

Durvalumab

Durvalumab received accelerated approval from the FDA in May 2017 based on the results reported in Study 1108, a Phase 1/2 trial in 182 patients with locally-advanced or metastatic urothelial carcinoma of the bladder.[5] Though PD-L1 status was evaluated using the VENTANA PD-L1 (SP263) assay, patients were enrolled into the study regardless of their PD-L1 status. An ORR of 17.0% was achieved in all evaluable patients. The ORR was highest (26.3%) in patients with ≥25% PD-L1 expression. In patients who had PD-L1 low or negative expression, ORR decreased to 4.1%. Overall, 14.3% of all evaluable patients achieved PR and 2.7% achieved CR. Amongst the 31 patients who responded, 45% had ongoing responses of 6 months or longer, and 16% had ongoing responses of 12 months or longer.

In patients who were treated with durvalumab, 4.4% experienced cardiorespiratory arrest, general physical health deterioration, sepsis, ileus, pneumonitis, or immune-mediated hepatitis that led to death. The most frequent serious adverse reactions include acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain, and pyrexia/tumor associated fever (2.7% each).[5]

[redacted]

1.2.7. Background Summary

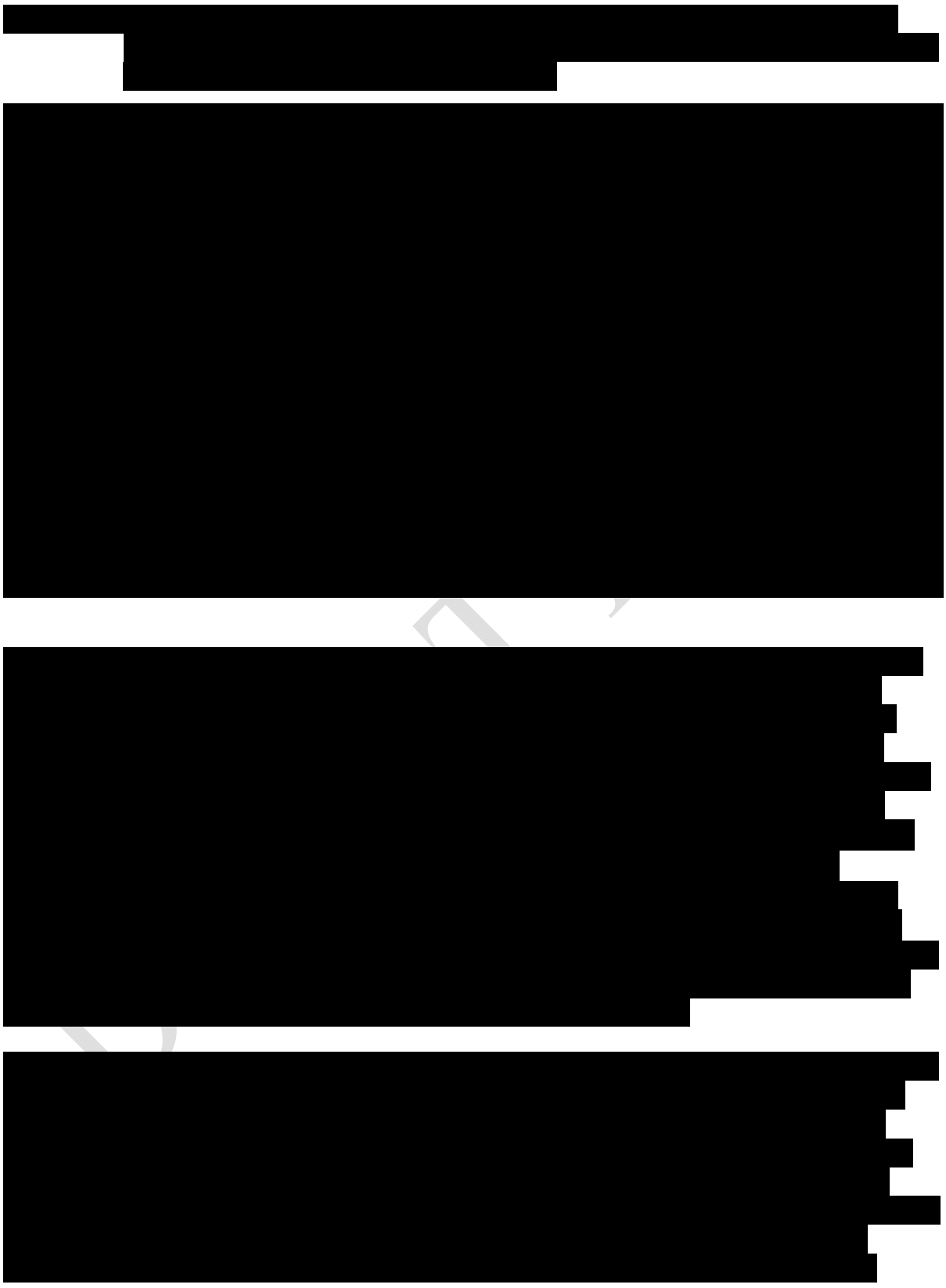
This protocol is the first clinical study of PF-06801591 in patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma, or other solid tumors with clinical evidence of response to anti PD-1 or PD-L1 agents, who are unresponsive to existing therapies, or for whom standard treatment is not available. After preliminary determination of safe and effective exposure levels of PF-06801591 in Part 1 in

multiple solid tumor types, Part 2 will enroll two cohorts of NSCLC and urothelial carcinoma patients in order to evaluate whether the safety and efficacy of 300 mg SC PF-06801591 will be comparable to what has been seen with other approved anti-PD-1 agents intravenously in NSCLC and urothelial carcinoma.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the investigator's brochure.

1.3. Nonclinical Efficacy

PF-06801591, a humanized hinge region stabilized PD-1 specific mAb, binds to PD-1 with high affinity and specificity and efficiently inhibits the interaction between PD-1 and its ligands (PD-L1 and PD-L2). The functional activity of PF-06801591 was confirmed in vitro, in a mixed lymphocyte reaction. [redacted]



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1.4. Nonclinical Safety

The nonclinical safety profile of PF-06801591 has been well characterized in nonclinical toxicology studies. Because PF-06801591 does not cross react with mouse or rat PD-1, but cross reacts with cynomolgus monkey PD-1 with similar affinity as human PD-1, monkeys are considered the most relevant toxicology species to assess human risk. In addition to in vivo monkey studies, in vitro tissue cross reactivity using monkey and human tissues and in vitro cytokine release assays using human whole blood or peripheral blood mononuclear cells (PBMC) were performed.

In the pivotal, Good Laboratory Practice (GLP) repeat-dose study, cynomolgus monkeys were treated once weekly for 1 month (5 times in total) at the dose levels of 0 (control), 20, 60, and 200 mg/kg PF-06801591 with a 2-month recovery period (control and 200 mg/kg groups only). Clinical and anatomic pathology were assessed at the end of the dosing and recovery phases. In order to assess the level of pharmacological inhibition of PD-1, an ex vivo Staphylococcal enterotoxin B (SEB) stimulation assay was performed on blood collected at various time points. In addition, immunophenotyping was performed to determine any effects on specific lymphocyte populations.

Repeated administration of PF-06801591 was well tolerated in cynomolgus monkeys when administered IV once weekly for 1 month (5 times in total) at doses up to 200 mg/kg. There were no test article-related abnormalities in food consumption, body weight change, electrocardiogram (ECG), blood pressure (BP), ophthalmology, urinalysis, hematology, gross pathology, or organ weights. Clinical pathology findings were limited to increases in globulin and total serum protein at the end of the dosing phase which reversed during the recovery phase. Anatomical pathology findings consisted of increased incidence and/or severity of mononuclear infiltration. At the end of the recovery phase, the infiltration in the brain was either similar to or slightly more severe compared with the dosing phase; additionally, there was also test article-related increased incidence and/or severity of mononuclear infiltrates in the spinal cord, peripheral nerve, pituitary, kidney and thyroid. None of the findings were considered severely toxic. The findings are consistent with the expected pharmacology of PD-1 blockade, and are similar to findings described for the marketed PD-1 antagonist drugs nivolumab and pembrolizumab; their presence at the end of recovery is consistent with exposure and target inhibition throughout the recovery period.

Results from the SEB assay demonstrate saturation of PD-1 in the peripheral blood of monkeys in all dose groups (≥20 mg/kg) during the dosing phase and in the 200 mg/kg group at the twenty-fourth day of the recovery phase (the last day evaluated). Immunophenotyping analysis demonstrated test article-related increases only on Day 15 for activated (CD8+HLA-DR+), and proliferating (CD4+Ki-67+, and CD8+Ki-67+) T cell sub-populations. These increases were not dose-related, suggesting maximal pharmacological effects at all dose levels. PF-06801591 serum levels at the end of the recovery phase were similar to serum levels in the 20 mg/kg group during the dosing phase, indicating saturation of PD-1 throughout the recovery phase.

In summary, weekly intravenous (IV) administration of PF-06801591 for 1 month was well tolerated up to 200 mg/kg without display of severe toxicity. Therefore, 200 mg/kg was considered the highest non-severely toxic dose (HNSTD) with associated area under the curve $(AUC)_{0\text{-}168}$ and maximum drug concentration (C_{max}) on Day 22 of 1,060,000 µg•h/mL and 10,500 µg/mL, respectively. Furthermore, the exposures and SEB assay results during the dosing and recovery phases indicate saturation of PD-1 throughout the entire 3 months of the study (dosing and recovery phases combined), and therefore recovery from test article-induced effects was not assessed.

In a separate GLP study on Days 1 and 29, male cynomolgus monkeys (4/sex/group) were administered either vehicle by IV and SC injection or PF-06801591 by SC injection at dose of 20 mg/kg. The terminal necropsy was on Day 43. PF-06801591 was well-tolerated up to the highest dose tested (20 mg/kg/month). There was no PF-06801591-related mortality, or changes in hematology, coagulation, clinical chemistry, urinalysis, body weight, body temperature, food consumption, local irritation, clinical observations, or macroscopic and microscopic findings. The no-observed-adverse-effect-level (NOAEL) was considered to be the highest dose tested, 20 mg/kg/month and was associated with a mean AUC_{670} on Day 29 of 166,000 µg•h/mL. Because PF-06801591 was well-tolerated and there were no signs of local irritation, as assessed by clinical signs and microscopic observations, this study supports clinical dosing via the SC route of administration.

In the tissue cross-reactivity study, PF-06801591 stained the cytoplasm and plasma membrane of mononuclear leucocytes primarily located within lymphoid tissues in both the human and cynomolgus monkey tissues, and staining was similar between the two species. No unexpected tissue cross-reactivity was observed in the human or cynomolgus monkey tissue panels.

To evaluate the potential for acute cytokine release syndrome, PF-06801591 was tested in two different in vitro cytokine release assays: a soluble phase assay with test articles added to human whole blood, and a solid-phase assay with human peripheral blood mononuclear cells (PBMCs) cultured with plate-bound test article. PF-06801591 did not elicit release of cytokines (TNF-α, IL-6, and IFN-γ) in the soluble phase assay. In the solid phase assay, there was substantial cytokine release above negative controls in a sample from 1 out of 10 donors. The cytokine release from this sample was not likely related to intended pharmacology and may have been an anomaly because two other samples from this donor were retested in two independent cultures and did not show significant cytokine release above the isotype control upon retest. Overall, the risk for acute cytokine toxicity with PF-06801591 in humans is considered low for several reasons, including: 1) the variability of in vitro findings (which do not provide strong evidence for consistent cytokine response), 2) the lack of clinical signs of cytokine toxicity in the GLP cynomolgus monkey study, and 3) the lack of clinical evidence for cytokine storm reactions with the marketed PD-1 antagonist drugs nivolumab and pembrolizumab.[2,4]

[redacted]

[redacted]

1.9. Clinical Experience

PF-06801591 is currently being tested in 2 clinical studies. Study B8011001 a Phase 1, open-label, multi-center, multiple-dose, dose escalation and expansion, safety, PK, and pharmacodynamic study of PF-06801591 in adult patients with locally advanced or metastatic solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents, who are unresponsive to currently available therapies or for whom no standard therapy is available.

The second clinical study is study B7791001, a Phase 1 study to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of a vaccine based immunotherapy regimen (VBIR) for prostate cancer (PrCa). [redacted]

1.9.1. Clinical Experience in Study B8011001

As of a 31 January 2017 data cut off, 26 pts (ovarian cancer, n=12; sarcoma, n=6; head and neck cancer [SCCHN]; n=5; melanoma, n=1; small cell lung cancer, n=1; and malignant peritoneal neoplasm, n=1) enrolled in Phase 1 dose-escalation phase: 0.5 (n=2), 1 (n=8), 3 (n=7), 10 (n=5) mg/kg IV, and 300 mg (n=4) SC. Maximum tolerated dose was not reached. Additionally, no dose-limiting toxicities were observed. All drug-related AEs were Grade 1 or 2, and the most frequently reported in >10% of pts include nausea (15.4%), fatigue (15.4%), decreased appetite (11.5%), and mucosal inflammation (11.5%). No dose relationship of adverse events was observed during IV dose escalation nor were any significant skin toxicities observed with SC administration. Three ovarian cancer patients had a confirmed partial response at 0.5, 1, and 10 mg/kg IV, and 1 SCCHN patient had a partial response at 300 mg SC. Three patients had stable disease lasting >24 wks.

Preliminary PK data from Cycle 1 of treatment were available for patients receiving IV (n=22) or SC (n=4) doses of PF-06801591 in Part 1. PF-06801591 exhibited PK characteristics typical of IgG4 monoclonal antibodies (mAbs), including those approved as anti-PD-1 therapies. Preliminary analysis showed that mean maximum serum concentration (C_{max}) and area under the serum concentration-time curve (AUC_t) of PF-06801591 increased in an approximately dose-proportional manner over the dose range of 0.5 -10 mg/kg

following IV administration. After SC administration at 300 mg, PF-06801591 was slowly absorbed, with a median maximum (or peak) serum concentration (T_{max}) of 182 hours. The mean exposure following SC administration of 300 mg PF-06801591, q4w was between the mean exposures observed following IV doses of 1 and 3 mg/kg, q3w. Preliminary data show full receptor occupancy of PD-1 was seen in all dose cohorts.

After data cut off of 31 January 2017, one drug related SAE was reported in a 72 year old with esophageal cancer in the 300 mg SC administration cohort. This patient experienced Grade 2 pneumonitis after receiving 3 cycles of study drug. Patient's respiratory status improved with steroids, and study treatment was discontinued permanently.

1.9.2. Clinical Experience in Study B7791001

Study B7791001 is a study of a vaccine-based immunotherapy regimen (VBIR) for prostate cancer (PrCa VBIR or PF-06753512). [redacted]

[redacted]

1.9.3. Risk Benefit Assessment

Although there is limited prior clinical experience with PF-06801591 and the full extent of therapeutic benefit to patients with advanced or metastatic tumors is currently unknown, the preliminary safety and efficacy data for PF-06801591 to date have been consistent with what is expected for an anti-PD-1 antibody. Drug products in the same pharmaceutical class have shown acceptable safety and efficacy and benefits outweighing the risks in patients with certain locally advanced or metastatic caners.

Overall, the nonclinical data package and existing preliminary clinical safety and efficacy data for PF-06801591 support its continued clinical development in the planned first-in-patient (FIP) study B8011001.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Part 1 Dose Escalation

Primary Objective(s):	**Primary Endpoint(s):**
• To assess safety and tolerability of increasing dose levels of PF-06801591 administered IV in patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents to establish the MTD. • To assess safety and tolerability of PF-06801591 administered SC in patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents.	• Dose Limiting Toxicities (DLTs) at escalated doses of PF-06801591. • AEs as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), timing, seriousness, and relationship to study therapy PF-06801591. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To characterize the single dose and multiple dose PK of PF-06801591 following IV or SC administration.	• PK parameters of PF-06801591: Cycle 1 and Cycle 4 maximum drug concentration (Cmax), area under the concentration versus time curve (AUC) from time zero to the last quantifiable time point prior to the next dose (AUClast), and if data permit, clearance (CL), volume of distribution (Vd)/volume of distribution at steady state (Vss), accumulation ratio (Rac) when feasible, and terminal elimination half-life (t1/2).
• To evaluate the immunogenicity of PF-06801591 following repeated administration.	• Incidence of anti-drug antibody (ADA) and neutralizing antibodies (NAb) against PF-06801591.
• To characterize PD-1 Receptor Occupancy (RO) in peripheral blood T cells following IV or SC PF-06801591 administration at each dose level.	• PD-1 RO by PF-06801591, as assessed by measuring the levels of unbound (free) cell surface PD-1 on circulating T cells over time following PF-06801591 administration.

• To evaluate preliminary anti-tumor activity of PF-06801591.	• Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 and immune related RECIST (irRECIST) and proportion of patients with partial response (PR) and immune related partial response (irPR), as appropriate >80%. • Time to event endpoints based on RECIST and irRECIST, and progression free survival (PFS), duration of stable disease (DOSD), and DOR (duration of response).
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2.2. Part 2 Dose Expansion

Primary Objective(s):	Primary Endpoint(s):
• To further characterize the safety and tolerability of PF-06801591 following SC administration in NSCLC and urothelial carcinoma.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy PF-06801591 administered by SC administration. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.
• To estimate clinical efficacy by overall response rate (ORR) of PF-06801591 following SC administration in NSCLC and urothelial carcinoma.	• ORR as assessed using RECIST version 1.1 and irRECIST.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To further evaluate preliminary anti-tumor activity of PF-06801591 following SC administration.	• Time to event endpoints by PF-06801591 administered by SC based on RECIST and irRECIST, including time to response (TTR) and time to progression (TTP) as well as PFS (and irPFS as appropriate), DOSD (and irDOSD as appropriate), and DOR (and irDOR as appropriate).
• To evaluate overall survival (OS).	• Median time to death, proportion of patients alive at 6 months, 1 year, and 2 years.
• To collect PF-06801591 drug concentration data in patients following SC administration for evaluation of population PK.	• Trough PF-06801591 concentrations for selected cycles.
• To evaluate the immunogenicity of PF-06801591 following repeated SC administration.	• Incidence of ADA and NAb against PF-06801591 administered by SC.
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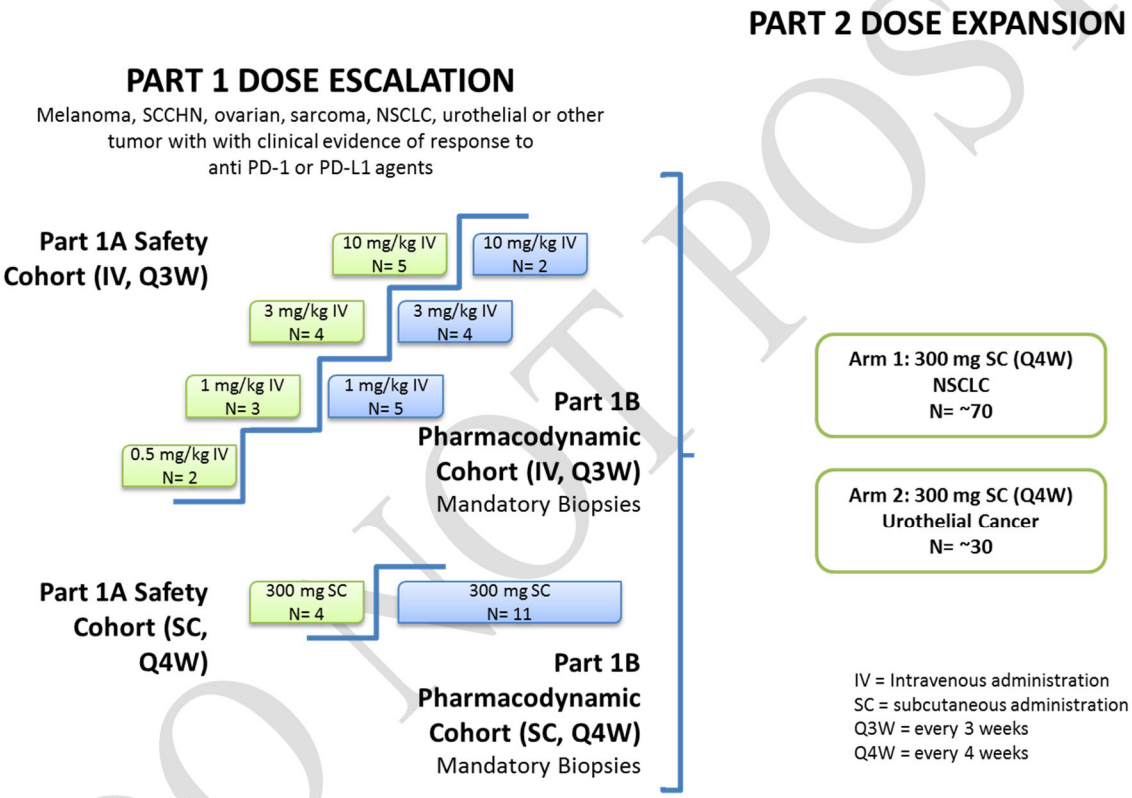
3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open-label, multi-center, multiple-dose, dose escalation and expansion, safety, PK, and pharmacodynamic study of PF-06801591 in previously treated patients with locally advanced or metastatic solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents. This clinical trial will include 2 parts: Part 1 dose escalation, and Part 2 dose expansion (see Figure 4). A total of approximately 140 patients will be enrolled into this study.

