A PHASE 1, OPEN-LABEL, DOSE ESCALATION STUDY OF PF-04518600 AS A SINGLE AGENT AND IN COMBINATION WITH PF-05082566 IN PATIENTS WITH SELECTED LOCALLY ADVANCED OR METASTATIC CANCERS

Compounds:	PF-04518600 and PF-05082566
Compound Name:	Not Applicable (N/A) for PF-04518600 Utomilumab for PF-05082566
United States (US) Investigational New Drug Application (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	2014-004107-75
Protocol Number:	B0601002
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Final Protocol Amendment 6	02 May 2018	Major changes to the protocol include the following: • Section 4.1.1 Part A2 Monotherapy. Change: Incorporated previous protocol administrative changes. Rationale: Nivolumab has been approved for the treatment of HCC by the FDA. Change: Revised Part A2 inclusion: Patients with histological or cytological diagnosis of advanced/metastatic HCC who are treatment naïve and have declined standard of care, or have had at least 1 prior line of systemic therapy. Prior anti-programmed death-ligand 1 / anti-programmed cell death protein-1 (anti-PD-L1/PD-1) therapy is allowed. Rationale: Clarification provided, as previous language allowed for 0 to 2 prior lines of therapy, and now includes prior anti-PD-L1/PD-1 for HCC as well. Change: Provided specific ANC inclusion value $\geq$1,000/mm^3 or 1.0 x 10 ^{9}L for HCC patients only. Rationale: Lowering the entry criteria from 1,500/mm^3 to 1,000/mm^3 for the HCC monotherapy cohort (A2) is not considered a significant safety risk based on previous cohort data. One out of 52 patients treated in the A1 monotherapy cohort experienced a treatment-related Grade 2 decrease in neutrophils. . The ANC threshold was lowered for just HCC, as HCC patients often have lower baseline ANC due to cirrhosis and portal hypertension. Change: Removed inclusion criteria 9 –Amylase and lipase <1.5 ULN for HCC only patients.

		Rationale: There is no safety concern for the removal of this criteria based on the previous cohort data. Asymptomatic elevations of amylase and lipase have been noted on the study without clinical consequences, and amylase and lipase are not reflective of liver function. • Section 3, Section 5, and the Study Design Section of the Protocol Summary. Change: Incorporated previous protocol administrative changes. Rationale: Selected dose for PF-04518600 in the B2 combination therapy dose expansion cohorts is 30 mg (a flat dose equivalent to 0.3 mg/kg) intravenously (IV) Q2W in combination with PF-05082566 20 mg IV every 28 days. • Section 3.1.2.2 Part B2 Dose Expansion Section 4.1 Inclusion Criteria, Sub-section 4.1.2 Part B Combination Therapy – Part B2 Arm 1 only (a). Change: (a) Ocular melanoma patients with advanced/metastatic disease. Rationale: Provided clarification to the inclusion criteria for the ocular melanoma patient population to now include all advanced/metastatic disease regardless of prior therapy. • Section 3.1.2.2 Part B2 Dose Expansion Section 4.1 Inclusion Criteria, Sub-section 4.1.2 Part B Combination Therapy – Part B2 Arm 1 only (b). Change: (b) Cutaneous/acral melanoma patients with advanced/metastatic disease who have received checkpoint inhibitor (anti-PD-L1, anti-PD-1, or anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA4)) based treatment on which disease progressed. [Note: Checkpoint inhibitor may have been part of a combination therapy, as long as the combination did not contain

		OX40 or 4-1BB agonist.] Any questions on prior treatment may be discussed with the Sponsor. Rationale: (1) The specification anti-PD-L1, anti-PD-1, or anti-CTLA4 "given as most recent line of therapy" was removed, as well as the text regarding specific prior systemic therapy for advanced/metastatic disease therapies for BRAF and MEK inhibitors. Change: (2) Removed conditional statement "as long as progression did not occur in the first 3 months of receiving checkpoint inhibitor treatment." Rationale: Stability on checkpoint inhibitors may not necessarily correlate with response to study treatment. As long as the cutaneous/acral melanoma patient has received checkpoint inhibitor based treatment and progressed, the patient qualifies for study entry. • Section 3.1.2.2 Part B2 Dose Expansion • Section 4.1 Inclusion Criteria, Sub-section 4.1.2 Part B Combination Therapy – Part B2 Arm 2 Change – Part B2 Arm 2: Histological or cytological diagnosis of NSCLC with advanced/metastatic disease. Patients must have previously received prior anti-PD-L1 or anti-PD-1 mAb on which disease progressed. [Note: Previous anti-PD-L1 or anti-PD-1 mAb may have been part of a combination therapy, eg, in combination with chemotherapy, as long as the combination did not contain OX40 or 4-1BB agonist.] Rationale: Checkpoint inhibitors are increasingly being used in combinations both as approved therapies such as with chemotherapy and experimental combinations. As a result, this amendment clarified combination therapy as an acceptable previous line of therapy. Change: The specification that previous

		anti-PD-L1 or anti-PD-1"given as most recent line of therapy" was removed for Part B2, Arm 2, as well as the conditional statement that NSCLC patients did not have progressive disease as best overall response on recent PD-L1/PD-1 therapy (ie, stable disease ≥3 months, PR, or CR). Rationale: Patients may have received treatment following a checkpoint inhibitor prior to enrollment. Stability on checkpoint inhibitors may not necessarily correlate with response to study treatment. Patient will now be eligible for enrollment regardless of prior best overall response.

Final Protocol Amendment 5	16 August 2017	Major changes to the protocol include the following: • The administrative changes described in past Protocol Administrative Change Letters (PACL) have been incorporated into the amendment. • Time ranges/windows of ±2 days have been added for follow-up phone calls to collect additional late immune related adverse event information. • Part B2 Arm 1 has been changed from head and neck squamous cell carcinoma (HNSCC) patients to melanoma patients (including both ocular and cutaneous melanoma). **Rationale for melanoma as tumor type:** 1) 2 confirmed partial responses (PR) in the melanoma patients enrolled to date: 1 in an ocular melanoma patient and 1 in a cutaneous melanoma patient; 2) no PRs observed in the HNSCC patients enrolled to date. • Part A2 hepatocellular carcinoma (HCC) patients are now allowed to have up to 2 prior lines of approved therapy. **Rationale:** Regorafenib has been approved for HCC. • Part A HCC patients with the following subtypes are exclusionary: fibrolamellar HCC, sarcomatoid HCC, and mixed cholangiocarcinoma. **Rationale:** It is important to exclude rare HCC subtypes, as these may introduce heterogeneity into the patient population and make it more difficult to choose a recommended phase two dose (RP2D). • Part A2 HCC patients: patients with chronic hepatitis C virus (HCV) infection are allowed; however, patients with hepatitis B virus (HBV) infection must be receiving effective antiviral therapy (viral load <100 IU/ml). Patients with active coinfection with HBV and HCV, active coinfection with HBV and hepatitis D virus are excluded. **Rationale:** The updated hepatitis requirements are more in-line with standard of care practices and with the patient population

		enrolled in the Checkmate 040 trial. • Part A2 HCC patients who are positive for HBsAg, HBcAb or HCV Ab at screening, must be retested every 3 months and at the EOT visit. **Rationale:** Enable the monitoring of viral load for patients with hepatitis. • Part A2 HCC patients with detectable viral load for hepatitis B at screening must also be tested for hepatitis D antibody (HDV Ab). **Rationale:** Enable the monitoring of the new HCC exclusion criteria of active coinfection with HBV and hepatitis D virus. • Allowed anticoagulation now includes factor Xa inhibitors, as well as heparin. **Rationale:** Factor Xa inhibitors are being increasingly used in the treatment of thromboembolism and to date there have not been major bleeding events related to study drug. • The Background sections have been updated with the most up to date information (1.2). • Melanoma tumor type rationale Section (1.2.5.1) has been updated with information on ocular melanoma. **Rationale:** Part B2 Arm 1 has been changed from HNSCC patients to melanoma patients (including both ocular and cutaneous melanoma). And there is no proven standard of care for ocular melanoma. • HCC tumor type rationale Section (1.2.5.3) has been updated with information on regorafenib. **Rationale:** Regorafenib has been approved for HCC. • Summary of benefit risk assessment has been added (Section 1.2.5.10). **Rationale**: Studies conducted in Europe and Canada should include a Summary of Benefit Risk Assessment. This study has sites in France and the Netherlands, so this section was added to be in compliance.