Figure 4. B8011001 Study Schematic



Part 1 will enroll patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma, or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents. Patients will receive 0.5, 1, 3, or 10 mg/kg PF-06801591 intravenously (IV) every 3 weeks (q3w), or 300 mg PF-06801591 subcutaneously (SC) every 4 weeks (q4w).

Part 1 will be further divided into Part 1A (safety cohort) and Part 1B (pharmacodynamic cohort). For both IV and SC administration portions, each safety cohort will enroll 2-4 patients per dose level. For IV administration portion, each pharmacodynamic cohort will enroll 2 to 5 patients per dose level. For SC administration portion, up to approximately 11 patients will be enrolled into the 300 mg dose level in Part 1B. Approximately 40 patients will be enrolled into Part 1.

All patients in Part 2 will receive 300 mg PF-06801591 subcutaneously q4w. Part 2 dose expansion will include 2 arms: Arm 1 will enroll approximately 70 patients with NSCLC who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable but have not previously received anti-PD-1 or anti-PD-L1. Arm 2 will enroll approximately 30 patients with urothelial cancer who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable but have not previously received anti-PD-1 or anti-PD-L1. Approximately 100 patients will be enrolled into Part 2.

All patients:

1. Will undergo up to 4 weeks of screening prior to study entry.

2. Receive treatment with investigational product for up to 2 years, or until one of the following:

    a. Disease progression by immune-related Response Evaluation Criteria in Solid Tumors (irRECIST, confirmed progressive disease [PD] or initial PD followed by rapid clinical deterioration), or

    b. Unacceptable toxicity occurs, or

    c. Withdrawal of consent, or

    d. Patient no longer willing to participate in trial, or

    e. Study termination.

    Any additional treatment beyond 2 years shall be discussed and approved by the sponsor. Patients will be allowed to stay on treatment in the case of initial radiological disease progression, if the investigator feels that it is in the patient's best interest. For example, if a patient does not have rapid clinical deterioration after initial assessment demonstrating unconfirmed PD. If a patient has a confirmed CR (ie, 2 consecutive CR assessments at least 4 weeks apart) by irRECIST, patient may also discontinue treatment at the discretion of the investigator and continue follow-up assessments.

3. Will complete a 1 month follow-up visit after the last dose for adverse event (AE) collection and serious adverse event (SAE) follow-up if necessary.

4. Will undergo assessment for late irAEs up to 120 days after completion of PF-06801591 administration (see Section 6.4 Follow-up for Late Immune-related Adverse Events).

5. After the 120-day follow-up period, the patient will be contacted by telephone every 8 weeks for survival data collection until end of trial (2 years from last patient first dose [LPFD], see Section 13.2). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call. After the completion of the end of treatment (EOT) visit subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in 120 day safety follow-up, and subsequently during survival follow-up.

3.1.1. Part 1 Dose Escalation

Part 1 will study sequential cohorts (0.5, 1, 3, and 10 mg/kg IV, or 300 mg SC) of PF-06801591 in adult patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma, or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents who are unresponsive to currently available therapies or for whom no standard therapy is available.

Part 1 will be further divided into Part 1A (safety cohort) and Part 1B (pharmacodynamic cohort). For both IV and SC administration portions, each safety cohort will enroll 2-4 patients per dose level. A mTPI method,[7] targeting a DLT rate of 27.5% will be utilized for dose escalation. In the IV administration portion, if based on Part 1A information the dose level is deemed safe and well- tolerated, an additional 2 to 5 patients will enroll into the same dose level in Part 1B. In the SC administration portion, if based on Part 1A information the 300 mg dose level is deemed safe and well- tolerated, up to an additional 11 patients (approximately) will be enrolled into Part 1B. Up to approximately 9 patients may be enrolled into each dose level in the IV administration portion, and up to approximately 15 patients may be enrolled into the 300 mg SC administration cohort (Part 1A and Part 1B combined). The mTPI approach would be applied across Parts 1A and 1B to ensure that administered doses do not surpass the toxicity boundaries. Safety data from all patients in Parts 1A (safety cohort) and available data at cutoff from Parts 1B (pharmacodynamic cohort) will be used to determine the MTD. Tumor biopsies collected at pre and post treatment time points (screening and C2D8) are mandatory for all Part 1B patients.

For patients enrolled into IV administration portion, each cycle will be 3 weeks and DLT observation period will be 21 days. For patients enrolled into subcutaneous dosing portion, each cycle will be 4 weeks and DLT observation period will be 28 days. Patients will receive 1 dose of PF-06801591 per cycle. A staggered start will be employed at all dose levels in both the IV and SC administration portions: a single patient will be dosed and observed for 48 hours. If no safety concerns arise during this 48-hour period, a second patient will be enrolled into the same dose level cohort.

Available safety information, provided by additional patients enrolled into each dose level expansion will also be taken into account for MTD determination. If the DLT rate is estimated to reach >33% or more at any dose level, enrollment at that level and all higher levels will be temporarily stopped, and safety data will be analyzed. The decision to move forward with enrollment will follow the same DLT target as described previously. Dose escalation will continue until an MTD has been established or a pre-specified maximum dose level has been reached.

The proposed doses, schedules and PK time points may be reconsidered and amended during the study based on emerging safety and PK data. Furthermore, in addition to the proposed dose levels, lower, intermediate, or higher dose levels may be explored (to a maximum of 20 mg/kg IV). For example, if DLT or clear efficacy is observed at 0.5 mg/kg IV, lower dose levels might be tested. Alternatively, if the MTD has not been reached at 10 mg/kg IV, and tumor specific immunomodulatory effects show evidence of not being maximized, higher dose levels might be tested. Higher dose levels will only be initiated if the lower dose level is deemed tolerable. For SC administration, a lower dose level of 150 mg maybe considered if toxicity boundary is exceeded per mTPI (see Section 9.2.1).

3.1.2. Part 2 Dose Expansion

Part 2 dose expansion will include 2 arms: Arm 1 will enroll approximately 70 patients with NSCLC who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable but have not previously received anti-PD-1 or anti-PD-L1. Arm 2 will enroll approximately 30 patients with urothelial cancer who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable but have not previously received anti-PD-1 or anti-PD-L1. All patients in Part 2 will receive 300 mg PF-06801591 subcutaneously q4w. The 300 mg SC dose level in Part 2 was selected based upon safety, PK, PD, and preliminary anti-tumor activity observed in Part 1, as well as the maximum injection volume considered feasible with the current formulation.

When the first 30 NSCLC patients have been enrolled and have either completed their first tumor assessment (at approximately 8 weeks post treatment), or have discontinued from the study before their first scheduled tumor assessment, preliminary assessment of safety and efficacy data maybe completed. This preliminary data may provide guidance in the decision to the increase or decrease the sample size of each arm, to add other tumor types in a future amendment, or to initiate additional clinical studies.

3.1.3. Starting Dose

The initial starting dose of PF-06801591 IV (Part 1) is 0.5 mg/kg, to be given on Day 1 of each 21-day cycle.

3.1.4. Criteria for Dose Finding

Maximum Tolerated Dose Selection for IV Administration

An mTPI method,[7] targeting a DLT rate of 27.5% and an acceptable DLT interval (22.5% to 32.5%), will be utilized in the Part 1A dose escalation phase. The IV dose levels to be evaluated for the MTD following IV administration are listed in Table 2. If a high DLT rate is observed at the starting dose, the study may explore a lower dose than the starting dose or be stopped. Cohorts of 2 to 4 patients (Part 1A) will be enrolled at each selected dose level. The required number of patients per dose level will be managed according to Table 3.

Table 2. Table of Pre-Specified PF-06801591 IV Dose Levels

Dose Level	Dose (mg/kg)
1	0.5
2	1.0
3	3.0
4	10

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in the current dose level to determine one of the following dose-finding decisions: the subsequent dose should be escalated, maintained at the current dose, or de-escalated in the next cohort of 2 to 4 patients (Part 1A), or the trial should be terminated (Table 3).

In principle, all patients must be evaluated for a minimum period of 21 days. If a patient withdraws from the study before Day 21 for reasons other than drug-related toxicity, another patient may be enrolled to replace that patient in the current cohort. However, if a patient discontinues close to Day 21 for reasons other than toxicity and due to an evident non drug-related event, the patient may be deemed evaluable for safety if safety assessments have been unremarkable and the investigator and sponsor's medical monitor both agree that the patient is evaluable for DLT safety observation.

1. The dose escalation Part 1 of the study will stop if any of the following criteria is met:

2. The maximum sample size has been achieved (approximately 40 patients in total);

3. 6 to 15 patients have been enrolled at a dose level that is predicted to be the MTD per the mTPI method; All dose levels explored appear to be overly toxic, and the MTD cannot be determined;

4. All pre-specified dose levels have been tested and all doses were deemed tolerable.

Table 3. Decision Rules for IV Administration

Number of Patients having DLT	Number of Patients Treated at a Dose Level													
	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12	n=13	n=14	n=15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E	E	E
2	U	D	S	S	S	S	S	S	S	E	E	E	E	E
3		U	U	D	D	S	S	S	S	S	S	S	S	S
4			U	U	U	U	D	D	D	S	S	S	S	S
5				U	U	U	U	U	D	D	D	D	D	S
6					U	U	U	U	U	U	U	D	D	D
7						U	U	U	U	U	U	U	U	U

Actions to be taken:
D = De-escalate the dose; E: Escalate the dose; S: Stay at the dose.
U = Unacceptable toxicity.

The SC dose data will not be used for IV dose escalation decision and the IV MTD determination. The mTPI approach as shown in Table 3, however, will be applied to ensure that administered SC dose does not surpass the toxicity boundaries. Subcutaneous doses may be de-escalated to 150 mg if the toxicity boundary is exceeded by the mTPI approach.

Intra- patient dose reductions may also occur upon discussion with the sponsor.

3.1.5. Dose-limiting Toxicity Definition

Previous anti-PD-1 mAbs were administered in >1000 patients and were associated in the clinic with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-mediated adverse reactions), likely to be related to the mechanism of action. Immune-mediated adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems.[12]

Severity of AEs will be graded according to CTCAE version 4.03. For the purpose of a dose finding decision, any of the following drug-related AEs occurring during the first cycle of treatment (21 days for IV, or 28 days for SC) will be classified as DLTs following review by the investigators and the sponsor:

- **Grade 5 AE**
- **Hematologic toxicity:**
  - Any Grade 4 hematologic AE, with the following clarifications:
  - Grade 4 neutropenia lasting >5 days from initiation of granulocyte-colony stimulating factor.

- Grade 4 thrombocytopenia with bleeding.
- Platelet transfusion requirement or a platelet count <10,000/uL.

- **Non-Hematologic Toxicity**
  - Grade 4 non-hematologic AE;
  - Grade 3 AE lasting >7 days despite optimal supportive care (see Appendix 8);
  - Grade 3 central nervous system AE regardless of duration;
  - Meets criteria for drug-induced liver injury (Section 8.6.2).

The following AEs will not be adjudicated as DLTs:

- Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement.
- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor).
- Isolated Grade 3-4 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Grade ≥3 infusion reactions and allergic reactions will not be considered dose limiting as they are unlikely to be dose related, but all available information on these events will be collected. If Grade ≥3 infusion reactions occur in ≥2 of the first 10 patients at any dose level, or if the occurrence is ≥5% thereafter, a mandatory pre-treatment regimen for all new patients will be implemented. The incidence of Grade 1 and 2 reactions will also be taken into account. If a total rate of >10% all-grade infusion or allergic reactions is observed, a mandatory pre-treatment regimen for all new patients will be implemented.

Information regarding the DLT observation period can be found in the Criteria for Dose Finding (Section 3.1.4). For dose escalation, DLT observation is required for 21 days for IV administration, or 28 days for SC administration. However, DLT observation will continue for at least 120 days from first dose (or completion of 5 cycles, if still on treatment) to assess late immune-related dose-limiting AEs, and available data from Part 1B at data cut off will be taken into account for MTD determination.

3.1.5.1. Late Immune-Related Dose-Limiting Toxicities

Late immune-related DLTs are irAEs (see Appendix 8) that meet the same grading criteria as DLT criteria but occur after the initial 21-day DLT period for IV administration, or 28 days for SC administration, and during the 120-day assessment period. Late immune-related DLTs will be added to the mTPI approach to reassess the dose-finding decisions (see Table 3).

For any patient being treated at dose levels that are subsequently considered to exceed the MTD, the option to reduce their dose will be discussed between the investigator and the sponsor's medical monitor. If the patient tolerated the above-MTD dose level well and is deriving clinical benefit, continuation of treatment at the above-MTD dose level will require re-consenting.

3.1.6. Maximum Tolerated Dose Definition

The MTD is defined as the highest dose with true toxicity probabilities in the equivalence interval (EI) where the EI is defined as 22.5%-32.5%.

In practice, the MTD will be the highest dose associated with the occurrence of DLTs ≤33% (eg, ≤3 of 9 evaluable patients experience a DLT during at least [90 days after the first dose]) or the first 5 treatment cycles if the patient remains on treatment.

3.1.7. Optimal Biological Dose Definition

The OBD is the lowest dose that can produce an efficacious and/or pharmacodynamic effect that is consistent with the proposed mechanism and with an acceptable toxicity. Examples of such a pharmacodynamic effect in peripheral blood may include increased expression of CD8+ T cell proliferation or activation markers such as Ki-67 or HLA-DR. Increased CD8+ T cell infiltration into melanoma tumor tissue has been observed in patients who exhibit a clinical response to PD-1 blockade.[52] In this study, pharmacodynamic effects that will be monitored to support the identification of the OBD will include, but not be limited to, change from baseline in Ki-67 and HLA-DR expression on peripheral blood CD8+ T cells and intratumoral CD8+ T cell and FoxP3+ regulatory T cell density in response to dosing with PF-06801591. Note: In addition to pharmacodynamic biomarkers, preliminary anti-tumor activity (CR, partial response [PR]), if observed, will also be taken into consideration.

3.1.8. Recommended Phase 2 Dose (RP2D) Definition

The 300 mg SC dose has been selected for Part 2 expansion based on existing PK, pharmacodynamic, safety, and preliminary efficacy data (see Section 1.9.1 Clinical Experience in Study B8011001). If anti-tumor efficacy and safety at this dose level is confirmed in Part 2, 300 mg SC q4w administration will be the recommended Phase 2 dose (RP2D) chosen for further investigational study.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

4.1.1. Part 1 Dose Escalation

1. Histological or cytological diagnosis of locally advanced metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, or urothelial carcinoma. Other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents (eg, mismatch repair deficient tumors, small cell lung cancer, renal cell carcinoma, gastric cancer, triple negative breast cancer, hepatocellular carcinoma) are required to be reviewed and approved by the sponsor prior to enrollment:

    - Patient must not be previously treated with anti PD-1 or PD-L1 agents.

    - Patient should have received at least 1 prior line of therapy for recurrent or metastatic disease, including both standards of care and investigational therapies. Patient must have progressed/relapsed, be refractory, or intolerant to standard therapy approved for the specific tumor type. Exception: Patients who actively decline chemotherapy or other standard therapies including approved anti PD-1 or PD-L1 agents for the treatment of advanced disease (unresectable or metastatic) are eligible upon documentation of their refusal.

    - A mandatory archived formalin-fixed paraffin embedded (FFPE) tumor tissue block (preferred) must be provided. If an FFPE tumor tissue block cannot be provided, sites should contact sponsor for approval to submit slides. Cytological or fine-needle aspiration samples are not acceptable. For Part 1A or 2, if an archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample can substitute and should be obtained in accordance with local institutional practice for tumor biopsies. For Part 1B, the archived FFPE tumor tissue sample is highly encouraged but can be waived if not available.

2. At least one measurable lesion as defined by RECIST version 1.1.

3. For Part 1B expansion cohorts: patient has consented to undergo a pre-treatment and on-treatment biopsy.

4. Adult (male or female) aged ≥18 years.

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 6).

6. In the opinion of the investigator, patient's current clinical status is likely to allow for at least 8 weeks of study treatment.

7. Adequate bone marrow function, as follows:

    a. White blood cells (WBC) ≥2,000/mm^3 or ≥2.0 x 10^9/L;

    b. Absolute neutrophil count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;

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

    d. Hemoglobin ≥9 g/dL. Limited transfusions to reach this value are allowed, after discussion with sponsor's medical monitor. There should not be a chronic need for transfusions in the recent past (approximately 3 months).

8. Adequate Renal Function, as follows:

    a. Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance (CrCl) ≥40 mL/min as measured or calculated using the Cockcroft-Gault formula below:

        - Female CrCl = [(140 - age in years) x weight in kg x 0.85]/[72 x serum creatinine in mg/dL];

        - Male CrCl = [(140 - age in years) x weight in kg x 1.00]/[72 x serum creatinine in mg/dL];

        If an estimated CrCl is believed to be inaccurate for a patient, 24-hour urine collection with actual assessment of CrCl is allowed.

9. Adequate Liver Function including:

    a. Total serum bilirubin ≤1.5 x ULN except patients with Gilbert syndrome who should have total serum bilirubin <3 x ULN;

    b. Aspartate and alanine aminotransferase (AST & ALT) ≤3.0 x ULN.

10. Thyroid stimulating hormone (TSH) within normal limits (WNL) for institution; supplementation is acceptable to achieve a TSH WNL; in patients with abnormal TSH if Free T4 and Free Thyroxine Index are normal and patient is clinically euthyroid, patient is eligible.

11. International Normalized Ratio (INR) or activated partial prothrombin time (aPTT) <1.5 x ULN.

12. Negative serum or urine pregnancy test (for women of childbearing potential) at screening and at the baseline visit (before the patient may receive the investigational product).

13. Male patients who are able to father children, and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 5 months after the last dose of assigned treatment.

14. Female patients who are not of childbearing potential as defined below, are eligible to be included (ie, meet at least one of the following criteria):

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

    b. Have medically confirmed ovarian failure; or

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

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

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

4.1.2. Part 2 Dose Expansion

1. Either histological or cytological diagnosis of locally advanced or metastatic NSCLC or locally advanced or metastatic urothelial carcinoma who have progressed on or were intolerant to standard of care systemic therapy, or for whom standard of care systemic therapy was refused (refusal must be documented) or unavailable.

2. No prior treatment with anti-PD-1 or anti-PD-L1 therapy.

3. NSCLC patients whose tumor <u>is not known</u> to have anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) mutation must not have received more than 1 line of prior systemic therapy and must have either:

    a. Progressed on or after platinum-containing systemic therapy, or

    b. Were intolerant to standard of care systemic therapy or

    c. Refused standard of care systemic therapy (refusal must be documented).

4. NSCLC patients whose tumor <u>is known</u> to be ALK or EGFR mutation positive must have received prior systemic therapies that only include one or more lines of ALK or EGFR targeting drugs and chemotherapy limited to one line of a platinum-based regimen, and they must have progressed on or after both types of therapies.

5. Urothelial carcinoma patients must have received up to 2 lines of prior systemic therapy and either:

    a. Progressed on or after platinum-containing systemic therapy, or

    b. Were intolerant to platinum-containing systemic therapy, or

    c. Had disease recurrence within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, or

    d. Were ineligible for platinum-containing systemic therapy, or

    e. Refused standard of care systemic therapy (refusal must be documented).

If patients are treatment naïve and eligible for platinum-containing systemic therapy but are refusing platinum chemotherapy, they must also be documented to have previous PD-L1 high status as defined in the following table:

PD-L1 assay	Result	Threshold for PD-L1 High
Dako 28-8	TC	≥5%
Dako 22C3	CPS	≥10%
Ventana SP142	IC	IC ≥5% and <10% (IC2); or, IC ≥10% (IC3)
Ventana SP263	TC, IC, ICP	TC ≥25%; or, ICP >1% and IC ≥25%; or, ICP = 1% and IC = 100%

TC: Tumor cells
CPS: Combined positive score
IC: Immune cells
ICP: Immune cells present

6. Patients must be able to provide an archived formalin-fixed paraffin embedded (FFPE) tumor tissue sample (block preferred). The sample must be taken within 2 years of start of study treatment. If an FFPE tumor tissue block cannot be provided, sites should contact sponsor for approval to submit slides. Cytological or fine-needle aspiration samples are not acceptable. A de novo (ie, fresh) tumor sample can be utilized as a substitute if an archived FFPE tissue is not available, and should be obtained in accordance with local institutional practice for tumor biopsies. Samples provided should be taken from the most recently conducted available biopsy.

7. At least one measurable lesion as defined by RECIST version 1.1.

8. Adult (male or female) aged ≥18 years.

9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 6).

10. In the opinion of the investigator, patient's current clinical status is likely to allow for at least 8 weeks of study treatment.

11. Adequate bone marrow function, as follows:

    - WBC $\geq$2,000/mm^3 or $\geq$2.0 x 10^9/L,
    - ANC $\geq$1,500/mm^3 or $\geq$1.5 x 10^9/L,
    - Platelets $\geq$100,000/mm^3 or $\geq$100 x 10^9/L,
    - Hemoglobin $\geq$9 g/dL. Limited transfusions to reach this value are allowed, after discussion with sponsor's medical monitor. There should not be a chronic need for transfusions in the recent past (approximately 3 months).

12. Adequate Renal Function, as follows:

    Serum creatinine $\leq$1.5 x upper limit of normal (ULN) or estimated creatinine clearance (CrCl) $\geq$30 mL/min as measured or calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.[63,64] If an estimated CrCl is believed to be inaccurate for a patient, 24-hour urine collection with actual assessment of CrCl is allowed.

13. Adequate Liver Function including:

    - Total serum bilirubin $\leq$1.5 x ULN except patients with Gilbert syndrome who should have total serum bilirubin <3 x ULN;
    - Aspartate and alanine aminotransferase (AST & ALT) $\leq$3.0 x ULN.

14. Thyroid stimulating hormone (TSH) within normal limits (WNL) for institution; supplementation is acceptable to achieve a TSH WNL; in patients with abnormal TSH if Free T4 and Free Thyroxine Index are normal and patient is clinically euthyroid, patient is eligible.

15. International Normalized Ratio (INR), activated partial prothrombin time (aPTT) or partial thromboplastin time (PTT) <1.5 x ULN.

16. Negative serum or urine pregnancy test (for women of childbearing potential) at screening and at the baseline visit (before the patient may receive the investigational product).

17. Male patients who are able to father children, and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 5 months after the last dose of assigned treatment.

18. Female patients who are not of childbearing potential as defined below, are eligible to be included (ie, meet at least one of the following criteria):

    - 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; a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

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

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

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

4.2.1. Part 1 Dose Escalation

1. Active brain or leptomeningeal metastases. Patients with brain metastases are eligible if these have been treated and magnetic resonance imaging (MRI) shows no evidence of progression for at least 8 weeks after treatment is complete and within 4 weeks prior to first dose of study drug. Patients are not eligible if they required high doses of systemic corticosteroids that could result in immunosuppression (>10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2. Ocular melanoma.

3. Active, known or suspected autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy or prior allogeneic bone marrow or hematopoietic stem cell transplant.

4. Active hepatitis B virus (HBV) or hepatitis C virus (HCV).

5. True positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

6. Patient is receiving chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study drug (exception: palliative radiotherapy to a limited field is allowed after consultation with Pfizer's medical monitor).

7. Patient has AE(s) due to cancer therapeutics administered >4 weeks earlier, which have not recovered to CTCAE Grade ≤1 (except alopecia, and except for AEs not constituting a safety risk by investigator judgment).

8. Patients with a history of interstitial lung disease, non-infectious pneumonitis, or active pulmonary tuberculosis. Those with active lung infections requiring treatment are also excluded.

9. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

10. History of Grade ≥3 immune-mediated AE (including AST/ALT elevations that where considered drug related and cytokine release syndrome) that was considered related to prior immune-modulatory therapy (eg, immune checkpoint inhibitors, co-stimulatory agents, etc.) and required immunosuppressive therapy.

11. Patients with intolerance to or who have had a severe (Grade ≥3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins.

12. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsade de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF, New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism or other clinical significant episode of thrombo-embolic disease. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, or QTcF interval >470 msec at screening (except in case of right bundle branch block, these cases must be discussed with sponsor's medical monitor). Cases must be discussed in detail with sponsor's medical monitor to judge eligibility. Anticoagulation (heparin only, no vitamin-K antagonists or factor Xa inhibitors) will be allowed if indicated.

13. Other malignancy within 5 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason 6 or below) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration) or other concurrent malignancy investigator feels has a very low likelihood to become metastatic.

14. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective method(s) of contraception as outlined in this protocol for the duration of the study and for at least 5 months after the last dose of investigational product or longer based upon the compound's half-life characteristics.

15. 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 patient inappropriate for entry into this study.

16. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

17. Patients 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 patients who are Pfizer employees directly involved in the conduct of the study.

4.2.2. Part 2 Dose Expansion

1. Active brain or leptomeningeal metastases. Patients with brain metastases are eligible if these have been treated and magnetic resonance imaging (MRI) shows no evidence of progression for at least 8 weeks after treatment is complete and within 4 weeks prior to first dose of study drug. Patients are not eligible if they required high doses of systemic corticosteroids that could result in immunosuppression (>10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2. Other malignancy within 5 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason 6 or below) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration) or other concurrent malignancy investigator feels has a very low likelihood to become metastatic.

3. Active hepatitis B virus (HBV) or hepatitis C virus (HCV). For example, patients with HBV surface antigen positive or HCV RNA positive will be excluded.

4. True positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

5. Active, known or suspected autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy or prior allogeneic bone marrow or hematopoietic stem cell transplant.

6. Patients with a history of interstitial lung disease, non-infectious pneumonitis, or active pulmonary tuberculosis. Those with active lung infections requiring treatment are also excluded.

7. Patient has AE(s) due to cancer therapeutics administered >4 weeks earlier, which have not recovered to CTCAE Grade ≤1 (except alopecia, and except for AEs not constituting a safety risk by investigator judgment).

8. History of Grade ≥3 immune-mediated AE (including AST/ALT elevations that where considered drug related and cytokine release syndrome) that was considered related to prior immune-modulatory therapy (eg, immune checkpoint inhibitors, co-stimulatory agents, etc.) and required immunosuppressive therapy.

9. Patients with intolerance to or who have had a severe (Grade ≥3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins.

10. Patient is receiving chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study drug (exception: palliative radiotherapy to a limited field is allowed after consultation with Pfizer's medical monitor).

11. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

12. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsade de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF, New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism or other clinical significant episode of thrombo-embolic disease. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, or QTcF interval >470 msec at screening (except in case of right bundle branch block, these cases must be discussed with sponsor's medical monitor). Cases must be discussed in detail with sponsor's medical monitor to judge eligibility. Anticoagulation (heparin only, no vitamin-K antagonists or factor Xa inhibitors) will be allowed if indicated.

13. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective method(s) of contraception as outlined in this protocol for the duration of the study and for at least 5 months after the last dose of investigational product or longer based upon the compound's half-life characteristics.

14. 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 patient inappropriate for entry into this study.

15. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

16. Patients 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 patients who are Pfizer employees directly involved in the conduct of the study.

17. For South Korea only, vaccination except inactivated vaccine within 4 weeks prior to the enrollment on the study or during the study.

18. For South Korea only, patients with active infection requiring systemic therapy will be excluded.

4.3. Lifestyle Guidelines

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive PF-06801591, which is a compound for which the teratogenic risk is currently unknown. Two methods of highly effective contraception must be used throughout the study and continue for at least 5 months after the last dose. The investigator or his/her designee, in consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his/her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly according to the Schedule Of Activities and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued or if pregnancy is known or suspected in the patient or patient'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:

1. Established use of oral, inserted, injected, implanted, or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device.

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

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

5. Bilateral tubal ligation or 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, and have a serum 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 coordinator's manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient 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 patient'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 patient directly, and if a patient 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 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

In Part 1, eligible patients will be enrolled to receive PF-06801591 in an open-label, unblinded manner. Patients will be registered and successively assigned to the next available treatment slot at a dose level decided upon after the previous cohort's safety evaluation and ongoing observations of earlier enrolled patients (or to a dose of 0.5 mg/kg IV, if being recruited for the first cohort). In Part 2, all eligible patients will receive a SC 300 mg flat dose administration of PF-06801591 in an open-label unblinded manner.

Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation and administration rate.

5.1.1. Part 1 Dose Escalation

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will email a complete Registration Form to the designated sponsor study team member. The sponsor will assign a patient identification number, which will be used on all case report forms (CRFs) and other study-related documentation or correspondence referencing that patient and email to the site.

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

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

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date. Treatment should begin no longer than 3 days from registration.

5.1.2. Part 2 Dose Expansion

Once the patient provides their written informed consent, and screening procedures have been completed to confirm that they meet all inclusion and exclusion criteria, the patient enrollment number will be assigned through the use of an interactive response technology (IRT) system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the patient identification number and the date of birth (if allowed by local authorities; if not, only the year of birth will need to be provided) of the patient. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when drug is being supplied via the IRT system. The IRT system will provide a confirmation report containing the patient identification number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Patient Compliance

The site will complete required dosage Preparation Record located in the study Investigational Product (IP) 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

PF-06801591 will be supplied by Pfizer.

Study centers will receive a supply of Clinical Trial Material upon activation with instructions on how to confirm drug receipt. Resupplies will be made during the course of the study based on need. The details on drug supply will be provided in the Investigational Product Manual. The study monitor should be contacted for any issues related to drug supplies.

[redacted]

[redacted]

5.3.2. Preparation and Dispensing

See the Dosage and Administration Instruction (DAI) located in the IP Manual for instructions on how to prepare the investigational product for administration. Each vial is designed for single use. 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.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of biologic agents.

5.4. Administration

5.4.1. IV Administration (Part 1 Only)

PF-06801591 will be administered intravenously, with adjustment for body weight at every cycle. Patient actual body weight will be used to calculate the mg/kg dose, and the calculated dose will be rounded off to the second decimal point. In each cycle, patients should be weighed within 72 hours prior to dosing to ensure they did not experience weight loss/gain of >10% from the prior weight used for PF-06801591 dose preparation calculations.

The decision to recalculate PF-06801591 dose based on the weight obtained at each cycle may be in accordance with institutional practice; however if the patient experienced either a weight loss or gain of >10% compared to the weight used to calculate the most recent dose, the amount of PF-06801591 required for study drug preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

PF-06801591 will be administered on an outpatient basis as an IV infusion on Day 1 of each 21-day treatment cycle, initially over 60 minutes ±10 minutes. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the investigational product, but gravity drips are allowed. Refer to the Investigation Product (IP) Manual for infusion rate and duration.

A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, IV administration cycles will be once every 21 days (+/- 2 days). Each patient may receive PF-06801591 until disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

The dose level for Part 1 will be assigned by the sponsor.

5.4.2. SC Administration (Parts 1 and 2)

Qualified and trained investigator site personnel will administer PF-06801591 at a fixed dose of 300 mg to patients by SC injection to the abdomen. A total volume of 6 mL must be administered subcutaneously for a dose of 300 mg of PF-06801591. Ideally, 3 subcutaneous injections of 2 mL should be administered to the abdomen, although, more injections can be done as needed, in order to have a total volume of 6 mL.

Study drug should be administered to two or more different quadrants of the abdomen (with preference given to the lower quadrants when possible); 1 or 2 injections per quadrant. The maximum number of injections per patient is 8 injections. Refer to Appendix 9 for details on administration of multiple injections to the abdomen. Study staff should refer to the IP Manual for specific instructions on the handling and administration of study drug.

Similar to intravenous dosing, a cycle is defined as the time from Day 1 dose to the next Day 1 dose. Patients will receive a single dose of PF-06801591 on Day 1 of each cycle. If there are no treatment delays, a cycle will be 28 days (+/- 2 days) for SC administration. Each patient may receive PF-06801591 until disease progression, unacceptable toxicity, withdrawal of consent, patient no longer willing to participate in trial, or study termination.

5.4.3. 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 as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of two ways:

- Within a cycle: dosing interruption until adequate recovery, 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.

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

5.4.3.1. Rules For Dose Delay/Interruption/Discontinuation

Events including, but not limited to, pneumonitis, colitis, creatinine, and liver function test (LFT) elevation should be monitored carefully with this class of agents. To facilitate the early recognition and prompt intervention in the event of clinically AEs related to study treatment, management algorithms have been developed for suspected pulmonary, gastrointestinal, liver, endocrine, skin, cardiac, renal, or other immune-related toxicities (See Appendix 8). For non-irAEs, please refer to the rules for dose delay/interruption/discontinuation below:

- Withhold treatment for: creatinine, AST, ALT, or total bilirubin for drug-related Grade 2 elevations except if they were >ULN at baseline.
- Withhold treatment for any other Grade 3 drug-related AEs.
- Resume treatment when drug-related AE recovers to Grade 0-1 except when creatinine, AST, ALT, or total bilirubin were >ULN at baseline.
- Discontinue treatment for drug-related Grade 3-4 creatinine, AST, ALT, or total bilirubin elevations except if they were >ULN at baseline.
- Discontinue treatment for any other Grade 4 drug-related AEs or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to <Grade 4 within 1 week of onset.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Discontinue treatment for persistent Grade 2-3 drug-related AE that do not recover to Grade 0-1 within 12 weeks after last dose except when creatinine, AST, ALT, or total bilirubin were >ULN at baseline.
- Discontinue treatment for any Grade 3-4 drug-related AE that recurs.
- If creatinine >ULN at baseline, withhold treatment for drug-related elevation >1.5 x baseline and resume when ≤1.5 x baseline. Discontinue treatment with drug-related elevation >3 x baseline or drug-related elevation that does not recover to ≤1.5 x baseline within 12 weeks after last dose.
- If AST, ALT, or bilirubin >ULN at baseline, withhold treatment for drug-related elevation >2 x baseline and resume when ≤2 x baseline. Discontinue treatment with drug-related elevation >3 x baseline or drug-related elevation that does not recover to ≤2 x baseline within 12 weeks after last dose.

- Discontinue treatment for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued PF-06801591 dosing.

- Isolated Grade 3-4 laboratory abnormalities that are not associated with clinical sequelae and/or are corrected with supplementation/appropriate management within 72 hours of their onset and may not necessarily lead to discontinuation of treatment, if agreed upon by the Medical Monitor and the Principal Investigator.

5.4.3.2. Infusion Reactions

Following the first administration of some antibody therapeutics, some patients experience fever, headache, nausea, vomiting, or hypotension. These AEs are generally ascribed to lysis of cellular targets, cytokine release, or complement activation.

Clinical management of these events, and the use of pretreatments for subsequent doses, are discussed in Appendix 7.

5.4.3.3. Hypersensitivity Types 1 and 3

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of administration and may include symptoms such as rash, urticaria, polyarthritis, myalgias, polysynovitis, fever, and, if severe, glomerulonephritis.

All patients should be closely observed while receiving investigational product and monitoring for clinical signs of a systemic reaction will continue thereafter for clinical signs of allergic reactions/hypersensitivity.

Clinical management of these events is discussed in Appendix 7.

5.4.3.4. Extravasation

In the event of extravasation IV infusions should be stopped immediately and the investigator needs to be consulted immediately. Treatment of extravasation should follow local standard of care.

5.4.3.5. Immune-Related Adverse Events

While theoretically any immune checkpoint–blockade toxicity can occur at any time, certain toxicities have been reported earlier in the treatment course, while others develop as later complications. Commonly encountered irAEs include rash/dermatitis, diarrhea/colitis, hepatitis, and endocrinopathies. Algorithms for the clinical management of these events are provided in Appendix 8.