		• In addition to palliative radiotherapy, consideration may be given for optional radiotherapy administered at palliative doses to a tumor between time of first progression by RECIST and when the patient has confirmed disease progression by irRECIST (Section 5.7.9). **Rationale**: There has been tumor regression observed in a non-irradiated tumor following palliative radiotherapy in a melanoma patient treated with 10 mg/kg of PF-04518600 who had initially met criteria for progression by RECIST. It is possible that radiation may have benefited the anti-tumor immune response from PF-04518600 similar to what has been reported in a preclinical study evaluating the anti-tumor activity of OX40 agonist and radiation. Therefore, this section has been added to allow for optional radiotherapy, at the discretion of the Investigator. • For Parts A1 and B1 the interval of radiographic assessments has an option for scans to be moved to every 12 weeks after 24 weeks. **Rationale**: Reducing scan interval to every 12 weeks will be more in alignment with standard of care. • For Parts A2 and B2 the interval of radiographic assessments was changed from every 8 weeks up to 48 weeks and then every 12 weeks to every 8 weeks up to **24** weeks and then every 12 weeks. **Rationale**: 48 weeks may be too long to perform more frequent scans. Reducing scan interval to every 12 weeks will be more in alignment with standard of care. • Table 6's rows for Other non hematologic toxicities and laboratory abnormalities Grade 4 has the following added: Amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis. **Rationale:** A patient on this study had transient, asymptomatic, Grade 4 lipase elevations but was able to remain on study treatment with clinical benefit and no clinical

		manifestations of pancreatitis. • Figure 4. Study Schematic has been updated with the above information. • In the Analysis Sets, the immunogenicity assessment set has been defined. **Rationale**: Wording added to define the immunogenicity assessment population, which will be part of the statistical analysis. • Appendix 6 has been updated with definitions of new measurable lesions for clarification purposes.

Final Protocol Amendment 4	08 February 2017	Major changes to the protocol include the following: • "PF-05082566" replaced with the proposed International Nonproprietary Name (INN), "utomilumab", throughout the protocol. • PF-04518600 and utomilumab clinical experience data (safety, efficacy, Pharmacokinetics [PK], and immunogenicity) updated in the Introduction section. • Tumor type rationales have been updated with recent publication findings. • Dosing rationales have been updated, including the addition of a rationale for flat dosing in Parts A2 and B2 (Section 1.4). • The administrative changes described in past Protocol Administrative Change Letters (PACL) have been incorporated into the amendment. • Part A1 Monotherapy was updated to reflect that the study is enrolling patients into the optional 10 mg/kg cohort, as the Maximum Tolerated Dose (MTD) has not been met. • Part A2 Monotherapy was updated to reflect that only hepatocellular carcinoma (HCC) patients will be enrolled into the 2 arms at a high and low flat dose of PF-04518600 (randomized 1:1) instead of an arm of HCC and an arm of melanoma patients at the same weight-based dose. **Rationale for HCC as tumor type:** 1) Tumor regressions seen in 5 of 19 patients with HCC, 1 confirmed partial response (PR) which is ongoing for >6 months; 2) Anti-programmed cell death protein-1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) are not standard therapy in HCC yet, so would be able to enroll immuno-oncology (IO) naïve patients. **Rationale to explore 2 dose levels of PF-04518600 (30 mg and 250 mg) at flat doses**: 1) 0.3 mg/kg appears to be the lowest dose at which full receptor occupancy (RO) occurred for all patients and had the most favorable safety, efficacy, PK, and pharmacodynamics (PD) data (30 mg

		equivalent). 2) Although no responses were observed in the 3 mg/kg cohort, increases in peripheral blood central memory CD4 T cell proliferation and activation were also observed at 3 mg/kg (250 mg equivalent). 3) Patients enrolled in 3 mg/kg were a distinctly different population from those enrolled in lower dose cohorts, which could have accounted for differences in clinical outcome. 4) Evaluating 30 mg and 250 mg in randomized arms with a single tumor type CCI [redacted] • Part A2 inclusion criteria has been changed to HCC patients who 1) have had 0 to 1 prior line(s) of systemic therapy (ie, progressed or intolerant to sorafenib or have declined standard therapy) and 2) who have not received prior anti-PD-L1/PD-1 therapy. Treatment of HCC is most effective in the early stages and limiting prior therapies may help to identify early stage patients. • Parts A2 and B2 on treatment biopsies were modified from 1 mandatory on-treatment biopsy at Cycle 4 Day 1(C4D1) to 2 to 3 mandatory on-treatment biopsies. The added mandatory on-treatment biopsy will be at time of initial progression or initial response. However, if the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient the medical monitor must be consulted. **Rationale**: Will provide an additional opportunity to obtain biomarker data at the point when treatment resistance (PD) or anti-tumor activity (PR) is occurring. • CCI [redacted]

		CCI [redacted] • The secondary endpoints of time to event endpoints have been re-categorized as "Anti-tumor activity assessments" to better reflect the endpoints as they are not all time to event endpoints in nature and this is more in alignment with the Food and Drug Administration (FDA) guidance for endpoints for cancer drugs. Time to Progression has also been added to this endpoint. • The Schedule of Events and Pharmacokinetic and Pharmacodynamic Sampling Schedules for Parts A2 and B2 have been broken out from Parts A1 and B1 and aligned to differentiate the dose escalation and dose expansion parts of the study. • For Parts A2 and B2 the interval of radiographic assessments was changed from every 6 weeks to every 8 weeks up to 48 weeks and then every 12 weeks. **Rationale**: 6 weeks may be too early to look for response and too frequent over the long term. Reducing scan interval will be more in alignment with standard of care. • The Pharmacokinetic and Pharmacodynamic Sampling Schedules have been modified to allow for less total blood volume from patients. • Flexible language has been added to allow for the evaluation of the 10 mg/kg A1 dose in Japanese patients to support potential future

		development at this dose in Japan. • Flexible language has been included for Part B1 to allow for an optional cohort of 10 mg/kg PF-04518600 in combination with 100 mg of utomilumab to be evaluated based on emerging data in the 10 mg/kg Part A1 cohort. • Part B Combination Therapy Exclusion #2 For Part B2, head and neck squamous cell carcinoma (HNSCC) patients will need to have either never been treated with anti-PD-L1 or anti-PD-1 mAb or those who 1) previously received prior anti-PD-L1 or anti-PD-1 mAb as most recent therapy, and 2) did not have progressive disease as best overall response on recent PD-L1/PD-1 therapy (ie, stable disease ≥3 months, PR, or complete response [CR]), and 3) who subsequently progressed, or are intolerant to PD-L1/PD-1 therapy. Pembrolizumab is now approved for HNSCC. • The following Part B inclusion criteria has been removed: Sum of the longest diameter(s) of metastatic liver lesion(s) should be <5 cm. No liver toxicity has been seen with either PF-04518600 or utomilumab that would warrant this criterion. • The following exclusion criteria has been modified and added to Part A and Part B, respectively: Patients who have undergone solid organ or hematopoietic transplant. **Rationale:** Avoid any graft versus host disease or graft rejection in all transplant patients. • Dosage Administration Instructions (DAI) has been replaced with Investigational Product (IP) Manual throughout the protocol. • Administration sections for Part A2 and B2 have been broken out from Part A1 and B1 to reflect the change to flat dosing from weight-based dosing mentioned above. • Table 4 Management of Immune-Related