Prior to administration of the next dose of PF-06801591, the investigator should perform a comprehensive review of systems with specific focus on common and serious toxicities, such as skin changes, diarrhea and abdominal pain, headache, fever, shortness of breath, cough, and neurologic changes. Routine laboratory testing, including hematologic profile, comprehensive metabolic panel, and TSH level, should be reviewed. Any new symptoms or abnormalities in examination or laboratory test results should be evaluated prior to administration of the next dose of PF-06801591.

5.4.5. Dose Delays

Patients experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment interrupted/delayed (see Section 5.4.3). Appropriate follow-up assessments should be done until adequate recovery (or until deemed irreversible) occurs as assessed by the Investigator.

Treatment resumption for patients recovering from treatment-related toxicity after 4 weeks of treatment interruption or cycle delay can be considered only if the patient 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.

If a treatment interruption continues beyond Day 21 (for IV) or Day 28 (for SC) of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

5.4.6. Dose Reductions

Intra-patient dose reductions are not permitted during the study unless it has been agreed upon following discussions with the sponsor. For example, during Part 1, if a patient's current dose level is deemed beyond the determined MTD.

Subcutaneous doses may be de-escalated to 150 mg if the toxicity boundary is exceeded by the mTPI approach in Part 1. Intra-patient dose reductions may also occur upon 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.

Investigational product should be stored in its original container and in accordance with the label. See the Product Specific Investigation Product Manual for storage conditions of the product once reconstituted and/or diluted.

Storage conditions stated in the single reference safety document (ie, Investigator's Brochure) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (eg, 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 (eg, 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 the 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.

Receipt of materials, door opening and closing, and other routine handling operations where the product is briefly out of the temperature range described in the labeling are not considered excursions. More specific details will be provided to the sites separately.

5.6. Investigational Product Accountability

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 PF-06801591 will be accounted for in the CRF and drug accountability inventory forms as instructed by Pfizer. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused must be returned to Pfizer or its appointed agent (eg, a contract research organization [CRO]).

Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from Pfizer.

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 patient's wellbeing may be given at discretion of the treating physician.

All concomitant treatments, blood products, and saline infusions, as well as non-drug interventions (eg, analgesic use for paracentesis) received by patients from screening until the end of study visit will be recorded on the CRF including the name of the procedure or medication, route and duration of treatment, and reason (eg, AE)).

For South Korea only, patients should not have vaccinations except an inactivated vaccine within 4 weeks prior to the enrollment on the study or during the study.

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

Additional anticancer treatment including chemotherapy, hormonal therapy, radiotherapy (with the exception of palliative radiation as described in Section 5.7.8), or experimental anticancer medications are not permitted while patients are receiving study treatment. Additionally, the concurrent use of herbal supplements for an anti-cancer treatment is not permitted.

5.7.2. 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.

5.7.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during Cycle 1, but may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines.[54]

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

5.7.4. Anti-Diarrhea, Anti Emetic Therapy

Primary prophylaxis of diarrhea, nausea, and vomiting is permitted in the first cycle. Primary prophylaxis in subsequent cycles 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.

5.7.5. Anti-inflammatory and Narcotic 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. Narcotic analgesic may hide colonic perforation in case of colitis and should be used with caution. Anti-TNF drugs are contraindicated in case of perforation, sepsis, or liver insufficiency.

5.7.6. Corticosteroids

Chronic, systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purpose is not permitted. Acute emergency and short-term administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed. If immune related AEs occur, immune suppressive treatment should be administered according to local standards or practice.

5.7.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06801591 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06801591 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-06801591 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.7.8. Radiation Therapy

Palliative radiotherapy to a limited field is allowed after consultation with Pfizer's medical monitor at any time during study participation, including during screening, unless clearly indicative of disease progression.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see Schedule Of Activities and Section 7 assessments.

All patients will be screened within 28 days prior to study entry to confirm that they meet the patient selection criteria for the study.

For all patients being considered for the study and eligible for screening, informed consent must be obtained prior to any study-specific procedures. The investigator (or appropriate delegate at the site) will obtain signed and dated informed consent from each patient in accordance with the procedures described in the Schedule Of Activities and Section 12.3. A patient identification number will be assigned.

The required screening assessments, including tumor history, medical history (including baseline signs and symptoms) and laboratory tests are summarized in the Schedule Of Activities and Section 7. Following completion of the screening assessments and confirmation of eligibility, patients may be enrolled.

6.2. Study Period

For treatment period procedures, see Schedule Of Activities and Section 7 Assessments.

6.3. One Month Follow-up Visit

For follow-up procedures see Schedule Of Activities and Section 7 Assessments.

At least 28 days and no more than 35 days after discontinuation of treatment, patients will return to undergo the assessments outlined in the Schedule Of Activities as well as a review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

In the event a patient is unable to return to the clinic for the follow-up visit, telephone contact with the patient to assess AEs and concomitant medications and treatment is expected. If laboratory assessments are needed to follow-up unresolved AEs, retrieval of assessments performed at an institution local to the patient is acceptable.

6.4. Follow-up for Late Immune-related Adverse Events

Patients will undergo telephone follow-ups at 90 and 120 day (±7 days) after the last dose of study drug to assess potential late irAEs. If any concern arises, patient will be called in for an inpatient follow up visit within 5 calendar days of initial phone call. For this inpatient follow-up visit, the Schedule Of Activities will be similar to the 1-month follow-up visit completed after EOT.

Patients continuing to experience late immune-related toxicity at this point (up to 120 days after last dose of study drug) will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

6.5. Survival Follow-up

To collect OS data, patients will be contacted by telephone every 8 weeks (±7 days) post 120 day follow up visit, until end of the trial (2 years after last patient first dose). If the patient is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call. After the completion of the EOT visit subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in 120 day safety follow-up, and subsequently during survival follow-up.

6.6. Patient Withdrawal

The reason for a patient's discontinuation from treatment will be documented in the end of study/withdrawal CRF. Patients will be followed for at least 120 days after the last dose of study drug for AEs.

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient 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;*
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

*In the case of radiological progression but in the absence of clinical deterioration, if investigator deems it to be in the patient's best interests, the patient will be allowed to stay on study.

Reasons for withdrawal from study follow-up may include:

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

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

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

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

7. ASSESSMENTS

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

7.1. Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, 12-lead ECG, local site injection tolerability assessment (SC administration cohort only), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

7.1.1. Pregnancy Testing or Postmenopausal Status

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory will be performed on 2 occasions prior to starting study treatment: once at the start of screening and once at the baseline visit immediately before investigational product administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment, at the 28-day Follow-Up visit, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive human chorionic gonadotropin test, the patient will be withdrawn from treatment but may remain in the study. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy is positive. Additional pregnancy tests may also be undertaken if requested by Investigational Review Boards/Ethics Committees (IRBs/ECs) or if required by local regulations. In Poland only, pregnancy tests should be performed after end of treatment on days 28, 60, 90, 120 and 150. Pregnancy tests on days 60, 90, 120 and 150 may be collected at home by the patient.

For female patients who achieved postmenopausal status and have not experienced their menses since at least 12 consecutive month, a serum FSH test must be conducted at screening only, in order to confirm a FSH level within the laboratory's reference ranges for post menopause.

7.1.2. Adverse Events

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

Adverse events that occur during the study, after the patient receives the first dose, will be recorded on the AE CRF page.

7.1.3. Laboratory Safety Assessment

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

Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody (HCV Ab), and HIV serology testing should be conducted at screening. Other tests may be conducted per standard practice to confirm an active hepatitis or HIV infection.

All laboratory safety assessments conducted on Cycle 1 Day 1 (C1D1) must be completed prior to dosing. If baseline assessments are performed within 72 hours prior to C1D1, there is no need to repeat assessments on C1D1. Assessments performed on Cycle 2 Day 1 (C2D1) and each subsequent cycle should be performed within 48 hours prior to dosing. Investigators may have additional blood tests performed for the purpose of planning treatment administration, dose modification, or following AEs. Day 1 safety laboratory test results need to be reviewed by the investigator prior to dosing at the beginning of each cycle for dosing confirmation and administration rate.

In addition, a serum sample will be collected at pre-dose C1D1. This sample will be utilized as a baseline sample for cytokine measurement should cytokine release syndrome occurs. Optional samples for cytokine analysis will be collected throughout the study, as clinically indicated.

Table 4. Laboratory Tests

Hematology	Chemistry	Coagulation	Serology	Immunology	Urinalysis[a]	Pregnancy Test or Postmeno-pausal Status
Hematocrit	ALT	INR/PT	HBsAg, HBcAb[b]	CRP or HsCRP (Part 1 only)	Urine dipstick for urine protein: If positive, collect a spot urine to calculate UPCR or collect 24-hr and microscopic (Reflex Testing).	For female patients of childbearing potential, serum or urine test (sensitivity ≥25 mIU/mL); For female postmenopausal patients who have not experienced their menses for at least 12 consecutive months. Serum FSH test at screening only, to confirm post menopause.
Hemoglobin	AST	aPTT or PTT	HCV Ab[b]	TBNK (whole blood, Part 1 only)		
	lactate dehydrogenase (LDH)		HIV serology	Cytokine		
Platelets	Alkaline Phosphatase					
WBC	Sodium					
Absolute Neutrophils	Potassium					
Lymphocytes	Magnesium				Urine dipstick for urine blood: If positive twice or as clinically indicated perform microscopic analysis (Reflex Testing).	
Monocytes	Chloride					
Eosinophils	Total Calcium					
Basophils	Total Bilirubin[c]					
CBC	BUN or Urea					
	Creatinine					
	Uric Acid					
	Glucose (non-fasted)					
	Albumin					
	Phosphorous or Phosphate					
	Lipase					
	Amylase					
	TSH + reflex free T4 and free T3					

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein HBsAg = hepatitis B antigen; FSH = follicle stimulating hormone; HBcAb = hepatitis B core antibody; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HPV = human papilloma virus; HsCRP = high sensitivity C-reactive protein; INR = international normalized ratio; partial thromboplastin time = PTT; T3 = triiodothyronine; T4 = thyroxine; TBNK = T cell/B cell/natural killer cell; TSH = thyroid stimulating hormone; UPCR = urine protein to creatinine ratio; WBC = white blood cells;

a. Dipstick is acceptable to perform urinalysis. Microscopic analyses if clinically indicated (eg, only after the second positive dipstick result for heme). If ≥2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24hr urine.
b. In the case of apparent ongoing HBV or HCV infection, reflex serum viral load testing will be performed.
c. For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids, and acetaminophen drug and/or protein adduct levels.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination to include weight, vital signs (temperature, sitting BP, sitting pulse rate after 5 minutes of rest, and pulse oximetry at rest and after exertion), assessment of ECOG performance status and height (height will be measured at screening only).

See Schedule Of Activities. Abbreviated PEs should be performed as appropriate at each visit where complete PEs are not required.

7.1.5. (12-Lead) Electrocardiogram

Electrocardiogram machines to be utilized in this study will be supplied by a third party vendor.

At screening, a single 12-lead ECG tracing (with a 10-second rhythm strip) will be obtained. For Cycle 1 Day 1 and all subsequent specified time points (see Schedule Of Activities), triplicate 12-lead ECG tracings (with a 10-second rhythm strip) will be obtained.

Generally, baseline and all corresponding time point ECGs should not be collected within 3 hours after food or beverage consumption and should be performed after the patient has rested quietly for at least 10 minutes in a supine position. All 12 lead ECGs should be confirmed by a qualified person at the institution and will be reviewed by a central laboratory. ECGs on Day 1 of each cycle will be collected prior to dosing, and at the end of infusion or SC injection (approximately 1 hour) following administration of each dose of PF 06801591. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, BP, and pulse rate.

When matched with PK sampling, the ECG should preferably be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

At each time point (see the Schedule Of Activities and ECG manual), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval; the average of the triplicate ECG measurements collected at each pretreatment time point on Day 1 of each cycle will serve as each patient's time-controlled baseline QTc value. If the mean QTcF is prolonged (≥45 msec from the pre-dose baseline or is ≥500 msec), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of ≥45 msec from the pre-dose baseline or is ≥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 ≥45 msec from the pre-dose baseline or is ≤500 msec depending on the type of change originally observed. If QTcF interval reverts to less than 45 msec from the pre-dose baseline or is ≤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 ≥45 msec from the pre-dose baseline or is ≥500 msec the investigational product will be held until the QTcF interval decreases to ≤45 msec from the pre-dose baseline or is ≤500 msec, depending on the type of change originally observed.

Note: If QTc values remain ≥500 msec (or ≥45 msec from the pre-dose baseline) for greater than 4 hours (or earlier at the discretion of the investigator); or QTc intervals get progressively longer, the patient should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the pre-dose baseline) after 8 hours of monitoring (or earlier at the discretion of the investigator).

Once the QTcF interval decreases to ≤45 msec from the pre-dose baseline or ≤500 msec, depending on the type of change originally observed, patients may restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to ≤45 msec from the pre-dose baseline or ≤500 msec after 2 weeks (depending on the type of change originally observed), or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

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

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

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

7.1.6. Local Site Injection Tolerability Assessment (SC Only)

Assessments made of the injection sites in the abdominal fat fold to monitor local tolerability to PF-068011591 SC injections will be performed for at least 1 hour following study drug administration, as per the Schedule Of Activities. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted. Refer to Appendix 9 for more details.

Site tolerability assessments should continue after each dosing day visit, only if injection site pain or injection site reaction (ISR) characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve. The injection sites will be assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after study drug dosing. The diameter of the affected area will be measured and the condition of the injection site will be recorded on the SC Injection Site Assessment CRF. Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported. ISRs should be immediately photographed in color, with scaled ruler placed by the reaction, and these photographs should be included in the patient's source documentation. When appropriate, at the discretion of the investigator, a patient with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR. The dermatology consultation is expected to take place at the dermatologist's practice location, or may occur within the same institution where this study is conducted.

7.2. Pharmacokinetic Assessments

7.2.1. Blood for PK analysis of PF-06801591

Blood samples (approximate 5 mL) to provide serum for the analysis of PF-06801591 concentrations will be collected as outlined in the Schedule Of Activities. The PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious 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, patient, and sponsor.

Sample for PK analysis will be assayed for PF-06801591 using a validated analytical method in compliance with Pfizer standard operating procedures. To increase the understanding of the PK of PF-06801591, samples may be used for the evaluation of the bioanalytical method as well as other internal exploratory purposes. 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.

7.3. Biomarker and Pharmacodynamic Assessments

Biopsies and tissue samples (including but not limited to tumor, peripheral blood, and plasma) will be collected before and after PF-06801591 dosing for biomarker evaluation and pharmacodynamic assessments.

Archived Biopsy Samples

All patients are required to provide an archival tissue sample at screening, or agree to a de novo tissue sample collection per institutional procedural standards. In Part 2, Patients must provide FFPE tissue from the most recent primary or metastatic tumor biopsy or resection prior to study entry, taken within 2 years of start of study treatment.

Fresh Biopsy Samples

Fresh tumor biopsies are optional (within 28 days of first dose) for the first 2 to 4 patients in Part 1A at each dose level and in Part 2 if adequate archival tissue is provided at baseline, but fresh biopsies are mandatory in Part 1B at screening (within 28 days of first study treatment dose) and on-treatment (on Cycle 2 Day 8 ±5 days). Optional biopsies are encouraged at disease progression and/or end of treatment (assuming available tumor to biopsy) and as clinically indicated throughout treatment for all patients. If biopsy is to be completed the same day as CT scan, it must be completed after the CT scan.

Blood and plasma will be collected at the time points specified in the Schedule Of Activities.

Biomarker evaluation will be performed on tumor tissue biopsies, whole blood, and plasma. Biopsy tissue will be submitted to analysis by IHC to assess target expression, phenotypes of infiltrating immune cells and markers associated with immune activation and tolerance. Tumor tissue may also be submitted to RNA, T cell receptor (TCR), and tumor Ag profiling by nucleotide sequencing. Immune cell phenotypes and PD-1 RO on T-cell subsets will be evaluated in whole blood by flow cytometry in Part 1 only.

Whole blood may be submitted to RNA profiling and TCR sequencing at select time points. Plasma will be collected to measure levels of soluble factors (eg, cytokines, chemokines, soluble PD-L1).

The primary objective of these analyses will be to confirm target occupancy, to identify pharmacodynamic activity, and to characterize immunophenotypes most likely to respond to PD-1 blockade.

Table 5 summarizes representative assays to be used and the source of the samples. Refer to the SCHEDULE OF ACTIVITIES for details pertaining to specific days of sample collection and to the Lab Manual for details of sample preparation, storage, and shipment.

Table 5. Sampling and Assays for Biomarkers

Biomarker	Matrix	Assay
PD-1 Receptor Occupancy (Part 1 Only)	Whole Blood	Flow Cytometry
[redacted]	[redacted]	[redacted]

7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C1D1, (2) performed using the method requirements (ie, RECIST v. 1.1), (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. Radiographic images may potentially be collected for central review.

Acceptable imaging may include CT, MRI (with contrast at minimum) of the chest, abdomen and pelvis, or other radiographic disease sites as clinically indicated. Brain MRI or CT scans will be performed at baseline and on-study for patients with known or suspected brain metastases or if disease is suspected or has been previously documented as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. FDG-PET may be performed for further characterization of tumors, but any CT scans performed concurrently with PET must be of diagnostic quality with contrast in order to be used for tumor assessments. Bone scans should be performed at baseline and on-study for patients with known or suspected bone metastases not well-visualized on other imaging or if disease is suspected or has been previously documented as appropriate to follow disease.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments whenever possible.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule Of Activities, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment, if not done in the previous 3 weeks, after end of treatment for patients who did not end treatment due to disease progression, death, or withdrawal of consent, a tumor assessment will be performed every 12 weeks until disease progression by irRECIST, initiation of a new anti-cancer treatment, or end of trial (2 years after LPFD, see Section 13.2), whichever is first. Note: If a patient is classified as having PD during an on-treatment tumor assessment, then confirmation of PD by a second scan in the absence of rapid clinical deterioration is required per irRECIST.

CT or MRI scans to be done every 6 weeks (±5 days) for patients on IV administration portion and every 8 weeks (±5 days) for Parts 1 and 2 SC administration portion from the start of study entry (defined as C1D1) until disease progression by immune-related RECIST (irRECIST), death, withdraw consent, or subsequent administration of an anti-chemotherapy agent. CT or MRI scans may be assessed every 12 weeks (±5 days) for patients who 1) have remained on treatment for ≥24 weeks, and 2) have no confirmed progression by irRECIST within the last 6 months, and 3) have demonstrated stability of disease. Tumor assessments should be fixed according to the calendar, regardless of treatment delays.

Confirmation of response (complete response [CR]/partial response [PR]) with a second consecutive scan at least 4 weeks later is preferred. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks (IV) or 8 weeks (SC) have passed since the last evaluation. CT or MRI scans should be completed before tumor biopsy samples are collected. If a patient is classified as having progressive disease (PD) at a post-baseline tumor assessment, then confirmation of PD by a second consecutive scan at least 4 weeks later in the absence of rapid clinical deterioration is required. After End of Treatment for patients who did not end treatment due to disease progression, death, or withdrawal of consent, a tumor assessment will be performed every 12 weeks (±1 week), until disease progression by irRECIST, or initiation of a new anti-cancer treatment, or end of trial (2 years after LPFD, see Section 13.2), whichever is first.

If imaging is used in disease assessment, the same imaging technique used to characterize each identified and reported lesion at baseline will be employed in post-baseline disease assessments whenever possible.

Disease response assessments will be based upon disease-specific response criteria: RECIST v 1.1 (Appendix 3) and irRECIST (Appendix 4).

7.5. CA-125 Tumor Marker Assessment (Ovarian Cancer Only)

Serum CA-125 is the standard for tumor markers in the evaluation of pelvic masses, particularly epithelial ovarian cancers. During treatment for ovarian cancer, CA-125 is a helpful indicator of disease activity and can be used to follow response to therapy and detect an early recurrence.[55,56] The first measurement for CA-125 must be collected within 2 weeks before treatment is started, during the screening period. Subsequent CA-125 levels will be measured on Day 1 of each cycle before treatment, at End of Treatment, and at Follow-up

visit 28 days after last dose administration. There is no need to repeat on C1D1, if the baseline (screening) assessment was performed within 72 hours prior to that day.

7.6. Immunogenicity Evaluations

Blood samples (approximately 10 mL) to provide serum for detection of anti-drug antibody (ADA) and neutralizing antibodies (Nab) against PF-06801591 will be collected into appropriately labeled tubes at times specified in the Schedule Of Activities. Additional instructions for sample collection, processing, storage, and shipping will be provided in the lab manual. A companion blood sample for the determination of PF-06801591 concentration will be collected in conjunction with the ADA sample collection to facilitate immunogenicity assessment.

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.

As part of understanding the immunogenicity of the study drug, samples may be used for additional characterization of an observed immunogenicity response and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and, if not used within this timeframe, will be destroyed.

7.7. Banked Biospecimen

7.7.1. 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 DNA, 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. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or EC decision.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification 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 post marketing 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 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 (K_2 edetic acid [ethylenediaminetetraacetic acid] whole blood collection optimized for DNA analysis) will be collected at the screening and Cycle 2 Day 8 visits (Part 1 only) and Cycle 1 Day 1 visits (Part 2 only) 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 specimens 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 a separate document.

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.

7.7.2. 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.

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 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. For adverse events that the investigator deems immune-related, that specific causality and whether an immunosuppressive therapy (eg, corticosteroids, other immunosuppressant drugs) is indicated, will be recorded on the CRF. For any adverse event, regardless of investigator determined causality, if the management requires administration of an immunosuppressive therapy, the use will be documented on a specific case report form that will record generic drug name, stop and start dates (duration), dose, units, route, frequency of administration, and response to medication. 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 150 calendar days after the last administration of the investigational product or until administration of subsequent anti-cancer therapy whichever comes first. Death must be reported as an SAE if it occurs within 150 calendar days after last administration of the investigational product, irrespective of any intervening treatment. 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.

If an SAE occurs after informed consent is signed and before study drug is administered, this information will be reported on an SAE Form and will be recorded in the safety database.

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. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. Additional, immune-related AEs will be collected with a follow-up phone call at 90 and 120 days after last dose administration date to collect post-treatment related AE information.

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.

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 is 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 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

An SAE 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.

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

Abnormal values of AST and/or 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 X 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 pre-existing 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 pre-existing 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, PT/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 pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing 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

Adverse events will be assessed in accordance with NCI CTCAE version 4.03, see Table 6.

Table 6. CTCAE Criteria for Adverse Events

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

CTCAE = Common Terminology Criteria for Adverse Events

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

8.9. 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 (EDP)

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

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

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), 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 6.6 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

Not applicable.

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

9.1.1. Safety Analysis Set

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

9.1.2. Full Analysis Set

The full analysis set includes all enrolled patients.

9.1.3. Per-protocol Analysis Set (evaluable for MTD)

The per protocol analysis set includes all enrolled patients who received at least one dose of study treatment and who did not have major treatment deviations during the Cycle 1. For the IV administration of PF-06801591, patients with major treatment deviations in the 21-day DLT observation period are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation.

For the SC administration of PF-06801591, patients with major treatment deviations in the 28-day observation period will not be evaluable for DLT.

Major treatment deviations include:

- Administration of <50% of the planned dose of PF-06801591, provided that the reduction is not due to toxicity attributable to PF-06801591.
- Administration of >150% of the planned dose of PF-06801591.

9.1.4. PK Analysis Sets

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

The PK concentration population is defined as all patients who receive PF-06801591, have no protocol deviations affecting the PK assessment, and have at least one post-dose concentration measurement.

9.1.5. Biomarker Analysis Set

The biomarker analysis set includes all enrolled patients with at least one of the pharmacodynamic/biomarker parameters evaluated at pre- and/or post-dose.

9.1.6. Immunogenicity analysis set

The immunogenicity analysis set is defined as patients who receive at least 1 dose of study treatment and have at least 1 ADA or NAb sample collected.

9.2. Statistical Methods and Properties

A primary study objective is to establish the MTD, defined as the dose that yields approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (equivalence interval) 22.5% to 32.5%. The 27.5% target, the symmetry of the equivalence interval and its upper limit <33% were chosen based on safety considerations. The prior distribution of DLT is set as a beta (0.5, 0.5), and the threshold probability for early termination and dose exclusion is set to 0.95. Doses with an incidence of DLT >33% (eg, 4 out of 10) will not be declared the MTD but will be allowed by the mTPI method.[7]

9.2.1. Dose Escalation/De-Escalation and MTD Estimation (Part 1)

Part 1 dose escalation phase of this study employs an mTPI design to estimate the MTD with the IV administration of PF-06801591. The mTPI design employs a simple beta-binomial model with prior a conjugated prior beta (0.5, 0.5). Decision rules are based on calculating the unit probability mass (UPM) of 3 intervals corresponding to underdosing, proper dosing, and overdosing in terms of dose limiting toxicity. A proper dosing interval is centered at the target toxicity rate (pT) of 27.5% with 5% uncertainty (0.225 < pT <0.325). The under dosing interval is (0, 0.225), and the overdosing interval is (0.325, 1). The 3 dosing intervals are associated with 3 different dose escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation, and proper-dosing corresponds to staying at the same current dose. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, decision E (to escalate) will be executed, and the next cohort of patients will be treated at the next-higher dose level. Under the mTPI design, a trial is terminated when either the lowest dose is above the MTD or a pre-specified maximum sample size of (for Part 1, n=60) is reached.

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 cohort size of n=3 and for a DLT that occurs in 10% of patients, there is a greater than 90% probability of escalating. Conversely, for a DLT that occurs with a rate of 70%, the probability of escalating is 3%. It is assumed that dose escalation occurs with either 0/3 or 1/6 patients with DLTs.

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

9.2.2. Dose Expansion (Part 2: 300 mg of SC PF-06801591)

Part 2 (N=100) of this study is intended to further characterize the safety, efficacy, PK, PD, and immunogenicity profiles of 300 mg of SC PF-06801591 in anti-PD-1 or anti-PD-L1 treatment naïve patients with NSCLC (N=70) and urothelial carcinoma (N=30) who have progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable.

Summary statistics will be provided for trough PF-06801591 concentrations, safety endpoints, immunogenicity, pharmacodynamic/biomarkers, and efficacy data.

When the first 30 NSCLC patients have been enrolled and have either completed their first tumor assessment (at approximately 8 weeks post treatment), or have discontinued from the study before their first scheduled tumor assessment, preliminary assessment of safety and efficacy data maybe completed. This preliminary data may provide guidance in the decision to the increase or decrease size of each arm, to add other tumor types in a future amendment, or to initiate additional clinical studies.

9.3. Sample Size Determination

The exact sample size for the dose escalation design in Part 1 cannot be specified in advance due to the dynamic features of mTPI. For the first dose level (0.5 mg/kg IV), in the absence of actual DLTs, a total of 2 patients will be enrolled: 2 patients in Part 1A and no patient in Part 1B. For subsequent dose levels it is anticipated that approximately 2 to 4 patients will be enrolled in Part 1A and approximately 2 to 5 patients in Part 1B with available pre- and on-treatment biopsies for IHC testing and up to 9 patients at dose levels 1, 3, and 10 mg/kg administered by IV in Part 1. A single cohort with SC administration at a dose level of 300 mg of PF-06801591 will be opened for enrollment shortly after the cohort at a dose level of 3 mg/kg IV in Part 1A will have completed enrollment and the 21-day DLT observation period. This cohort at a dose level of 300 mg SC will seek 2 to 4 patients in Part 1A, up to 11 patients in Part 1B with available pre- and on-treatment biopsies for IHC testing, and up to 15 patients in Part 1. The actual Part 1 sample size may be smaller, depending on the underlying dose toxicity profile, and the number of dose levels studied.

Part 2 of the study will enroll approximately 70 patients with NSCLC who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable. but are treatment naïve for anti-PD-1 or anti-PD-L1. NSCLC was selected for historical comparability to prior large anti-PD-1 studies and dosing of 300 mg SC in Part 2 has been selected based on safety, PK, available biomarker data and preliminary anti-tumor activity from Part 1. There is no hypothesis testing in Part 2. Estimation approach is used to characterize the precision of response data. The estimation of ORR using N=70 is described as follows. Suppose that the ORR estimate is 19% in Part 2 with N=70, then the 80% and 90% confidence intervals of the true ORR will be (13.4, 25.2%) and (12.2, 27.3%) respectively. Note that an ORR of 19% was observed in a clinical trial for nivolumab in previously treated NSCLC patients. In Part 2, approximately 30 urothelial cancer patients will also be enrolled; the sample size is based on clinical considerations of expanding the safety database.

9.4. Efficacy Analysis

In this first-in-patient study, anti-tumor activity is a secondary objective in Part 1 dose escalation. Overall response rate (ORR) are primary objectives in Part 2 dose expansion. Other efficacy endpoints are secondary objectives in Part 2.

In Part 1 of the study, tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor response at each visit, and best overall response. In addition, disease progression date, death date, date of first response, and last tumor assessment date, and date of last contact will be listed. Summary tables may be generated by dose level, if deemed necessary.

In Part 2 of the study, the following analyses will be performed:

1. Approximately 8 weeks after the first 30 NSCLC patients have enrolled, a data snapshot will be taken for an early data assessment. Descriptive statistics (frequency and percentage) for tumor response (CR, PR, PD, stable disease [SD] etc.) from the first tumor assessment; ORR, the proportion of patients who achieved unconfirmed CR or PR, and the 95% confidence interval for ORR; DCR (disease control rate), the proportion of patients who achieved unconfirmed CR or PR or SD, and the 95% confidence interval for the DCR will be presented. If tumor response data are collected based on both RECIST 1.1 and irRECIST, separate presentations will be generated for each response criterion. In this data snapshot, some patients may have gone through their second tumor assessment as of the data snapshot, however only data through the first tumor assessment will be used for this analysis. The above described analyses may be repeated, if deemed necessary, when the first 40 or 45 NSCLC patients are enrolled and have gone through their first tumor assessment. This preliminary data may provide guidance in the decision to the increase or decrease the sample size of each arm, to add other tumor types in a future amendment, or to initiate additional clinical studies.

2. In the early data assessment, a Bayesian approach will be used to calculate the posterior probability that the true ORR is greater than or equal to the minimal expected ORR. For example, the minimal expected ORR if all patients received only one tumor assessment is approximately 10% but may be adjusted based on how many patients had assessments beyond 8 weeks and the PD-L1 status of patients which will be tested at baseline. A beta prior (0.235, 1) is chosen, where the parameter beta is set to be 1, and parameter alpha 0.235 was calculated from a reference product pembrolizumab on NSCLC patients where a 19% ORR was observed. For example, if 4 responders are observed out of the first 30 patients as of the first tumor assessments, the posterior probability that the true ORR is greater than a minimal expected ORR of 10% is approximately 70%.

3. When all 70 NSCLC patients and 30 urothelial cancer patients are enrolled and have completed their scheduled tumor assessments, another snapshot will be taken. Descriptive statistics (frequency and percentage) will be presented for each tumor type (NSCLC or urothelial cancer) for the following endpoints:

   - Tumor response (CR, PR, PD, SD etc.) at each assessment;
   - Best overall response up to week 16 (ie, across the first two tumor assessments plus the next consecutive tumor assessment when a confirmatory scan is needed);
   - Best overall response across all assessments;
   - ORR, the proportion of patients who achieved CR or PR, by week 16 and the 95% confidence interval for ORR;
   - DCR (disease control rate), the proportion of patients who achieved CR or PR or SD, by week 16 and the 95% confidence interval for the DCR.

   If tumor response data are collected based on both RECIST 1.1 and irRECIST, separate presentations will be generated for each response criterion.

   Time to event data (overall survival [OS], progression-free survival [PFS], time to response [TTR], time to progression [TTP], DOR, and duration of stable disease [DOSD]) will be analyzed by the Kaplan-Meier approach for each tumor type.

   The analyses may be separated and performed at two separate time points if the 70 NSCLC and 30 urothelial cancer patients do not complete enrollment at approximately the same time.

4. A final analysis will be performed at the end of the study, which will be 2 years from LPFD.

Detailed analyses for these efficacy endpoints will be described in the Statistical Analysis Plan (SAP).

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. PF-06801591 Pharmacokinetic Analysis

The concentration-time data of PF-06801591 will be summarized by descriptive statistics (n, mean, and standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) according to dosing cohort and time for each part of the study. In addition, the concentration-time data from Part 2 will also be summarized by descriptive statistics according to tumor type.

For patients enrolled in Part 1 of the study, the individual concentration-time data of PF-06801591 during Cycle 1 and Cycle 4 will be analyzed separately by non-compartmental methods to estimate the PK parameters. The PK parameters estimated will include C_{max}, T_{max}, and AUC_{last}. If data permit or if considered appropriate, $t_{1/2}$, CL, volume of distribution (V_d)/ volume of distribution at steady state (Vss), and accumulation ratio (Rac, when feasible) will also be estimated for Cycle 1 and Cycle 4. The PK parameters will be summarized descriptively by dose level and cycle.

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

For patients enrolled in Part 2 of the study, trough PF-06801591 concentrations will be summarized descriptively by cycle and tumor type.

9.5.2. Analysis of Pharmacodynamics

9.5.2.1. Analysis of Biomarker Endpoints

For biopsy samples, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and post-treatment. For each pair of specimens, the percent change from baseline of these same parameters will also be calculated.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA). The statistical approach will examine correlations of biomarker results with PK parameters and measures of anti-tumor efficacy.

9.5.3. Population Pharmacokinetic Analysis or Pharmacokinetic (PK)/ Pharmacodynamic Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-06801591 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.6. Safety Analysis

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

9.6.1. Analysis of the Primary Endpoint in Part 1

Dose-limiting toxicity is the primary endpoint for Part 1 dose escalation component of the study. The occurrence of DLTs observed in the dosing cohorts will be used to estimate the MTD as described in the Section 3.1. AEs constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints

Adverse Events

Adverse Events as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy PF-06801591 will be tabulated.

Adverse Events will be graded by the investigator according to the NCI CTCAE version 4.03, and coded using the Medical Dictionary for Regulatory Activities. The focus of AE summaries will be on treatment emergent AEs, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

Laboratory Test Abnormalities

Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing will be summarized by treatment group. Baseline corrected QTcF interval at the maximum plasma concentration at steady state at the MTD will be tabulated by treatment group. Central assessment of the QTcF interval would be considered primary but listings will be produced for the local (study site) assessment as well.

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

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

9.6.3. Electrocardiogram

The analysis of ECG results will be based on patients in the Safety Analysis Set with baseline and on-treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

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

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

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

Shift tables will be provided for baseline vs worst on treatment corrected QT (1 or more correction methods will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

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

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS interval will be summarized by treatment and visit.

The number (%) of patients with maximum post dose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc

	Borderline (msec)	**Prolonged (msec)**
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

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

If more than one ECG is collected at a nominal time post dose (eg, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the patient's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also ≥500 msec. Changes from baseline will be defined as the change between QTc post dose from the time-matched average baseline triplicates on Day 0, or the average of the pre-dose triplicate values on Day 1.

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

9.7. Analysis of Other Endpoints

9.7.1. Analysis of Anti-Drug Antibody for PF-06801591

Summary of number of patients and incidence of developed ADA against PF-06801591 will be tabulated by dose level cohort. For patients with positive ADA or NAb, the magnitude (titre), time of onset, and duration of ADA or NAb response will also be described, if data permit. Subgroup analysis may be performed to assess the PK or pharmacodynamics response if data warrant.

9.8. 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 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.

Part 2: When approximately 30 patients have had the opportunity for a Week 8 tumor assessment, a preliminary analysis will be performed to evaluate safety and efficacy and to explore the possibility of extending the protocol to additional tumor types or to maintain the current study design.

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/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with 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 1996 and 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

13.1. End of Trial in a Member State

End of trial in a Member State of the EU is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

End of trial is defined as 2 years after last patient first dose (LPFD).