		Adverse Events has been updated to align with similar protocols so there is a uniform approach to studies involving the same or similar compounds. • Redundant information has been minimized throughout the protocol to help minimize discrepancies between sections. • The reporting period for adverse events (AEs) and serious adverse events (SAEs) has been aligned between the Schedule of Activities and Section 8.2 so it is clear. • The maximum approximate sample size has been updated to better reflect the current estimates. • Section 9.3.1 Part A Monotherapy has additional information on the confidence interval of objective response rate (ORR) as it pertains to sample size. • It was clarified that there are no planned formal interim analyses. • The end of study was defined in Section 6.3, as it had been absent. • The term subject has been replaced with patient throughout the protocol for consistency.
Final Protocol Amendment 3	29 February 2016	1. Protocol Summary, Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part B Combination Therapy, Section 1.5 Biomarker Rationale, Section 2.1.2 Objectives for Part B Combination Therapy, Section 2.2.2 Endpoints for Part B Combination Therapy, and Section CCI have been revised to clarified that 4-1BB receptor assay will not be completed due to lack of an appropriate Ab reagent. Therefore target engagement (TE) of PF-05082566 will not be evaluated CCI 2. Schedule of activities: Part A monotherapy,

		Schedule of activities: Part B combination therapy, and Section 7.1.3 Laboratory Safety Assessments. Protocol has been revised to include monitoring of cardiac enzymes troponin I and prohormone brain natriuretic peptide (NT-proBNP) for patients who have a history of adriamycin (doxorubicin) treatment. Adriamycin is a known cardiac toxic agent and innate immunity activation may contribute to its toxicity. 3. Schedule of activities: Part A monotherapy, Schedule of activities: Part B combination therapy, and Section 7.1.6 Echocardiogram or Multigated Acquisition (MUGA) Scan. Protocol has been revised to include echocardiogram or MUGA assessments for patients who have a history of adriamycin treatment. Adriamycin is a known cardiac toxic agent and innate immunity activation may contribute to its toxicity. 4. Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part B Combination Therapy CCI [redacted] 5. Section 3.1 Study Overview and Section 5.4 Administration. A cycle has been revised to be defined as 2 weeks in duration rather than 14 days to take into account the +/- 2 day window allowed for Cycle 2 and beyond per Schedule of Assessment tables. 6. Section 3.1.1 Part A Monotherapy: Participation of Japan in Part A1 has been clarified such that Japanese enrollment into 3 mg/kg dose level will only occur after safety of that dose level has been established in patients enrolled in non-Japanese sites. 7. Section 3.1.2 Part B Combination Therapy. Protocol has been clarified such that Japan will only participate in Part B after safety of PF-04518600 as a single agent has been evaluated in Japanese patients.

		8. Section 3.1.5.2 Criteria for Dose Escalation for Part B Combination Therapy. Administrative edits has been completed to align this section with statistical methods outlined in Section 9.2.1.2. CCI [redacted] 12. Section 3.3 Maximum Tolerated Dose (MTD). Definition has been clarified that the option to terminate the study will be considered for late immune related DLTs that are consistently observed in all dose levels. 13. Section 3.4 Maximum Administered Dose (MAD). Definition has been clarified to state that the MAD will be the highest dose actually administered instead of "not planned to be administered". 14. Section 4.1.1 Inclusion Criteria for Part A Monotherapy. Administrative edits to state that only clear cell renal cell carcinoma (RCC) patients will be enrolled, which aligns with protocol synopsis and Section 3 Study Design. 15. Section 4.2.1 and 4.2.2 Exclusion Criteria. Added "patients with a previous history of adriamycin treatment and are at risk of cardiac failure (New York Heart Association [NYHA]

		Class II or above)" since adriamycin is a known cardiac toxic agent and innate immunity activation may contribute to its toxicity. CCI [redacted] 17. Section 7.1.3 Laboratory Safety Assessments. Hematocrit assessment has been added to table to align with the hematology tests outlined in footnotes for Schedule of Activities.
Final Protocol Amendment 2	04 December 2015	1. Title: Administrative edits based on tumor types to be evaluated 2. Throughout protocol: Objective tumor response will be evaluated by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 and irRECIST, instead of RECIST version 1.1 and irRC. 3. Throughout protocol: the term "study drug" has been replaced with "investigational product". 4. Schedule of Activities: Tables have been updated and now includes a table for monotherapy (Part A), and combination therapy with 4-1BB (Part B). Administrative edits have been completed for Schedule of Activities for Part A to align schedules with footnotes. 5. Schedule of Activities: For Japan, a follow up consent is required prior to initiation of Cycle 3 in Parts A1 and B1. 6. Schedule of Activities and Section 7.1.3. Thyroid stimulating hormone (TSH) and gamma-glutamyltransferase (GGT) tests have been added to the blood chemistry panel, and an alpha fetoprotein test has been added for hepatocellular carcinoma (HCC) patients. For TSH, should abnormalities be observed, a T4 thyroxine test will be performed. 7. Schedule of Activities and Section 8.2. To align with monitoring period for late immune toxicities, serious adverse events (SAEs) will be reported through 98 calendar days from first

		administration of the investigational product, or up to 60 days after last administration of investigational product, whichever is later. 8. Schedule of Activities, and Sections 3.1 and 5.4. A window of ±5 minutes has been incorporated for investigational product administration. 9. Pharmacokinetic and pharmacodynamics sample schedule: Tables have been updated and now includes a table for monotherapy (Part A), and combination therapy with 4-1BB (Part B). Administrative edits have been completed for Schedule of Activities for Part A to include the wording "other" for procedures that are to be completed every other cycle. Sampling window for 1 hr samples have been clarified. A banked specimen sample for C4D1 pre-dose has been added for Parts A and B. 10. Section 1.2.1 Background and Study Rationale for OX40 has been updated to include nonclinical pharmacokinetics data. 11. Section 1.2.2 Background and Study Rationale: 4-1BB, and OX40/4-1BB background and study rationale have been included. 12. Section 1.2.4 Tumor Type Rationale: Rationale for selection of bladder cancer, cervical cancer, non-small cell lung cancer (NSCLC) and gastric cancer have been included. Information regarding selection of tumor types based on the cancer genome atlas (TCGA) analysis has been included. 13. Section 1.3.2 Combination starting dose rationale: rationale for starting doses for PF-04518600/PF-05082566 combination study has been included. 14. Section 1.4 Rationale for pre-treatment and on-treatment biopsies: information for 4-1BB and combination study has been added. 15. Section 1.5 Rationale for biomarker assessments has been included. 16. Section 2.1 Objectives. Administrative edits to objectives for Part A monotherapy include combining objectives for dose escalation and

		dose expansion into 1 section based on similarities between the objectives. Objectives for Part B combination therapy have been included. CCI [redacted] 18. Section 2.2 Endpoints. Administrative edits to objectives for Part A monotherapy include combining endpoints for dose escalation and dose expansion into 1 section based on similarities between the objectives. Endpoints for Part B combination therapy have been included. Anti-drug antibody (ADA) endpoint for Part A Monotherapy is now a secondary endpoint in alignment with pharmacokinetics (PK) secondary objective. CCI [redacted] 20. Section 3.1 and Protocol Synopsis: Study design has been revised, and the study is now divided into a Part A monotherapy phase and a Part B combination therapy phase. Japan only information has been included. A study schematic, information regarding Part B combination therapy, an enrollment prioritization section (Section 3.1.4) has been added. 21. Section 3.1.5 Starting dose: Starting dose information for Part B combination therapy phase has been added. 22. Section 3.1.6 Criteria for dose escalation: Criteria for dose escalation in Part B combination therapy phase have been added.