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as 2 years after last patient first dose (LPFD).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06801591 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 pre-specified 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 has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by 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

Abbreviation	Term
Ab	antibody
AdC68	adenovirus C38
ADA	anti-Drug Antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
Ag	antigen
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the curve
AUC_t	area under the serum concentration-time curve
AUC_∞	area under the concentration-time curve
BCG	bacillus calmette-guérin
BP	blood pressure
BUN	blood urea nitrogen
C	cycle
C2D8	cycle 2 day 8
CAR	chimeric antigen receptor
CCL	chemokine (C-C motif) ligand
CD	cluster of differentiation
CHF	congestive heart failure
cHL	classic Hodgkin lymphoma
CI	confidence interval
CKD-EPI	chronic kidney disease epidemiology collaboration
CL	clearance
C_{max}	maximum drug concentration
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSA	clinical study agreement
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Term
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
D	day
DAI	dosage and administration instructions
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DOSD	duration of stable disease
DR	D related
DU	dispensable unit
EC	ethics committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EI	equivalence interval
EOT	end of treatment
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDG-PET	fluordeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin embedded
FIP	first in patient
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNSTD	highest non-severely toxic dose
HR	Hazard ratio
ICH	International Conference on Harmonization
ICOS	inducible T cell co-simulator
ID	Identification
IDO	indoleamine 2,3 dioxygenase
IFN-γ	interferon-gamma
Ig	Immunoglobulin

Abbreviation	Term
IHC	Immunohistochemistry
IL	Interleukin
IND	investigational new drug application
INR	international normalized ratio
IP	investigation product
irAE	immune-related adverse event
IRB	institutional review board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IRT	interactive response technology
ISR	injection site reaction
IV	Intravenous
JAK/STAT	janus kinase/signal transducer and activator of transcription
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LFT	liver function test
LPFD	last patient first dose
LPLV	last patient last visit
mAb	monoclonal antibody
MAPA	magnesium ammonium phospholineate-palmitoleate anhydride
MCC	merkel cell carcinoma
MCP-1	monocyte chemoattractant protein-1
MG	myasthenia gravis
MIP	macrophage inflammatory protein
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NA	not available
NAb	neutralizing antibodies
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NHP	non-human primates
NMIBC	non- muscle invasive bladder cancer
NOAEL	no observed adverse effect level
NSCLC	non-small-cell lung cancer
OBD	optimal biological dose
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L	programmed death ligand
PET	positron emission tomography

Abbreviation	Term
PGE_2	prostaglandin E_2
PFS	progression-free survival
PK	Pharmacokinetics
PR	partial response
PrCa	prostate cancer
PT	prothrombin time
PTT	partial thromboplastin time
q2w/q3w/q4w	every 2 weeks/every 3 weeks/every 4 weeks
QT	time between the start of the Q wave and the end of the T wave
Rac	accumulation ratio
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
irRECIST	immune related Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SEB	staphylococcal enterotoxin B
SNF	skilled nursing facility
SOA	schedule of activities
SOCS1	suppressor of cytokine signaling 1
SPD	sum of the products of the greatest diameters
SRSD	single reference safety document
$t_{1/2}$	half-life
TBNK	T cell/B cell/natural killer cell
TCR	T cell receptor
TE	target engagement
TGFβ	transforming growth factor beta
T_H	T helper cell
TIL	tumor-infiltrating lymphocytes
TIMP1	tissue inhibitor of metalloproteinase 1
T_{max}	maximum (or peak) serum concentration
TNF	tumor necrosis factor
T_{reg}	regulatory T-cell
TPS	Tumor proportion score
TSH	thyroid stimulating hormone
TTP	time to progression
TTR	time to response

Abbreviation	Term
ULN	upper limit of normal
UPM	unit probability mass
US	United States
V_d	volume of distribution
VBIR	vaccine based immunotherapy regimen
VP	virus particles
Vss	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WNL	within normal limits

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

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

- With 2 patients treated at current dose level

  0 DLT > escalate
  1 DLT > remain at the same dose
  2 DLTs > de-escalate and consider current dose as intolerable

- With 3 patients treated at current dose level

  0 DLT > escalate
  1 DLT > remain at the same dose
  2 DLTs > de-escalate
  3 DLTs > de-escalate and consider current dose as intolerable

- With 4 patients treated at current dose level

  0 DLT > escalate
  1-2 DLTs > remain at the same dose
  3-4 DLTs > de-escalate and consider current dose as intolerable

- With 5 patients treated at current dose level

  0-1 DLT > escalate
  2 DLTs > remain at the same dose
  3 DLTs > de-escalate
  4-5 DLTs > de-escalate and consider current dose as intolerable

- With 6 patients treated at current dose level

  0-1 DLT > escalate
  2 DLTs > remain at the same dose
  3 DLTs > de-escalate
  4-6 DLTs > de-escalate and consider current dose as intolerable

- With 7 patients treated at current dose level

  0-1 DLT > escalate
  2-3 DLTs > remain at the same dose
  4-7 DLTs > de-escalate and consider current dose as intolerable

- With 8 patients treated at current dose level

  0-1 DLT > escalate
  2-3 DLTs > remain at the same dose
  4 DLTs > de-escalate
  5-8 DLTs > de-escalate and consider current dose as intolerable

- With 9 patients treated at current dose level

  0-1 DLT > escalate
  2-3 DLTs > remain at the same dose
  4 DLTs > de-escalate (mTPI suggests “remain at the same dose”)
  5-9 DLTs > de-escalate and consider current dose as intolerable

- With 10 patients treated at current dose level

  0-1 DLT > escalate
  2-3 DLTs > remain at the same dose
  4 DLTs > de-escalate (mTPI suggests “remain at the same dose”)
  5 DLTs > de-escalate
  6-10 DLTs > de-escalate and consider current dose as intolerable

- With 11 patients treated at current dose level

  0-2 DLT > escalate
  3-4 DLTs > remain at the same dose
  5 DLTs > de-escalate (mTPI suggests “remain at the same dose”)
  6-11 DLTs > de-escalate and consider current dose as intolerable

- With 12 patients treated at current dose level

  0-2 DLTs > escalate
  3-4 DLTs > remain at the same dose
  5 DLTs > de-escalate (mTPI suggest “remain at the same dose”)
  6-12 DLTs > de-escalate and consider current dose as intolerable

- With 13 patients treated at current dose level

  0-2 DLTs > escalate
  3-4 DLTs > remain at the same dose
  5 DLTs > de-escalate (mTPI suggest “remain at the same dose”)
  6 DLTs > de-escalate
  7-13 DLTs > de-escalate and consider current dose as intolerable

- With 14 patients treated at current dose level

  0-2 DLTs > escalate
  3-4 DLTs > remain at the same dose
  5-6 DLTs > de-escalate (mTPI suggest “remain at the same dose”)
  7-14 DLTs > de-escalate and consider current dose as intolerable

- With 15 patients treated at current dose level

  0-2 DLTs > escalate
  3-4-5 DLTs > remain at the same dose
  6 DLTs > de-escalate (mTPI suggest “remain at the same dose”)
  7-15 DLTs > de-escalate and consider current dose as intolerable

Appendix 3. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from Eisenhauer E.A., et al.[57]

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

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

Non-measurable disease

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

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

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

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

Target lesions

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

- If 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 CRF (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

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

Target disease

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

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

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

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

- Indeterminate: Progression has not been documented, and:

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

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

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

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

Non-target disease

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

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

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of 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 7. 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

If the protocol allows enrollment of patients with only non-target disease, the following Table 8 will be used:

Table 8. 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 RECIST (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-cytotoxic T lymphocyte-associated protein-4 (CTLA-4) 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.[1,58,59] 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.

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.[60,61,62]

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

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

- Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented; and

- Does not necessarily score the appearance of new lesions as PD 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) nor immune related progressive disease (irPD, compared to nadir).

- Overall 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) with a minimum absolute increase of 5 mm, 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 at each assessment time point.

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

Appendix 5. Overall Response Derived from Changes in Index, Non-index, and New Lesions

Overall responses derived from changes in index, non-index, and new lesions are outlined in Table 9.

Table 9. 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	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.

Appendix 6. 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

Source: Oken M et al. 1982.[63]

Appendix 7. Recommendations for Management of Infusion Related Reactions Including Allergic/Hypersensitivity Reactions, Cytokine Release Syndrome or Anaphylaxis

Following the first infusion of some monoclonal antibody therapeutics, some patients experience fever, headache, nausea, vomiting or hypotension. These AEs are generally ascribed to lysis of cellular targets, cytokine release, or complement activation.

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of infusion and may include symptoms such as rash, urticaria, polyarthritis, myalgias, polysynovitis, fever, and, if severe, glomerulonephritis.

All patients should be closely observed while receiving investigational product infusions. Monitoring for clinical signs of a systemic reaction should continue thereafter for clinical signs of allergic reactions/hypersensitivity.

Infusion reactions

If chills and fever (>100.4°F/38.0°C) or hypotension occur, the infusion should be interrupted. Patients should be treated symptomatically according to best medical and nursing practice and the infusion should be restarted at 50% of the original rate.

If infusion reactions, characterized by fever and chills, and less commonly hypotension, are experienced either by an individual patient or in other patients, pretreatment medication may be administered prior to subsequent doses to reduce the incidence and severity. The following pretreatment regimen is suggested, although a different regimen based on local standard of care is permitted:

- Patients should be pretreated with acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each PF-06801591 administration. Pretreatment medications will not be supplied by Pfizer. Suggested starting doses are 650 to 1000 mg acetaminophen and 50 mg diphenhydramine (or equivalent of other antihistamine) IV or oral. Two (2) additional doses of acetaminophen may be administered approximately every 4-6 hours after the initial pretreatment or as needed.

Hypersensitivity reactions:

In the case of a hypersensitivity reaction, the patient will be treated symptomatically, with supportive care and further monitoring until the end of the study. Study infusions may be stopped.

Guidelines for the management of hypersensitivity reactions are as follows:

1. NCI-CTCAE Grade 1 allergic reaction or cytokine release syndrome:

   a. Monitor for worsening condition. If the reaction worsens, stop the infusion. Use premedication for subsequent infusions, as described above.

2. NCI-CTCAE Grade 2 allergic reaction or cytokine release syndrome:

   a. Stop PF-06801591 infusion.

   b. Administer bronchodilators, oxygen, acetaminophen, etc. as medically indicated.

   c. Resume infusion at 50% of previous rate once reaction has decreased to ≤Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop infusion. Institute premedication for subsequent infusions as described above.

3. NCI-CTCAE Grade 3 or Grade 4 allergic reaction or cytokine release syndrome or anaphylaxis:

   - Grade 3 anaphylaxis (hypersensitivity reaction) consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or hypotension.

   - Grade 4 anaphylaxis (hypersensitivity reaction) is a life-threatening event requiring urgent intervention.

   a. Stop the PF-06801591 infusion immediately and disconnect infusion tubing from the patient.

   b. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically indicated.

   c. Telephone sponsor or designated representative to report an SAE as per Section 8.6.

   d. For a NCI-CTCAE Grade 3 or 4 hypersensitivity reaction, discontinue study treatment.

4. Re-treatment following Grade 1 or Grade 2 allergic reactions or cytokine release syndrome:

   a. Once the PF-06801591 infusion rate has been decreased due to an allergic reaction or cytokine release syndrome, it will remain decreased for all subsequent infusions.

b. If the patient has a second reaction at the lower infusion rate, the infusion should be stopped and the patient should receive no further PF-06801591.

c. If the patient experiences a Grade 3 or 4 allergic reaction, cytokine release syndrome, or anaphylaxis at any time, the patient should receive no further PF-06801591.

d. If there are questions concerning whether an observed reaction is consistent with an allergic reaction, cytokine release syndrome, or anaphylaxis, the medical monitor should be contacted immediately to assist with grading the reaction.

Sampling for PK, pharmacodynamics and ADA should continue as long as the sampling does not interfere with the medical treatment of the patient.

In cases of suspected cytokine release syndrome, a serum sample should be provided for cytokine release assay analysis by the central lab so as long as the sampling does not interfere with the medical treatment of the patient.

Detailed guidance on treatment, dose interruptions and potential retreatment is provided in the DAI.

Appendix 8. Management of Immune-related Adverse Events (irAEs)

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 5mg/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		

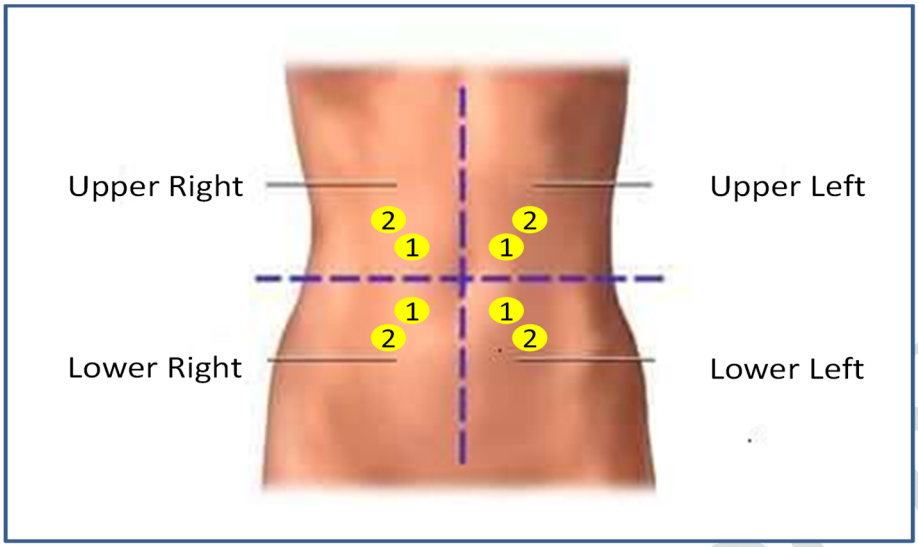
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Continue study treatment. -Endocrinology consult if needed. -Start thyroid hormone replacement therapy (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.	-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.

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
	-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.	

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.

Appendix 9. Subcutaneous Injection Site Location Diagram



Injection site locations include a maximum of 8 unique administration sites distributed across 4 abdominal quadrants with a possibility of up to 2 injection locations per quadrant. Location 1 is proximal to the umbilicus and Location 2 is distal to the umbilicus.

Administer the required number of injections in the following order:

1. Lower Left Quadrant Location 1
2. Lower Right Quadrant Location 1
3. Lower Left Quadrant Location 2
4. Lower Right Quadrant Location 2
5. Upper Right Quadrant Location 1
6. Upper Left Quadrant Location 1
7. Upper Right Quadrant Location 2
8. Upper Left Quadrant Location 2

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

Track the patient's injection site(s) sequentially on this diagram with a red pen and mark the injection sites on the patient's abdomen according to your clinic's standard practice.

Record the location, time of each injection and any injection site reactions in the patient's source records and study CRF. Complete one CRF per injection.

Protocol B8011001

A Phase 1, Open-Label, Dose Escalation and Expansion Study of PF-06801591 in Patients with Locally Advanced or Metastatic Melanoma, Squamous Cell Head and Neck Cancer, Ovarian Carcinoma, Sarcoma, Non-Small Cell Lung Cancer, Urothelial Carcinoma or other Solid Tumors

Statistical Analysis Plan
(SAP)

Version: Amendment 1

Author: [redacted]

Date: 07-NOV-2017

[redacted]

TABLE OF CONTENTS

1. VERSION HISTORY

Amendment 1	Section	Update
	All	Texts taken directly from the protocol are made *italicized*
	2.1	Objectives are updated and reformatted per protocol amendment 3
	2.2	Study design is updated per protocol amendment 3
	3	Endpoints are updated per protocol amendment 3
	4	Analysis sets are updated per protocol amendment 3
	5.2.2.	Statistical decision rules are updated for Part 2 per protocol amendment 3
	5.3	General statistical methods are updated with additional details for programming personnel
	6	Details about unconfirmed and confirmed tumor response and progression for RECIST 1.1 and irRECIST added.
	6.1	Cycle delay is updated; Cycle skip is added
	6.3.1	Editorial changes were made to the efficacy endpoints analyses
	7	Informal data monitoring is added
	9.6	All lymphoma response assessment is removed per protocol amendment 3

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B8011001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. This SAP amendment is based on the protocol amendment 3 dated June 3, 2017.

Note: in this document any text taken directly from the protocol is *italicized*.

2.1. Study Objectives

Part 1 (Dose-Escalation) Primary Objective

- *To assess safety and tolerability of increasing dose levels of PF-06801591 in patients with locally advanced or metastatic melanoma, SCCHN, ovarian carcinoma, sarcoma, NSCLC, urothelial carcinoma or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents to establish the MTD.*

- *To assess safety and tolerability of PF-06801591 administered SC in patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents.*

Part 1 (Dose-Escalation) Secondary Objective

- *To characterize the single-dose and multiple-dose PK of PF-06801591 following IV or SC administration.*
- *To evaluate the immunogenicity of PF-06801591 following repeated administration.*
- *To characterize PD-1 receptor occupancy (RO) in peripheral blood T cells following IV or SC PF-06801591 administration at each dose level.*
- *To evaluate preliminary anti-tumor activity of PF-06801591.*

Part 1 (Dose-Escalation) Tertiary and Exploratory Objective

- *To evaluate the phenotypes, and quantity of tumor-infiltrating lymphocytes (TILs) before and after PF-06801591 treatment.*
- *To evaluate the peripheral pharmacodynamic activity and immunomodulatory effects at increasing dose levels of PF-06801591 in patients with selected advanced or metastatic solid tumors in order to estimate OBD and/or dose range.*
- *To explore effects of PF-06801591 on the diversity of the T cell repertoire, the diversity of tumor epitope expression, and the balance of immune activation versus regulatory proteins and transcripts in tumor tissue.*
- *To correlate preliminary evidence of PF-06801591 anti-tumor activity with pharmacodynamic activity and immunophenotypes described in Section 1.3.*
- *To evaluate overall survival (OS).*
- *To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.*

Part 2 (Dose-Expansion) Primary Objective

- *To further characterize the safety and tolerability of PF-06801591 following SC administration in NSCLC and urothelial carcinoma.*
- *To estimate clinical efficacy by overall response rate (ORR) of PF-06801591 following SC administration in NSCLC and urothelial carcinoma.*

Part 2 (Dose-Expansion) Secondary Objective

- *To further evaluate preliminary anti-tumor activity of PF-06801591 following SC administration.*
- *To evaluate overall survival (OS).*
- *To collect PF-06801591 drug concentration data in patients following SC administration for evaluation of population PK.*
- *To evaluate the immunogenicity of PF-06801591 following repeated SC administration.*

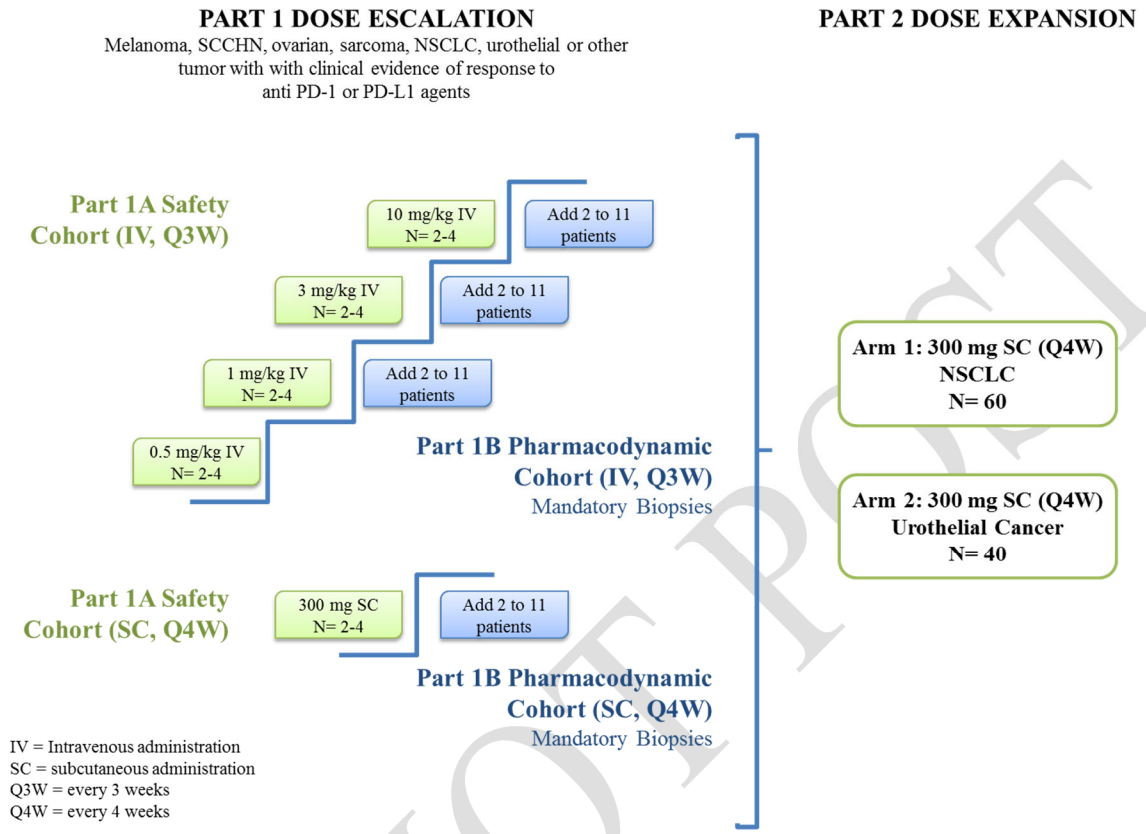
Part 2 (Dose-Expansion) Tertiary and Exploratory Objective

- *To evaluate PD-L1 expression and the phenotypes, and quantity of tumor infiltrating lymphocytes (TIL) before PF-06801591 treatment.*
- *To evaluate the diversity of the T cell repertoire, the diversity of tumor epitope expression, and the balance of immune activation versus regulatory proteins and transcripts in tumor tissue before PF-06801591 treatment.*
- *To evaluate the pharmacodynamic activity and immunomodulatory effects of subcutaneous administration of PF-06801591 in patients with locally advanced or metastatic NSCLC or urothelial carcinoma.*
- *To correlate preliminary evidence of PF-06801591 anti-tumor activity with pharmacodynamic activity described in Section 1.8.*
- *To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.*

2.2. Study Design

This is a Phase 1, open-label, multi-center, multiple-dose, dose escalation and expansion, safety, PK, and PD study of PF-06801591 in previously treated patients with locally advanced or metastatic solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents. This clinical trial will include 2 parts: Part 1 dose escalation and Part 2 dose expansion (Figure 1). A total of approximately 140 patients will be enrolled into this study.