		23. Section 4.1 Inclusion Criteria. Inclusion criteria for Part B combination phase have been added. 24. Sections 4.1 Inclusion Criteria and 4.3 Lifestyle guides. All patients must agree to use two highly effective method(s) of contraception for at least 90 days after the last dose of assigned treatment. 25. Section 4.2 Exclusion Criteria. Inclusion criteria for Part B combination phase have been added. 26. Section 4.3 Lifestyle guides: or transdermal hormonal methods of contraception has been added as an example and criteria for female partner who meets the criteria for non-childbearing potential has been incorporated. 27. Section 4.4 Sponsor's Qualified Medical Personnel: administrative edits have been incorporated to definition. 28. Section 5: Definition of investigational product has been included. 29. Section 5.3.1 Dosage forms and packaging: information for PF-05082566 has been added. 30. Section 5.4 Administration. Administration information for PF-04518600/PF-05082566 combination therapy has been added. Administrative edits have been incorporated to include information on PF-05082566 and 4-1BB. 31. Section 5.4.3.4 Immune-related adverse events (irAEs). Information regarding the management and follow up of immune related adverse events have been added for different types of irAEs. 32. Section 5.4.3.6 Dose reductions, interruptions and discontinuation criteria. Information regarding dose reductions and treatment modifications for Part B combination has been added. 33. Section 5.4.4 Treatment after initial evidence of radiological disease progression section has been added. 34. Section 5.5 Drug Storage. Use of investigational

		product after temperature excursion will now be considered a deviation. 35. Section 5.6 Drug accountability. Information for destruction of investigational product has been added. 36. Section 7.1.3 Laboratory safety assessments: In alignment with schedule of activities tables, hematology, chemistry and urinalysis tests must be reviewed by a physician prior to dosing. 37. Section 7.1.5 12 Lead Electrocardiogram. In alignment with schedule of activities tables, a single electrocardiogram (ECG) will be completed at screening. 38. Section 7.2.1 Pharmacokinetic assessments. Information for PF-04518600/PF-05082566 combination therapy has been added. 39. Section 7.3.1 Tumor Biopsy Markers. In alignment with Section 3, fresh pre-treatment and on-treatment biopsies for the first 2-4 patients in Parts A1 and B1 will not be required. CCI [redacted] 41. Section 7.5.1 Markers of drug response. Specific information for the Netherlands has been added. 42. Section 10 Quality control and quality assurance. Investigator will notify Pfizer of any regulatory inspections, and Pfizer or representative will be present during inspections if feasible. 43. Section 10.1. New section regarding good clinical practice (GCP) training has been added. 44. Section 12.4 Patient recruitment. Pfizer will review any recruitment materials before use. 45. Section 15 Publication of study results. Administrative edits have been incorporated, including revised language on posting of basic results, and referencing of primary publications

		by investigators. 46. Appendix 4: Management of infusion reactions has been updated to include PF-05082566. 47. Appendix 6: irRECIST information has been added.
Final Protocol Amendment 1	08 January 2015	1. Schedule of activities has been updated to include adverse event and concomitant medication assessments on Cycle 7 Day 1 (C7D1). 2. Schedule of activities and footnote 26, and Section 6.3.1 have been updated to include a follow up visit on 14 (for patients who withdraw after 6 cycles), 42 (for patients who withdraw after 4 cycles), 56 (for patients who withdraw after 3 cycles), 70 (for patients who withdraw after 2 cycles), or 84 (for patients who withdraw after 1 cycles) days after end of treatment to enable the collection of late immune related adverse events. 3. Section 3.1.1 study overview part 1 has been revised to include a statement that includes late immune related Dose Limiting Toxicities (DLTs) in the determination of Maximum Tolerated Dose (MTD). 4. Section 3.1.4 criteria for dose escalation has been revised to include 3-fold, or one- half a log changes to a dose if a DLT related to PF-04518600 or a grade ≥2 cytokine release syndrome, infusion reaction, or allergic reaction is observed. 5. Section 3.2 DLT definition has been revised to include ≥Grade 3 cytokine release syndrome, infusion reactions and allergic reactions as DLTs, except those that have not been maximally treated. 6. Section 3.2 DLT definition has been revised to include a statement regarding collection of safety and tolerability assessment for the first 98 days for estimation of MTD, even though dose escalation is based on 28 days. 7. Section 3.2.1 Late immune related DLTs section

		has been added. This includes a definition of a late immune related DLT, and stopping rules should these events be observed within 98 days of starting treatment (C1D1). Also includes the need to re-consent a patient if treatment at a dose subsequently found to be above MTD is to be continued. 8. Section 3.3 MTD definition has been revised to include MTD dose considerations if a grade 3 or 4 cytokine release syndrome, infusion reaction, or allergic reaction arises. 9. Section 3.3 MTD definition has been revised to include MTD dose considerations that take into account cumulative incidence of all late immune related DLTs. 10. Section 5.4.3 Dose reduction section has been revised to include the possibility of dose reductions if a late immune related DLT occurs. 11. Section 9.2.2 statistical method for estimating the MTD has been modified to include assumptions if grade 4 or 3 cytokine release syndrome, infusion reaction or allergic reaction is observed.
Original Protocol	18 November 2014	Not Applicable (N/A)

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

ABBREVIATIONS

This is a list of abbreviations that may or may not be used in the protocol.	
Abbreviation	**Term**
4-1BBL	4-1BB ligand
Ab	Antibody
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AEs	adverse events
AIDS	acquired immunodeficiency syndrome
ALK	Anaplastic lymphoma kinase
Alk Phos	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
APCs	antigen presenting cells
ARCTIC	A Global Study to Assess the Effects of MEDI4736, Given as Monotherapy or in Combination With Tremelimumab Determined by PD-L1 Expression Versus Standard of Care in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{τ}	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve from time zero to infinity
AUC_{ss}	area-under-the-curve at steady state
AUC_{sdo}	area-under-the-curve at single dose
BCG	bacillus Calmette-Guérin
BCL	B-cell lymphoma
BP	blood pressure
BRAF or $BRAF^{V600}$	B-Raf proto-oncogene
BUN	blood urea nitrogen
C	Cycle
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
C_{av}	average concentration
C_{max}	maximum concentration
C_{min}	minimum concentration
C_D_	cycle _ day _
CBA	cytometric bead array
CBC	complete blood count
CD38	cluster of differentiation 38

CD4 T_{CM}	central memory CD4 T cells
CDS	core data sheet
CHF	congestive heart failure
CI	confidence interval
CL	Clearance
coBRIM	Cobimetinib combined with vemurafenib in advanced $BRAF^{V600}$-mutant melanoma
CNS	central nervous system
CRF	case report form
CR	complete response
CRO	a contract research organization
CSA	clinical study agreement
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTC	common terminology criteria
CTCs	circulating tumor cells
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T-lymphocyte antigen 4
CV	coefficient of variation
CYT	cytotoxic
D	Day
DAI	dosage and administration instructions
DC	dendritic cells
DeCOG	German Dermatologic Cooperative Oncology Group
DLI	donor lymphocyte infusion
DLT	dose limiting toxicities
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	duration of response
EBV	Epstein–Barr virus
EC	ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	eastern cooperative oncology group
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EDV	end diastolic volume
EFS	event free survival
EOT	end of treatment
EGFR	epidermal growth factor receptor
Erk	extracellular signal-regulated kinases
ESV	end systolic volume
EudraCT	European clinical trials database

Factor Xa	trypsin-like serine protease
FcγRs	Fc-gamma receptors
FDA	food and drug administration (United States)
FDAAA	food and drug administration amendments act (United States)
FFPE	formalin-fixed paraffin-embedded
FIP	first in patient
FoxP3	forkhead box P3
FSH	follicle-stimulating hormone
GBM	Glioma
GCP	good clinical practice
GGT	gamma-glutamyltransferase
GITR	glucocorticoid-induced tumor necrosis factor receptor
GLP	good laboratory practice
G-CSF	granulocyte-colony stimulating factors
Gp100	glycoprotein 100
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV Ab	hepatitis D by antibody
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
CCI	[redacted]
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
HR	heart rate
huPBL	human peripheral blood lymphocytes
IB	investigator's brochure
IARC	international association of research in cancer
ICD	informed consent document
ICH	international conference on harmonization
ICOS	inducible t-cell co-stimulator
IEC	institutional ethics committee
ID	Identification
IFN-γ	interferon gamma
IgG	immunoglobulin g
IHC	immunohistochemistry
IL-	Interleukin
IM	Immunomodulatory
IND	investigational new drug application
INN	International Nonproprietary Name

INR	international normalized ratio
IO	Immuno-Oncology
IP Manual	Investigational Product Manual
irAEs	immune related adverse events
IRB	institutional review board
irRC	immune-related response criteria
irRECIST	immune-related response criteria derived from RECIST v1.1
irSD	Stable disease per Immune-related Response Criteria Derived from RECIST
IUD	intrauterine device
IV	intravenous
JAK2	Janus kinase 2
JAK3	Janus kinase 3
JAVELIN LUNG 200	Avelumab in Non-Small Cell Lung Cancer
Jnk	c-Jun N-terminal kinases
KLH	keyhole limpet hemocyanin
KRAS	Kirsten rat sarcoma proto-oncogene
LAG3	lymphocyte-activation gene 3
LFT	liver function test
LLN	lower limit of normal
LPD	local product document
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
mTPI	modified toxicity probability interval
mAb	monoclonal antibody
MAD	maximum administered dose
MAP kinase	mitogen-activated protein kinases
MCC	merkel cell carcinoma
MCL	Mantle Cell Lymphoma
MCP-1	monocyte chemoattractant protein-1
MD	multiple dose
MedDRA	medical dictionary for regulatory activities
MEK	MAPK/ERK kinase
MIP-1α	macrophage inflammatory protein-1 alpha
MIP-1β	macrophage inflammatory protein-1 beta
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition
MYSTIC	Phase III Open Label First Line Therapy Study of MEDI 4736 (Durvalumab) With or Without Tremelimumab Versus SOC in Non Small-Cell Lung Cancer (NSCLC)
N/A	not applicable

NAb	neutralization assays
NCI	National Cancer Institute
NCT	National Clinical Trial
NEPTUNE	Study of 1st Line Therapy Study of Durvalumab With Tremelimumab Versus SoC in Non Small-Cell Lung Cancer (NSCLC)
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHL	non-Hodgkin's lymphoma
NK	natural killer
NKT	natural killer T cells
NMIBC	non- muscle invasive bladder cancer
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
NYHA	New York Heart Association
OBD	optimal biological dose
ORR	objective response rate
OS	overall survival
PACL	Protocol Administrative Change Letters
pT	target probability
PBMCs	peripheral blood mononuclear cells
PCD	primary completion date
PCR	Polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PE	physical exam
PET	positron emission tomography
PFS	progression free survival
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha
PK	Pharmacokinetics
PLTS	Platelets
PMDA	pharmaceuticals and medical devices agency
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	Every 3 weeks
Q4W	every 4-weeks
QD	every day
QT	time between the start of the Q wave and the end of the T wave
R	Ratio
RCC	renal cell carcinoma
RD	response/remission duration
RECIST	response evaluation criteria in solid tumor

RFS	relapse free survival
RNA	ribonucleic acid
RO	receptor occupancy
ROS1	ROS proto-oncogene 1
RP2D	recommended phase 2 dose
RR	response rate
s4-1BB	soluble 4-1BB
sOX40	soluble OX40
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SCID	severe combined immune deficiency
SCLC	small cell lung cancer
SD	stable disease
SDo	single Dose
SOC	System Organ Class
SPC	summary of product characteristics
SRSD	single reference safety document
T	Time
$T_{1/2}$	terminal elimination half-life
T4	thyroxine
TBNK assay	T, B, NK lymphocyte assay
TCGA	the cancer genome atlas
TCR	T-cell receptor
TE	target engagement
TEAEs	treatment-emergent adverse events
Th	T-helper
TILs	tumor infiltrating lymphocytes
TME	tumor microenvironment
TNFRSF	tumor necrosis factor receptor superfamily
TNF	tumor-necrosis factor
TNF-α	tumor-necrosis factor alpha
TNF-β	tumor-necrosis factor beta
TNFR	tumor-necrosis factor receptor
TP53	tumor protein p53 gene
TRAF	TNFR-associated factor
TNFSF4	tumor necrosis factor (ligand) superfamily, member 4
Tregs	T regulatory cells
TSH	thyroid-stimulating hormone
TTL	target toxicity level
TTP	time to progression
ULN	upper limit of normal
UPM	unit probability mass

US	United States
USPI	United States package insert
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady state
WBC	white blood cell count

PROTOCOL SUMMARY

Background and Rationale:

Immunotherapy offers the opportunity to not only stop tumor growth, but also decrease the rate of tumor recurrence.[1] By activating and expanding tumor-associated antigen T cells, it may be possible to enhance tumor immunity. However, T cell activation is not mediated by antigen stimulation alone. Instead, co-stimulatory receptors are required. OX40 (CD134) and 4-1BB (CD137) are co-stimulatory receptors that act on antigen stimulated T cells but not native T cells.[2,3] OX40 plays a key role in T cell survival, proliferation, and activation. Upon OX40 ligand (also known as OX40L, CD252 or TNFSF4 [tumor necrosis factor (ligand) superfamily, member 4]) binding, OX40 signaling upregulates anti-apoptotic molecules including B-cell lymphoma-2 (Bcl-2), Bcl-xL, and survivin,[4] and increases interleukin-2 (IL-2), IL-4, IL-5, and interferon gamma (IFN-γ) cytokine secretion. Similarly, activation of 4-1BB signaling leads to an upregulation of pro-survival factors Bfl-1 and Bcl-xL, down-regulation of pro-apoptotic protein Bim, increased T cell proliferation and differentiation into T memory cells.[5]

PF-04518600 is a fully human Immunoglobulin G2 (IgG2) agonistic monoclonal antibody (mAb) specific for human OX40 (CD134). By binding to OX40 on activated tumor infiltrating T cells, PF-04518600 may reverse T cells' anergic state, and enhance tumor immunity.

Utomilumab (PF-05082566) is a fully human IgG2 agonist monoclonal antibody specific for human 4-1BB. The safety and tolerability of utomilumab is currently being evaluated in a First-in-Patient Phase 1 study as a single agent and in combination with rituximab (Study B1641001, IND 109,154).[6] Utomilumab has been well tolerated (thus far up to 10 mg/kg) when administered as a single agent every 4 weeks (Q4W). The safety profile of utomilumab either as single agent or in combination with rituximab was manageable without occurrence of treatment related life threatening (>Grade 4) adverse events (AEs).

In this clinical study, PF-04518600 as a monotherapy (Part A), and PF-04518600 in combination with utomilumab (Part B) will be evaluated for the treatment of adult patients with select locally advanced or metastatic cancers who are unresponsive to current available therapies, or for whom no standard therapy is available.