Figure 1 B8011001 Study Schematic



Part 1 will enroll patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma, or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents. Patients will receive 0.5, 1, 3, or 10 mg/kg PF-06801591 intravenously (IV) every 3 weeks (q3w), or 300 mg PF-06801591 subcutaneously every 4 weeks (q4w). The Part 1 dose escalation phase will enroll approximately 8 to 15 patients per dose level.

Part 1 will be further divided into Part 1A (safety cohort) and Part 1B (pharmacodynamic cohort). For both IV and SC administration portions, each safety cohort will enroll 2-4 patients per dose level. For IV administration portion, each pharmacodynamic cohort will enroll 2 to 5 patients per dose level. For SC administration portion, up to approximately 11 patients will be enrolled into the 300 mg dose level in Part 1B. Approximately 40 patients will be enrolled into Part 1.

All patients in Part 2 will receive 300 mg PF-06801591 SC q4w. Part 2 dose expansion will include 2 arms: Arm 1 will enroll approximately 60 patients with NSCLC who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable but have not previously received anti-PD-1 or anti-PD-L1. Arm 2 will enroll approximately 40 patients with urothelial carcinoma who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable but have not previously received anti-

PD-1 or anti-PD-L1. Approximately 100 patients will be enrolled into Part 2.

2.2.1. MTD Determination (Part 1)

Part 1 will study sequential cohorts (0.5, 1, 3, and 10 mg/kg, or 300 mg SC) of PF-06801591 in adult patients with locally advanced or metastatic melanoma, SCCHN, ovarian cancer, sarcoma, NSCLC, urothelial carcinoma, or other solid tumor types with clinical evidence of response to anti PD-1 or PD-L1 agents who are unresponsive to currently available therapies or for whom no standard therapy is available. An mTPI method, targeting a dose limiting toxicity (DLT) rate of 27.5% will be utilized for dose escalation. *In the IV administration portion, if based on Part 1A information the dose level is deemed safe and well- tolerated, an additional 2 to 5 patients will enroll into the same dose level in Part 1B. In the SC administration portion, if based on Part 1A information the 300 mg dose level is deemed safe and well- tolerated, up to an additional 11 patients (approximately) will be enrolled into Part 1B. Up to approximately 9 patients may be enrolled into each dose level in the IV administration portion, and up to approximately 15 patients may be enrolled into the 300 mg SC administration cohort (Part 1A and Part 1B combined). The mTPI approach would be applied across Parts 1A and 1B to ensure that administered doses do not surpass the toxicity boundaries. Safety data from all patients in Parts 1A (safety cohort) and available data at cutoff from Parts 1B (pharmacodynamic cohort) will be used to determine the MTD.* The dose finding decision will be based on 1-cycle (21-day) DLT observation for patients enrolled into IV administration portion and 1-cycle (28-day) DLT observation for patients enrolled into subcutaneous dosing portion. A staggered start will be employed at all dose levels. A single patient will be dosed and observed for 48 hours. If no safety concerns arise during this 48-hour period, a second patient will be enrolled into the same dose level cohort.

Late immune-related DLTs are irAEs that meet the same grading criteria as DLT criteria but occur after the initial 21-day DLT period for IV administration, or 28 days for SC administration, and during the 120-day assessment period. Late immune-related DLTs will be added to the mTPI approach to reassess the dose-finding decisions.

Safety information, provided by additional patients enrolled into each dose level expansion will also be taken into account for MTD determination. If the DLT rate is estimated to reach >33% or more at any dose level, enrollment at that level and all higher levels will be temporarily stopped, and safety data will be analyzed. The decision to move forward with enrollment will follow the same DLT target as described previously. Dose escalation will continue until an MTD has been established or a prespecified maximum dose level has been reached.

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in the current dose level to determine one of the following dose-finding decisions: the subsequent dose should be escalated, maintained at the current dose, or de-escalated in the next cohort of 2 to 4 patients, or the trial should be terminated (see Table 1).

In principle, all patients must be evaluated for a minimum period of 21 days (q3w dosing interval) or 28 days for the subcutaneous cohort. If a patient withdraws from the study before Day 21 (or 28 days for the subcutaneous cohort) for reasons other than drug- related toxicity, another patient may be enrolled to replace that patient in the current cohort. However, if a

patient discontinues close to Day 21 (or 28 days for the subcutaneous cohort) for reasons other than toxicity and due to an evident nondrug-related event, the patient may be deemed evaluable for safety if safety assessments have been unremarkable and the investigator and sponsor's medical monitor both agree that the patient is evaluable for DLT safety observation.

Table 1. Decision Rules

Number of Patients having DLT	Number of Patients Treated at a Dose Level													
	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12	n=13	n=14	n=15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E	E	E
2	U	D	S	S	S	S	S	S	S	E	E	E	E	E
3		U	U	D	D	S	S	S	S	S	S	S	S	S
4			U	U	U	U	D	D	D	S	S	S	S	S
5				U	U	U	U	U	D	D	D	D	D	S
6					U	U	U	U	U	U	U	D	D	D
7						U	U	U	U	U	U	U	U	U

Actions to be taken:
D = De-escalate the dose; E: Escalate the dose; S: Stay at the dose.
U = Unacceptable toxicity.

The dose escalation Part 1 of the study will stop if any of the following criteria is met:

1. The maximum sample size has been achieved (approximately 40 patients in total);
2. 6 to 15 patients have been enrolled at a dose level that is predicted to be the MTD per the mTPI method;
3. All dose levels explored appear to be overly toxic, and the MTD cannot be determined;
4. All candidate dose levels have been tested and deemed safe.

2.2.2. Part 2 Dose Expansion

Part 2 dose expansion will include 2 arms: Arm 1 will enroll approximately 60 patients with NSCLC who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable but have not previously received anti-PD-1 or anti-PD-L1. Arm 2 will enroll approximately 40 patients with urothelial carcinoma who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable but have not previously received anti-PD-1 or anti-PD-L1. All patients in Part 2 will receive 300 mg PF-06801591 SC q4w. The 300 mg SC dose level in Part 2 was selected based upon safety, PK, PD, and preliminary anti-tumor activity observed in Part 1, as well as the maximum injection volume considered feasible with the current formulation.

After the first 30 NSCLC patients have been enrolled and have either completed their first tumor assessment (at approximately 8 weeks post treatment), or have discontinued from the study before their first scheduled tumor assessment, preliminary assessment of safety and efficacy data maybe completed. This preliminary data may provide guidance in the decision to the increase or decrease the sample size of each arm, to add other tumor types in a future amendment, or to initiate additional clinical studies. The specific details for this data look are described in Section 7.

3. ENDPOINTS AND COVARIATES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Part 1:

- *DLTs at escalated doses of PF-06801591.*The specific definition of DLT is provided in the study protocol.
- *Adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), timing, seriousness, and relationship to study therapy PF-06801591.*
- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.*

Part 2:

- *AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness and relationship to study therapy PF-06801591 administered by SC administration.*
- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03) and timing.*
- *ORR as assessed using RECIST version 1.1 and irRECIST. ORR is defined as the proportion of patients who achieved completed response (CR) or partial response (PR) per RECIST 1.1, or irRECIST.*

3.2. Secondary Endpoint(s)

Part 1:

- *PK parameters of PF-06801591: Cycle 1 and Cycle 4 C_{max}, area under the concentration versus time curve (AUC) from time zero to the last quantifiable time point prior to the next dose (AUC_{last}), and if data permit, CL, V_d, volume of distribution at steady state (Vss), accumulation ratio (Rac) when feasible, and terminal elimination $t_{1/2}$.*

- *Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) against PF-06801591.*

- *PD-1 receptor occupancy (RO) by PF-06801591, as assessed by measuring the levels of unbound (free) cell surface PD-1 on circulating T cells over time following PF-06801591 administration.*

- *Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 and immune-related RECIST (irRECIST); and proportion of subjects with PR (and irPR, as appropriate).*

- *Time-to-event endpoints based on RECIST and irRECIST and PFS (and irPFS as appropriate), Duration of stable disease (DOSD, or irDOSD as appropriate), and Duration of response (DOR, or irDOR as appropriate).*

    - PFS is defined as the time from treatment start date to date of first documentation of progression or death due to any cause.
    - Duration of stable disease is defined from the start of the treatment until the criteria for progression are met, taking as reference the smallest tumor measurements recorded since the treatment started, including the baseline measurements. This endpoint is applicable to the subset of patients who achieved a best overall response of stable disease (SD) , those patients whose best overall response is not SD will be excluded from this endpoint analysis. A minimum of 6 weeks (with a - 5 days window, which is essentially a minimum of 35 days) interval of two assessments is required for this endpoint.
    - Duration of response is defined as the time from start date (which is the date of first documentation of PR or CR) to date of first documentation of objective progression or death. DOR is only applicable to those patients with an objective response.

Part 2:

- *Time to event endpoints by PF-06801591 administered by SC based on RECIST and irRECIST, including time to response (TTR) and time to progression (TTP) as well as PFS (and irPFS as appropriate), DOSD (and irDOSD as appropriate), and DOR (and irDOR as appropriate).* Time to response is defined as the time from the study treatment date to the first documentation of PR or CR. Time to progression is the time from start date to date of first documentation of objective progression.

- *Median time to death, proportion of patients alive at 6 months, 1 year, and 2 years.* Time to death (i.e. overall survival) is the time from treatment start date to date of death due to any cause.

- *Trough PF-06801591 concentrations for selected cycles.*

- *Incidence of ADA and NAb against PF-06801591 administered by SC.*

3.4. Covariates

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

4. ANALYSIS SETS

4.1. Full Analysis Set

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

4.2. Safety Analysis Set

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

4.3. 'PER PROTOCOL' Analysis Set

The per protocol analysis set includes all enrolled patients who received at least one dose of study treatment and who did not have major treatment deviations during the Cycle 1. For the IV administration of PF-06801591, patients with major treatment deviations in the 21-day DLT observation period are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation.

For the SC administration of PF-06801591, patients with major treatment deviations in the 28-day observation period will not be evaluable for DLT.

Major treatment deviations include:

- *Administration of <50% of the planned dose of PF-06801591, provided that the reduction is not due to toxicity attributable to PF-06801591.*
- *Administration of >150% of the planned dose of PF-06801591.*

4.4. PK Analysis Set

4.4.1. PK Concentration Set

The PK concentration population is defined as all patients who receive PF-06801591, have no protocol deviations affecting the PK assessment, and have at least 1 post-dose concentration measurement.

4.4.2. PK Parameter Set

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

4.5. PD Biomarker Analysis Set

[redacted]

The biomarker analysis set includes all enrolled patients with at least one of the pharmacodynamic/biomarker parameters evaluated at pre- and/or post-dose.

4.6. Modified Intent-to-Treat Set

The modified intent-to-treat (mITT) population is defined as all the randomized subjects who have received at least 1 dose of study medication, have measurable disease baseline assessment (within 28 days prior to study entry) and at least 1 post baseline assessment or disease progression or death before the first tumor assessment. The mITT population will be used for anti-tumor assessment.

4.7. Immunogenicity analysis set

The immunogenicity analysis set is defined as patients who receive at least 1 dose of study treatment and have at least 1 ADA or NAb sample collected.

4.8. Treatment Misallocations

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

4.9. Protocol Deviations

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

5. GENERAL METHODOLOGY AND CONVENTIONS

This is an open-label dose escalation study and no interim analysis or blinding is planned for this study.

5.1. Statistical Hypotheses

There are no statistical hypotheses.

5.2. Statistical Decision Rules

5.2.1. Part 1 (MTD Finding)

Part 1 dose escalation phase of this study employs an mTPI design to estimate the MTD. The mTPI design employs a simple beta-binomial model with prior a conjugated prior beta (0.5, 0.5). Decision rules are based on calculating the unit probability mass (UPM) of 3 intervals corresponding to underdosing, proper dosing, and overdosing in terms of dose limiting toxicity. A proper dosing interval is centered at the target toxicity rate (pT) of 27.5% with 5% uncertainty (0.225 < pT <0.325). The under dosing interval is (0, 0.225), and the overdosing interval is (0.325, 1). The 3 dosing intervals are associated with 3 different dose escalation decisions. The underdosing interval corresponds to a dose escalation (E),

overdosing corresponds to a dose de-escalation, and proper-dosing corresponds to staying at the same current dose. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, decision E (to escalate) will be executed, and the next cohort of patients will be treated at the next-higher dose level. Under the mTPI design, a trial is terminated when either the lowest dose is above the MTD or a pre-specified maximum sample size for Part 1 (approximately 40) is reached.

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 cohort size of n=3 and for a DLT that occurs in 10% of patients, there is a greater than 90% probability of escalating. Conversely, for a DLT that occurs with a rate of 70%, the probability of escalating is 3%. It is assumed that dose escalation occurs with either 0/3 or 1/6 patients with DLTs.

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

5.2.2. Part 2 (Dose Expansion)

Part 2 (N=100) of this study is intended to further characterize the safety, efficacy, PK, PD, and immunogenicity profiles of 300 mg of SC PF-06801591 in anti-PD-1 or anti-PD-L1 treatment naïve patients with NSCLC (N=60) and urothelial carcinoma (N=40) who have progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable.

Summary statistics will be provided for trough PF-06801591 concentrations, safety endpoints, immunogenicity, pharmacodynamic/biomarkers, and efficacy data.

When the first 30 NSCLC patients have been enrolled and have either completed their first tumor assessment (at approximately 8 weeks post treatment), or have discontinued from the study before their first scheduled tumor assessment, preliminary assessment of safety and efficacy data may be completed. This preliminary data may provide guidance in the decision to increase or decrease the size of each arm, to add other tumor types in a future amendment, or to initiate additional clinical studies.

5.2.3. Sample Size Determination

The exact sample size for the dose escalation design in Part 1 cannot be specified in advance due to the dynamic features of mTPI. For the first dose level (0.5 mg/kg IV), in the absence of actual DLTs, a total of 2 patients will be enrolled: 2 patients in Part 1A and no patient in Part 1B. For subsequent dose levels it is anticipated that approximately 2 to 4 patients will be enrolled in Part 1A and approximately 2 to 5 patients in Part 1B with available pre- and on-treatment biopsies for IHC testing and up to 9 patients at dose levels 1, 3, and 10 mg/kg administered by IV in Part 1. A

single cohort with SC administration at a dose level of 300 mg of PF-06801591 will be opened for enrollment shortly after the cohort at a dose level of 3 mg/kg IV in Part 1A will have completed enrollment and the 21-day DLT observation period. This cohort at a dose level of 300 mg SC will seek 2 to 4 patients in Part 1A, up to 11 patients in Part 1B with available pre- and on-treatment biopsies for IHC testing, and up to 15 patients in Part 1. The actual Part 1 sample size may be smaller, depending on the underlying dose toxicity profile, and the number of dose levels studied.

Part 2 of the study will enroll approximately 60 patients with NSCLC who progressed on or were intolerant to systemic therapy or for whom systemic therapy was refused or unavailable and are treatment naïve for anti-PD-1 or anti-PD-L1. NSCLC was selected for historical comparability to prior large anti-PD-1 studies and dosing of 300 mg SC in Part 2 has been selected based on safety, PK, available biomarker data and preliminary anti-tumor activity from Part 1. There is no hypothesis testing in Part 2. Estimation approach is used to characterize the precision of response data. The estimation of ORR using N=60 is described as follows. Suppose that the ORR estimate is 19% in Part 2 with N=60, then the 80% and 90% confidence intervals of the true ORR will be (13.3, 26.3%) and (12.1, 28.6%) respectively. Note that an ORR of 19% was observed in a clinical trial for nivolumab in previously treated NSCLC patients. In Part 2, approximately 40 urothelial cancer patients will also be enrolled, the sample size is based on clinical considerations of expanding the safety database.

5.3. General Methods

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

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

5.3.1. Analyses for Time to Event Data

Time to event endpoints in this study include progression-free survival (PFS), duration of response (DOR), duration of stable disease (DoSD), time to response (TTR), time to progression (TTP), and overall survival (OS). When appropriate and data permits, the immune-response version of these endpoints based on irRECIST will also be explored. The specific definitions of these endpoints are provided in Section 3. These endpoints will be summarized using the Kaplan-Meier method[2] and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint (Brookmeyer and Crowley, 1982)[3] will be provided.

5.3.2. Analyses for Binary Data

Binary endpoints in this study include ORR, complete response (CR), partial response (PR) based on RECIST 1.1. When appropriate and data permits, the immune-response version of these

endpoints based on irRECIST will also be explored. If deemed necessary disease control rate (i.e. DCR, which is defined as the proportion of patients that achieved CR, or PR, or stable disease) may also be calculated for Part 2. Descriptive statistics along with the corresponding 2-sided 95% confidence intervals using an exact method will be provided for these endpoints.

5.3.3. Analyses for Continuous Data

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

5.4. Methods to Manage Missing Data

5.4.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of onset cannot be prior to day one date). In this case, the date resulting in 0 time duration will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration). This excludes the pharmacokinetic, ECG, and pharmacodynamic analyses, which will only use the actual date collected or if date not available deem the data missing.

5.4.2. Efficacy Analysis

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

5.4.3. Pharmacokinetics

Concentrations below the limit of quantification

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

Deviations, missing concentrations and anomalous values

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

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

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of

the data are missing.