Study Design:

This is a Phase 1, open label, multi-center, multiple dose, dose escalation, safety, pharmacokinetic, and pharmacodynamic study of PF-04518600 monotherapy in Part A, and PF-04518600 in combination with utomilumab in Part B. Each part includes a dose escalation phase, and a dose expansion phase. A maximum of approximately 210 patients are expected to be enrolled into the study.

All patients will complete up to 4 weeks of screening. Following the initial dose(s), treatment with investigational product will continue until disease progression by immune-related response evaluation criteria in solid tumors (irRECIST), patient refusal, unacceptable toxicity occurs, or the end of the study, whichever occurs first. Patients will be allowed to stay on study, if the treating physician feels that it is in the patient's best interest in the case of radiological progression, and the absence of clear clinical progression (see Section 5.4.6 Treatment after Initial Evidence of Radiological Disease Progression). A follow-up visit approximately 4 weeks after the last dose for adverse event (AE) and serious AE (SAE) collection will be conducted. Late immune related responses will be evaluated up to 98 days after the first dose(s) of Cycle 1. Because atypical tumor responses after growth of pre-existing lesions or appearance of new lesions have been observed with immune checkpoint inhibitors, study B0601002 will assess tumor response based on both response evaluation criteria in solid tumor (RECIST) and Immune-related Response Criteria Derived From RECIST v1.1 (irRECIST). Survival data will also be collected (see Section 5.4.6 Treatment after Initial Evidence of Radiological Progression, Section 6.3 Follow-up Visit, Section 7.4 Tumor Response Assessments, and Appendix 6). The time on study can vary depending on the observed toxicity and potential benefit an individual patient derives. It's estimated that patients will remain on treatment for approximately 12-18 weeks, making total study duration approximately 20-26 weeks (exclusive of 2 year survival follow-up). Actual duration can be longer, if a patient derives benefit from study treatment.

Part A Monotherapy:

Part A1 Monotherapy Dose Escalation.

Part A1 monotherapy dose escalation phase will enroll approximately 58 adult patients with locally advanced or metastatic cancers hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC) or head and neck squamous cell carcinoma (HNSCC). The actual number of patients enrolled will depend on the observed safety and tolerability profile of PF-04518600, the number of dose levels that will be tested and expanded to characterize the pharmacodynamic or immunomodulatory (IM) effects, and the number of dose levels required to identify the maximum tolerated dose (MTD) or optimal biological dose (OBD). Six dose levels are proposed: 0.01, 0.1, 0.3, 1.5, 3 and 10 mg/kg. Each cohort will include an initial cohort of 2-4 patients that may be expanded to approximately 10 patients. Approximately 3 patients enrolled in Japan will be included for at least 2 dose levels (see Section 3.1.1.3 Japan Participation in Part A Monotherapy).

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 hr period, a second patient will be enrolled into the same dose level cohort. A modified toxicity probability interval (mTPI) method, targeting a dose limiting toxicities (DLT) rate of 25% and an acceptable DLT interval (20%-30%),[7] will be utilized for dose escalation (see Section 3.1.5 Criteria for Dose Escalation). If peripheral blood samples indicate preliminary signs of immune modulation in the first 2-4 patients, the dose level will be expanded for pharmacodynamic evaluation; these additional patients will undergo mandatory pre-treatment and on treatment biopsies. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for

the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted (see Section 1.4 Rationale for Pretreatment and On-treatment Biopsies). Depending on observed safety data and pharmacodynamic data, additional cohorts (lower, intermediate or higher dose levels, up to maximum of 20 mg/kg, see Section 3.1.5 Criteria for Dose Escalation) may also be tested.

Part A2 Monotherapy Dose Expansion.

Part A2 monotherapy dose expansion phase will randomize HCC patients 1:1 to flat dose levels of either 30 mg (Arm 1) or 250 mg (Arm 2) of PF-04518600 given every 2 weeks. Both doses were chosen based on data from Part A1. Each arm in Part A2 will include approximately 20 HCC patients.

Based on emerging data from the 10 mg/kg cohort of Part A1, an additional flat dose level of 800 mg PF-04518600 (approximately equivalent to 10 mg/kg), may be added after initiation of enrollment into Arms 1 and 2.

Patients will undergo mandatory pre-treatment and on treatment biopsies as specified in the Schedule of Activities. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted (see Section 1.4 Rationale for Pretreatment and On-treatment Biopsies).

Part B Combination Therapy:

Part B1 Combination Therapy Dose Escalation.

Part B1, the combination therapy dose escalation phase, will enroll approximately 55 patients. At least 6 patients must have been evaluated for the 28 day DLT observation period at the 0.3 mg/kg dose level in Part A1 PF-04518600 (OX40 agonist) monotherapy before Part B1 can be initiated. Part B1 will study sequential dose levels of PF-04518600 (0.1, 0.3, 1.0 and 3 mg/kg with an option of 10 mg/kg pending data from Part A1) combined with either 20 mg or 100 mg of utomilumab (4-1BB agonist) in adult patients with non-small cell lung cancer (NSCLC), HNSCC, melanoma, bladder, gastric or cervical cancer who are unresponsive to currently available therapies or for whom no standard therapy is available. The starting dose level will be 0.1 mg/kg of PF-04518600 and 20 mg of utomilumab, given no sooner than 30 minutes apart (for dosing schedule, please see Section 5.4.3 Administration Part B Combination Therapy). Based on emerging data in the 10 mg/kg Part A1 cohort, an optional cohort of 10 mg/kg PF-04518600 in combination with 100 mg of utomilumab may be evaluated.

A mTPI method, targeting a DLT rate of 25% and an acceptable DLT interval (20%-30%),[7] will be utilized for dose escalation (see Section 3.1.5 Criteria for Dose Escalation). If peripheral blood samples indicate preliminary signs of immune modulation in the first 2-4 patients, the dose level will be expanded for pharmacodynamic evaluation; these additional patients will undergo mandatory pre-treatment and on treatment biopsies. In case of intolerable toxicity at the starting dose level, the dose combination will be reduced to

0.1 mg/kg of PF-04518600 and 10 mg of utomilumab. Subsequent to the starting dose level, if dose de-escalation is recommended after evaluation, intermediate dose levels between the previous dose combination and current dose combination may be studied. Intrapatient dose reductions are not permitted during the combination therapy with PF-04518600 and utomilumab unless, in discussion with the sponsor, a dose combination level is deemed beyond the determined MTD for the combination. Each dose combination level will include an initial cohort of 2-4 patients that may be expanded up to approximately 10 patients based on peripheral pharmacodynamic assessments (see Section 7.3 Biomarker and Pharmacodynamic Assessments). To allow for better characterization of pharmacodynamic effects, these additional patients will undergo mandatory pre-treatment and on treatment biopsies. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted (see Section 1.4 Rationale for Pretreatment and On-treatment Biopsies). The safety of the first patient at each dose combination level will be observed for 48 hours prior to enrolling subsequent patients.

Part B2 Combination Therapy Dose Expansion.

Part B2 combination therapy dose expansion phase will further evaluate safety and anti-tumor activity of PF-04518600/utomilumab combination with a dosing regimen selected based on results of Part B1 with flat dose equivalents of PF-04518600.

From the results of Part B1, the selected dose for PF-04518600 in the B2 combination therapy dose expansion cohorts is 30 mg (a flat dose equivalent to 0.3 mg/kg) intravenously (IV) every 2 weeks (Q2W) in combination with PF-05082566 20 mg IV every 28 days.

Part B2 will be divided into 2 arms:

Arm 1 will enroll melanoma patients who have either:

a. Ocular melanoma patients with advanced/metastatic disease, or

b. Cutaneous/acral melanoma patients with advanced metasatic disease who have received checkpoint inhibitor (anti-PD-L1, anti-PD-1, or anti-cytotoxic T-lymphocyte antigen 4(anti-CTLA4)) based treatment on which disease progressed. [Note: Checkpoint inhibitor may have been part of a combination therapy, as long as the combination did not contain OX40 or 4-1BB agonist]. Any questions on prior treatment may be discussed with the Sponsor.

Arm 2 will enroll patients with histological or cytological diagnosis of NSCLC with advanced/metastatic disease. Patients must have previously received prior anti-PD-L1 or anti-PD-1 mAb on which disease progressed. [Note: Previous anti-PD-L1 or anti-PD-1 mAb may have been part of a combination therapy, eg, in combination with chemotherapy, as long as the combination did not contain OX40 or 4-1BB agonist.]

Part B2 will enroll up to 20 patients in each arm (including approximately 5 ocular melanoma patients in Arm 1), and all patients will undergo mandatory pre- and on-treatment tumor biopsies. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted (see Section 1.4 Rationale for Pretreatment and On-treatment Biopsies).

Study Objectives:

Objectives for Part A1 Monotherapy Dose Escalation:

Primary Objective:

- To assess safety, and tolerability at increasing dose levels of PF-04518600 in patients with selected advanced or metastatic solid tumors in order to establish the MTD.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity induced by PF-04518600 in patients with selected advanced or metastatic solid tumors solid tumors.
- To characterize the single dose and multiple dose pharmacokinetics (PK) of PF-04518600 following intravenous (IV) administration.
- To evaluate the immunogenicity of PF-04518600 following IV administration.
- To characterize the degree of target engagement (TE) by PF-04518600 at multiple doses by measuring unbound (free) cell surface OX40 in peripheral blood.

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

Objectives for Part A2 Monotherapy Dose Expansion:

Primary Objectives:

- To establish the recommended phase 2 dose (RP2D) of PF-04518600 in patients with selected advanced or metastatic HCC.
- To further characterize the safety and tolerability of PF-04518600 in patients with selected advanced or metastatic HCC.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in patients with selected advanced or metastatic HCC.
- To characterize the single dose and multiple dose PK of PF-04518600 following IV administration.
- To evaluate the immunogenicity of PF-04518600 following IV administration.

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Objectives for Part B1 Combination Therapy Dose Escalation:

Primary Objective:

- To assess safety and tolerability at increasing dose levels of PF-04518600 in combination with utomilumab in patients with selected advanced or metastatic solid tumors and to estimate MTD of the combination.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in combination with utomilumab.
- To characterize single and multiple dose pharmacokinetics of PF-04518600 and utomilumab when given in combination.
- To evaluate immunogenicity of PF-04518600 and utomilumab when given in combination.

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Objectives for Part B2 Combination Therapy Dose Expansion:

Primary Objective:

- To further assess safety and tolerability of PF-04518600 in combination with utomilumab in patients with melanoma or NSCLC in order to establish RP2D for the combination.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in combination with utomilumab.
- To characterize single and multiple dose pharmacokinetics of PF-04518600 and utomilumab when given in combination.
- To evaluate immunogenicity of PF-04518600 and utomilumab when given in combination.

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Endpoints:

Endpoints for Part A1 Monotherapy Dose Escalation:

Primary Endpoints:

- Dose limiting toxicities (DLTs) observed in each patient during the first 98 days in order to determine the MTD.
- Adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03, timing, seriousness and relationship to study therapy PF-04518600.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: progression free survival (PFS), Time to Progression (TTP), duration of stable disease (SD), duration of response (DR) by RECIST version 1.1 and irRECIST and overall survival (OS).
- Overall survival rates at 6 months, 1 year and 2 years.
- Pharmacokinetic parameters of PF-04518600:
  Single Dose (SDo) - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit. Multiple Dose (MD) (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, and R_{ac} ($AUC_{ss,\tau}/AUC_{sdo,\tau}$) as data permit.
- Incidence of anti-drug antibody (ADA) and neutralizaing antibody (NAb) against PF-04518600.
- Levels of free OX40 receptor expressed on T cells in peripheral blood.

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

Endpoints for Part A2 Monotherapy Dose Expansion:

Primary Endpoints:

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to study therapy PF-04518600.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 years.
- Pharmacokinetic parameters of PF-04518600:
  SDo - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit. MD (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, and R_{ac} ($AUC_{ss,\tau}/AUC_{sdo,\tau}$) as data permit.
- Incidence of ADA and NAb against PF-04518600.

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- [redacted]
- [redacted]

Endpoints for Part B1 Combination Therapy Dose Escalation:

Primary Endpoints:

- DLTs observed in each patient during the first 98 days in order to determine the MTD.
- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to PF-04518600/utomilumab combination.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 years.
- Pharmacokinetic parameters of PF-04518600 and utomilumab:
  SDo - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit. MD (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, and R_{ac} ($AUC_{ss,\tau}/AUC_{sdo,\tau}$) as data permit.
- Incidence of ADA and NAb against PF-04518600 and utomilumab.

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

Endpoints for Part B2 Combination Therapy Dose Expansion:

Primary Endpoints:

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to PF-04518600/utomilumab combination.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 years.
- Pharmacokinetic parameters of PF-04518600 and utomilumab:
  SDo - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit. MD (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, and R_{ac} ($AUC_{ss,\tau}/AUC_{sdo,\tau}$) as data permit.
- Incidence of ADA and NAb against PF-04518600 and utomilumab.

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SCHEDULE OF ACTIVITIES: Part A1 Monotherapy

The schedule of activities table provides 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.

Part A1 Monotherapy		**Treatment Period**											**Post Treatment**					
		Cycle 1 Only (Days 1 to 14)			**Cycle 2 (Days 1 to 14)**		**Cycle 3 (Days 1 to 14)**		**Cycles 4 to 6 (Days 1 to 14)**	**Cycle 7 (Days 1 to 14)**	**Subsequent Cycles (Days 1 to 14)[31]**	**End of Treatment (EOT)[29]**	**Follow Up (Days after EOT visit)[30]**					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Informed Consent[2]	X																	
Tumor History[3]	X																	
Medical History[4]	X																	
Complete Physical Examination	X	X										X		X				
Abbreviated Physical Examination[5]			X	X	X	X	X	X	X	X	X							
Baseline Signs and Symptoms[6]		X																
Height	X																	
Weight[7]	X	X			X		X		X	X	X	X		X				
Vital signs (BP/PR/Temp)[8]	X	X	X	X	X	X	X	X	X	X	X	X		X				

Part A1 Monotherapy		Treatment Period											Post Treatment					
		Cycle 1 Only (Days 1 to 14)			Cycle 2 (Days 1 to 14)		Cycle 3 (Days 1 to 14)		Cycles 4 to 6 (Days 1 to 14)	Cycle 7 (Days 1 to 14)	Subsequent Cycles (Days 1 to 14)[31]	End of Treatment (EOT)[29]	Follow Up (Days after EOT visit)[30]					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Eastern cooperative oncology group (ECOG) Performance Status[9]	X	X			X		X		X	X	X	X		X				
Triplicate 12 Lead ECG[10]	X (single ECG only)	X	X	X	X	X	X	X	X	X	X	X						
Laboratory																		
Hematology[11]	X	X		X	X	X	X	X	X	X	X	X		X				
Blood Chemistry[12]	X	X		X	X	X	X	X	X	X	X	X		X				
Coagulation[13]	X	X		X	X	X	X	X	X	X	X	X		X				
Urinalysis[14]	X			X	X	X	X	X	X	X	X	X		X				
Pregnancy Test[15]	X	X			X		X		X	X	X	X						
Hepatitis B, C and HIV tests[16]	X																	
Cardiac enzymes[17]	X	X					X		X (Cycle 5 only)	X	X (Cycle 9 and every other cycle)	X						
Alpha Fetoprotein for HCC patients only	X	Every 6 weeks																