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

Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter, this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.4.4. Pharmacodynamic Parameters

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

6. ANALYSES AND SUMMARIES

For efficacy related endpoints in this study, as both RECIST 1.1 and irRECIST will be used for tumor assessments, and there are different requirements in these criteria in terms of confirming tumor response or progression, the following analysis plan will be implemented:

Endpoint	**Part 1**		**Part 2**	
	RECIST 1.1	irRECIST	RECIST 1.1	irRECIST
ORR (or irORR)	Unconfirmed	Both	Both	Both
PFS (or irPFS)	Unconfirmed	Both	Unconfirmed*	Both
DOR (or irDOR)	Unconfirmed	Both	Both	Both
DOSD (or irDOSD)	Unconfirmed	Both	Both	Both
TTP	Unconfirmed	Both	Unconfirmed*	Both
TTR	Unconfirmed	Both	Both	Both

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

In the "unconfirmed" analyses (i.e. tumor response or progression without confirmation required),

all tumor assessments data will be included for analyses. Specifically, regardless if a patient's tumor response or progression is subsequently confirmed or not, the patient data will all be included in the "unconfirmed" analyses. This is a more comprehensive analysis where tumor confirmation is not required and not taken into account. For example in the ORR analysis, if a patient achieved CR or PR, regardless it is subsequently confirmed or not, the patient will be included in the numerator.

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

6.1. Standard Analyses

Study Conduct and Patient Disposition

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

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

Baseline Characteristics

Baseline characteristics such as demographics, prior medication, medical history, ECOG performance status, and primary diagnosis will be tabulated and listed. For ECOG performance status a shift table (worst post-baseline vs baseline may be produced). The Safety Analysis Set will be used.

Treatment Administration/Compliance

Listings and tables by dose level will be provided. Cycle length is 21 days (+/- 2 days) for IV infusion and 28 days (+/- 2 days) for subcutaneous administration. Day 1 of a cycle is the first date of dose within that cycle. The safety analysis set will be used.

Dose modifications may occur in the following ways:

- Cycle delay—Day 1 of current cycle starts later than 21 (+2) days from Day 1 of the previous cycle (only applies to cycle 2 and above). For subcutaneous administration, 28 (+2) days, rather than 21 (+2) days, will be used in determining cycle delay. For example, after cycle 1 ended for a patient in Part 2, a new cycle didn't start until 28 (+2) days after (but before 56 days after) cycle 1 day 1, the

newly started cycle will be considered as cycle 2, and cycle 2 is considered delayed.

- Cycle skip – Day 1 of current cycle starts later than 42 (+4) days from Day 1 of the previous cycle (only applies to cycle 2 and above). For subcutaneous administration, 56 (+4) days, rather than 42 (+4) days, will be used in determining cycle skip. For example, After cycle 1 ended for a patient in Part 2, a new cycle didn't start until 56 (+4) days after cycle 1 day 1, the newly started cycle will be considered as cycle 3, and cycle 2 is considered skipped for this patient.

- Dose reduction— a decrease in the administered total daily dose (non-zero) compared to the planned total daily dose upon enrollment. If in the CRF the prescribed dose unit is mg/kg, but the actual dose is in mg the actual dose mg/kg should be calculated considering the body weight of the patient at that visit. Intrapatient dose reductions are not permitted during the study unless, in discussion with the sponsor, a dose level is deemed beyond the determined MTD.

The following will be summarized by subject for overall and each dose level:

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

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

- Total number of cycles started;
- Number of cycles started per subject (median, range);
- Number of cycles before 1st delay (median, range);
- Number of cycles before 1st reduction (median, range);

- Number of cycles before 1st interruption (median, range).
- Number of cycles before 1st dose skip (median, range).

The following will be summarized for cumulative dose by dose level and cycle:

- Summary statistics (mean, median, standard deviation and range) of cumulative dose and percent of starting dose (compared to Day 1 dose of each cycle).

Listings by subject (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0 mg), administered total daily dose for each period, any missed doses with unknown dates (Y/N), number of missed doses with unknown dates, reason for any dosing changes.

Listings by subject and each cycle (ordered by dose level): cycle length, total planned dose, administered total dose, percentage of planned dose, dose delay (yes/no), dose reduction (yes/no), and dose interruption (yes/no).

Prior, Concomitant, and Further Therapies

Prior, concomitant, and further therapies (drug and non-drug treatments) will be coded by the World Health Organization (WHO) medical dictionary. Listings of prior, concomitant, and further therapies will be provided separately.

6.2. Analysis of Primary Endpoint

6.2.1. DLT (Part 1)

Dose Limiting Toxicity is the primary endpoint of the dose escalation phase of the study, which will be summarized by dose level using the Per Protocol Analysis Set for patients in the dose escalation portion of the study. A listing of the DLTs will also be provided. If necessary, a summary and listing of the DLT by malignancy may be provided using the Per Protocol Analysis Set for patients in the MTD expansion portion of the study.

6.2.2. Safety Endpoints (Part 1 and Part 2)

Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 4.03 and coded using the MedDRA.[4] The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1) for overall and each dose. The Safety Analysis Set will be used. Part 1 and Part 2 data will be summarized separately and will also be pooled together for analysis. Pfizer standard on safety data reporting will be followed.

Laboratory Tests Abnormalities

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

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

6.2.3. ORR (Part 2)

ORR, as assessed using RECIST version 1.1 and irRECIST, is a primary efficacy endpoint for Part 2. The following analyses will be performed in the mITT population by tumor type (NSCLC or urothelial carcinoma) and pooled:

1. ORR by visit, separately for RECIST 1.1 and irRECIST: investigator provided tumor response CR, PR, and CR+PR will be presented by descriptive statistics (frequency and percentage) and 95% confidence interval.

2. Best overall response of CR, PR, and CR+PR, separately for RECIST 1.1 and irRECIST. This will include best overall response derivation without confirmation and with confirmation. Descriptive statistics (frequency and percentage) and 95% confidence interval will be provided.

6.3. Analysis for Secondary Endpoints

6.3.1. Efficacy Endpoints Analysis

Except ORR for Part 2, efficacy is a secondary objective. The efficacy analysis will be performed in the mITT population. Part 1 and Part 2 data will be summarized separately, and may also be pooled together for analysis if deemed necessary. Efficacy data assessed by RECIST will be analyzed separately from those assessed by irRECIST.

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

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

Summary tables of best overall response rate, PFS, OS, DOSD, and DOR may be provided

by the groups aforementioned when deemed necessary (e.g. if there are ≥5 patients in a specific group).

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

Swimmer plot for individual clinical response and time on treatment, waterfall plot for individual tumor size percent change from baseline, and spider plot for individual tumor size percent change from baseline over time will be presented for RECIST and irRECIST separately.

The following table provides an overview of the efficacy analysis.

Endpoint	**Analysis Set**	**Statistical Method**	**Model/ Covariates/ Strata**	**Missing Data**
Overall response	mITT	Exact CI	See aforementioned summary descriptions on data pooling across dose and tumor type	Observed case
Overall Survival	ITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored at last visit
Progression Free Survival (PFS)	mITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling3721 across dose and tumor type	Censored per Appendix 9.2
Time to Progression (TTP) and Time to Response (TTR)	mITT	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 9.2

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data
Duration of Response (DOR)	mITT	Kaplan-Meier	See aformentioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 9.2
Duration of Stable Disease (DOSD)	mITT	Kaplan-Meier	See aformentioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 9.2

6.3.2. Pharmacokinetics Analyses

The concentration-time data of PF-06801591 will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) according to dosing cohort and time for each part of the study. In addition, the concentration-time data from Part 2 will also be summarized by descriptive statistics according to tumor type.

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

Presentation of PF-06801591 concentration-time data

The concentration-time data of PF-06801591 will be presented as below:

- a listing of all concentrations by cohort, subject ID and nominal time. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- a summary of concentrations by cohort and nominal time, where the set of statistics will include n, mean, standard deviation, median, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- for the concentration-time data after the 1st and 4th dose, median concentration-time plots (on both linear and semi-log scales) against nominal time postdose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time postdose).
- for the concentration-time data after the 1st and 4th dose, mean concentration-time plots (on both linear and semi-log scales) against nominal time postdose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by

cohort and time postdose).

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

Calculation of PF-06801591 PK parameters

For patients enrolled in Part 1 of the study, the individual concentration-time data of PF-06801591 during Cycle 1 and Cycle 4 will be analyzed separately by non-compartmental methods to estimate the PK parameters. The PK parameters estimated will include C_{max}, T_{max}, and AUC_{last} (AUC_{tau} at steady state). If data permit or if considered appropriate, $t_{1/2}$, CL (or CL/F for SC cohort), V_d (or V_d/F for SC cohort; V_{ss} at steady state), and accumulation ratio (R_{ac}) will also be estimated for Cycle 1 and Cycle 4. For IV cohorts in Part 1, individual Cycle 6 pre-dose concentrations will be used in lieu of Cycle 5 pre-dose concentrations while calculating Cycle 4 PK parameters. The PK parameters will be summarized descriptively by dose level and cycle.

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

For patients enrolled in Part 2 of the study, trough concentrations of PF-06801591 will be summarized descriptively by cycle and by tumor type.

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

Parameter	*State*	*Method of Determination*
AUC_{tau}	sd, ss	Linear/Log trapezoidal method
AUC_{last}	sd,ss	Linear/Log trapezoidal method
AUC_{inf} [a]	sd	AUClast + (Clast*/kel), where Clast* is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	sd, ss	Observed directly from data
T_{max}	sd, ss	Observed directly from data as time of first occurrence
CL and CL/F	sd, ss	Dose / AUC_{inf} for sd[a] Dose / AUC_{tau} for ss

[redacted]

Vd/F	sd, ss	Dose / AUC_{inf} for sd Dose / (AUC_{τ} / kel) for ss
Vss [a]	sd, ss	CL * MRT, where MRT is the mean residence time adjusted for the duration of infusion
t½[a]	sd	Loge(2)/kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration time curve.

[a] if data permit

6.3.3. Immunogenicity Assessment

For the immunogenicity data, the percentage of patients with positive ADAs and neutralizing antibodies will be summarized by overall, tumor type, and dose within tumor type as data permit. For patients with positive ADAs, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. In addition, efforts will be made if data permit, as appropriate, to examine possible correlations of the ADA response with clinical data on the PK, safety and/or efficacy.

6.3.4. RO of PD-1 by PF-06801591 in Circulating T Cells

Descriptive statistics of PD-1 receptor occupancy by PF-06801591 evaluated from the percentage of free (ie unbound) PD-1 on the surface of circulating T cells will be summarized by overall, tumor type, and dose within tumor type as data permit.

[redacted]

6.5.Population PK and PK/PD Modeling

Pharmacokinetic and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-06801591 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

[redacted]

6.6. ECG and Vital Sign Data Analysis

The analysis of ECG results will be based on patients in the Safety Analysis Set with baseline and on-treatment ECG data, and will follow the ICH E14 guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.[5]

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

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

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

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

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

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

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

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

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

7. INTERIM ANALYSES

There is no formal interim analysis planned in this study. In Part 2, a Bayesian approach will be used aiming to detect early sign of efficacy. The following analyses will be performed:

1. *Approximately 8 weeks after the first 30 NSCLC patients have enrolled, a data snapshot will be taken for an early data assessment. Descriptive statistics (frequency and percentage) for tumor response (CR, PR, PD, stable disease [SD] etc.) from the first tumor assessment; ORR, the proportion of patients who achieved unconfirmed CR or PR, and the 95% confidence interval for ORR; DCR (disease control rate), the proportion of patients who achieved unconfirmed CR or PR or SD, and the 95% confidence interval for the DCR will be presented. If tumor response data are collected based on both RECIST 1.1 and irRECIST, separate presentations will be generated for each response criterion. In this data snapshot, some patients may have gone through their second tumor assessment as of the data snapshot, however only data through the first tumor assessment will be used for this analysis. The above described analyses may be repeated, if deemed necessary, when the first 40 or 45 NSCLC patients are enrolled and have gone through their first tumor assessment. This preliminary data may provide guidance in the decision to the increase or decrease the sample size of each arm, to add other tumor types in a future amendment, or to initiate additional clinical studies.*

2. *In the early data assessment, a Bayesian approach will be used to calculate the posterior probability that the true ORR is greater than or equal to the minimal expected ORR. For example, the minimal expected ORR if all patients received only one tumor assessment is approximately 10% but may be adjusted based on how many patients had assessments beyond 8 weeks and the PD-L1 status of patients which will be tested at baseline. A beta prior (0.235, 1) is chosen, where the parameter beta is set to be 1, and parameter alpha 0.235 was calculated from a reference product pembrolizumab on NSCLC patients where a 19% ORR was observed. For example, if 4 responders are observed out of the first 30*

patients as of the first tumor assessments, the posterior probability that the true ORR is greater than a minimal expected ORR of 10% is approximately 70%.

A final analysis will be performed when all 60 NSCLC patients and 40 urothelial cancer patients are enrolled and have completed their scheduled tumor assessments.

This is an open label study, the Pfizer study team will review safety, immunogenicity, pharmacodynamics, exploratory efficacy and other data throughout the study.

8. REFERENCES

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9. APPENDICES

9.1. Details of Definitions of Endpoints

DLT Definitions

Previous anti-PD1 mAbs were administered in >1000 patients and were associated in the clinic with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-mediated adverse reactions), likely to be related to the mechanism of action. Immune-mediated adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal or other organ systems.[9]

Severity of AEs will be graded according to CTCAE version 4.03. For the purpose of a dose finding decision, any of the following drug-related AEs occurring during the first cycle of treatment (21 days, or 28 days for subcutaneous administration) will be classified as DLTs following review by the investigators and the sponsor:

- Grade 5 AE.
- Hematologic toxicity:
    - Any Grade 4 hematologic AE, with the following clarifications.
    - Grade 4 neutropenia lasting >5 days from initiation of granulocyte-colony stimulating factor.
    - Grade 4 thrombocytopenia with bleeding.
    - Platelet transfusion requirement or a platelet count <10,000/uL.
- Non-Hematologic Toxicity:
    - Grade 4 non-hematologic AE.
    - Grade 3 AE lasting >7 days despite optimal supportive care.
    - Grade 3 central nervous system AE regardless of duration.
    - Concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3X upper limit of normal (ULN) and total bilirubin >2X ULN (potential Hy's law case see section Potential Cases of Drug-Induced Liver Injury).

The following AEs will not be adjudicated as DLTs:

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

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

- Isolated Grade 3-4 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

- Grade ≥3 infusion reactions and allergic reactions will not be considered dose limiting as they are unlikely to be dose related, but all available information on these events will be collected. If Grade ≥3 infusion reactions occur in ≥2 of the first 10 patients at any dose level, or if the occurrence is ≥5% thereafter, a mandatory pre-treatment regimen for all new patients will be implemented. The incidence of Grade 1 and 2 reactions will also be taken into account. If a total rate of >10% all-grade infusion or allergic reactions is observed, a mandatory pre-treatment regimen for all new patients will be implemented.

Information regarding the DLT observation period can be found in the Criteria for Dose Finding (See protocol Section 3.1.4). For dose escalation, DLT observation is required for 21 days for IV infusion and 28 days for subcutaneous administration. However, DLT observation will continue for at least 120 days from first dose (or completion of 5 cycles, if still on treatment) to assess late immune-related dose-limiting AEs, and will be taken into account for MTD determination.

Late immune-related DLTs

Late immune-related DLTs are irAEs (see protocol Appendix 9) that meet the same grading criteria as DLT criteria but occur after the initial 21-Day DLT period for IV or 28-day DLT period for SC and during the first 120-day assessment period. Late immune-related DLTs will be added to the mTPI approach to reassess the dose-finding decisions.

For any patient being treated at dose levels that are subsequently considered to exceed the MTD, the option to reduce their dose will be discussed between the investigator and the sponsor's medical monitor. If the patient tolerated the above-MTD dose level well and is deriving clinical benefit, continuation of treatment at the above-MTD dose level will require re-consenting.

Maximum tolerated dose (MTD)

The maximum tolerated dose (MTD) is defined as the highest dose with true toxicity probabilities in the equivalence interval (EI) where the EI is defined as [22.5%-32.5%].

In practice, the MTD will be the highest dose associated with the occurrence of DLTs ≤33% (eg, ≤3 of 9 evaluable patients experience a DLT during at least [90 days after the first dose]) or the first 5 treatment cycles if the patient remains on treatment.

Recommended Phase 2 Dose (RP2D) Definition

The recommended Phase 2 dose (RP2D) is the dose chosen for further study combining the MTD and OBD, based on Phase 1 study results, from the primary and secondary endpoints of the study. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D lower than the MTD. Next to safety assessment, careful consideration will be given to immunomodulatory effects, PK information, and preliminary anti-tumor activity. If an OBD can be determined, this will be a key factor in the determination of the RP2D.

9.2. Time to Event Data Analysis Censoring Rules

Table 9.2.1: Progression Free Survival and Duration of Response

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

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

2. Or within 28 days of discontinuation of treatment.

Table 9.2.2: Time to Progression

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

Situation	Date of Progression/Censoring[1]	Outcome
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation[2]	Censored
New anticancer treatment <28 days after discontinuation of treatment without progression	Date of last objective tumor assessment prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Start date (C1D1)	Censored
Death without objective progression prior to treatment discontinuation[2]	Date of last objective tumor assessment prior to death	Censored
Progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1. For censoring date, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.

2. Or within 28 days of discontinuation of treatment.

DOSD and DOR

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

9.3. Categorical Classes for ECG and Vital Signs

Categories for QTcB and QTcF

QTcB/QTcF (ms)	max. ≤450	450< max. ≤480	480< max.≤500	max. >500
QTcB/QTcF (ms) increase from baseline	max. <30	30≤ max. <60	max. ≥60	

Categories for PR and QRS

PR (ms)	max ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max ≥200	
QRS (ms) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Categories for Vital Signs

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

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

9.4. RECIST 1.1 Tumor Assessment Criteria

Adapted from E.A. Eisenhauer, P. Therasseb, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.[6]

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

Measurable Lesions

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

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

Non-measurable Lesions

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

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

Special Considerations Regarding Specific Lesions

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

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

Recording Tumor Measurements

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

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

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

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

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

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- **Complete Response (CR):** disappearance of all target lesions.
- **Partial Response (PR):** at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.

- **Stable Disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

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

Non-Target Lesions

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

Response in non-target lesions is defined as follows:

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG-PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up.
- No FDG-PET at baseline and a positive FDG-PET at follow- up: if the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Determination of Overall Response by the RECIST 1.1 Criteria

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

Table 10.4.1: Response Evaluation Criteria in Solid Tumors by RECIST 1.1

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Target lesions	Non-target lesions	New Lesions	Overall response
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease,			
PD = progressive disease, and NE = inevaluable.			

Best overall response

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

Table 10.4.2 Best Overall Response When Confirmation of CR and PR Required

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

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

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

9.5. Immune-related RECIST (irRECIST) Tumor Assessment Criteria

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-cytotoxic T lymphocyte-associated protein 4 (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. 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.

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.

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare type responses into the RECIST v1.1 (irRECIST).[7]

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

- Requires confirmation of both progression and response 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) with a minimum absolute increase of 5 mm, 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.