Part A1 Monotherapy		Treatment Period											Post Treatment					
		Cycle 1 Only (Days 1 to 14)			Cycle 2 (Days 1 to 14)		Cycle 3 (Days 1 to 14)		Cycles 4 to 6 (Days 1 to 14)	Cycle 7 (Days 1 to 14)	Subsequent Cycles (Days 1 to 14)[31]	End of Treatment (EOT)[29]	Follow Up (Days after EOT visit)[30]					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Registration and Treatment																		
Registration[18]		X																
PF-04518600 Treatment[19]		X			X		X		X	X	X							
Tumor Assessments																		
CT or MRI scan or equivalent[20]	X	Every 6 weeks until confirmed progressive disease. Scans may be moved to every 12 weeks after 24 weeks until confirmed progressive disease.																
Other samplings																		
CCI [redacted]	[redacted]								[redacted]	[redacted]		[redacted]						
[redacted]		[redacted]																
[redacted]		[redacted]																
Blood Samples for PK[23]		See Pharmacokinetic and Pharmacodynamic Sampling Schedule Table below.																
Blood Sample for Anti-PF-04518600 Antibodies[24]		See Pharmacokinetic and Pharmacodynamic Sampling Schedule Table below.																
CCI [redacted]		[redacted]																

Part A1 Monotherapy		Treatment Period											Post Treatment					
		Cycle 1 Only (Days 1 to 14)			Cycle 2 (Days 1 to 14)		Cycle 3 (Days 1 to 14)		Cycles 4 to 6 (Days 1 to 14)	Cycle 7 (Days 1 to 14)	Subsequent Cycles (Days 1 to 14)[31]	End of Treatment (EOT)[29]	Follow Up (Days after EOT visit)[30]					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Other clinical assessments																		
Adverse Events[26]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication and non-drug supportive interventions[27]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram or MUGA[28]	X	Every 3 months										X						

Except for safety assessments, all other activities performed during Cycle 1 can be performed ±1 day, and for Cycle 2 onwards ±2 days. Safety assessments must be performed prior to dosing (see footnotes for details).

Footnotes

1. Screening: to be obtained within 28 days prior to treatment start.
2. Informed Consent: must be obtained prior to undergoing any study specific procedures. For Japan Part A1 only: after completion of 2 treatment cycles and prior to initiation of Cycle 3, a follow up consent must be obtained to confirm patient's willingness to continue on study. All Japanese patients in Part A1 should be hospitalized until 2nd dosing.
3. Tumor History: will be collected within 28 days during screening prior to treatment start. Includes history of disease under study including details of primary diagnosis and treatment history.
4. Medical History: Includes history of disease process other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
5. Abbreviated Physical Examination (PE): Abbreviated PEs should be performed as appropriate at each visit where complete physical exams are not required. Refer to Section 7.1 Assessments for further details.

6. 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. During the study, any new or worsened conditions since baseline will be recorded on the Adverse Events (AE) case report form (CRF) page.
7. Weight: Patient's body weight will be measured prior to the preparation of investigational product (PF-04518600) and patient's dose of PF-04518600 for that cycle will be based on the patient's body weight (see Administration Section 5.4).
8. Vital signs: includes temperature (oral, tympanic, temporal or axillary), blood pressure (BP), and pulse rate to be recorded in the sitting position after 5 minutes of rest. On Day 1 of each cycle, vital signs should be measured prior to infusion start (pre-dose) and 1 hour after the start of the infusion.
9. Performance status: use Eastern Cooperative Oncology Group (ECOG) scale in Appendix 1.
10. Triplicate 12-leads electrocardiogram (ECG): Triplicate ECGs will be collected at times specified in the Schedule of Activities. At each time point, at least a 10 second strip, three consecutive 12-lead ECGs will be performed 1-5 minutes apart to determine mean QTcF interval. The Screening ECG will be a single, 12 lead ECG. 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-04518600. Additional ECGs will be collected on Cycle 1 Day 2 (C1D2), Cycle 1 Day 8 (C1D8), Cycle 2 Day 8 (C2D8), and Cycle 3 Day 8 (C3D8) and EOT. 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. All ECGs will be reviewed by a centralized ECG vendor. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. Refer to Section 7.1.5 (12-Lead) ECG for further details.
11. Hematology: complete blood count (CBC) to include hematocrit, hemoglobin, platelets, white blood cells (WBC), absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Assessments conducted on Cycle 1 Day 1 (C1D1) must be completed within 48 hours prior to dosing. If screening 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 Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for Laboratory Tests list.
12. Blood Chemistry: Tests for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (Alk Phos), gamma-glutamyltransferase (GGT), sodium, potassium, magnesium, chloride, total calcium, total bilirubin, blood urea nitrogen (BUN) or urea, creatinine, uric acid, glucose (non-fasted), albumin, phosphorous or phosphate, amylase, lipase and thyroid stimulating hormone (TSH) will be performed. Assessments conducted on C1D1 must be completed within 48 hours prior to dosing. If screening assessments are performed within 72 hours prior to C1D1, there is no need to repeat assessments on C1D1. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. If abnormalities are observed in TSH values, a T4 thyroxine test will be performed. See Assessments Section 7.1.3 for laboratory tests list.
13. Coagulation Assays: prothrombin time (PT) and partial thromboplastin time (PTT). Assessments conducted on C1D1 must be completed within 48 hours prior to dosing. If screening assessments are performed within 72 hours prior to C1D1, there is no need to repeat assessments on C1D1. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for laboratory tests list.
14. Urinalysis: Dipstick is acceptable. Microscopic analyses required if dipstick abnormal. If ≥2+ protein on urine dipstick, then collect 24 hr urine. Assessments conducted on C1D1 must be completed within 48 hours prior to dosing. No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for Laboratory Tests list.
15. Pregnancy Test (Serum/Urine): For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at C1D1, before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle prior to dosing during the active treatment period, at the end of study therapy and additionally

whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Results will be obtained prior to initiating therapy at all times. Additional pregnancy tests may also be undertaken if requested by institutional review board (IRB)/institutional ethics committee (IEC)s or if required by local regulations.

16. 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.
17. Cardiac enzymes: Troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) will be evaluated in patients with previous history of anthracycline treatment. Assessments must be performed prior to dosing. No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment performed within 72 hours prior to that date. Assessments performed on Cycle 3 Day 1 (C3D1) and Day 1 of each subsequent odd number cycles should be performed within 48 hours prior to dosing. Assessments should also be performed when clinically indicated. See Assessments Section 7.1.3 for Laboratory Tests list.
18. Registration: Patient number and dose level allocation provided by Pfizer Inc. Treatment should begin no longer than four days from registration.
19. PF-04518600 Treatment: PF-04518600 will be administered once every 2 weeks as an IV infusion over 60 minutes (-5 to +15 minutes) and should include the time needed to flush the infusion line. Day 1 safety labs (blood chemistry, hematology, and urinalysis) need to be reviewed by a physician prior to dosing at the beginning of each cycle. Treatment with investigational product will continue until disease progression by irRECIST, patient refusal, unacceptable toxicity occurs, or the end of the study, whichever occurs first.

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23. PK Sampling: Specific timing for collection of pharmacokinetic samples can be found in the pharmacokinetic and pharmacodynamic sampling schedule table below.

24. Anti PF-04518600 Antibodies: Specific timing for collection of anti-PF-04518600 antibody samples can be found in the Pharmacokinetic and Pharmacodynamic Sampling Schedule table below.

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26. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.03. Patients must be followed for adverse events (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. However, late immune-related DLTs that are not SAEs need to be collected consistent with Section 3.2.1. 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 98 calendar days from first administration of the investigational product, or up to 60 days after last administration of investigational product, whichever is later. Serious adverse events 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 serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
27. Concomitant 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), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
28. Echocardiogram or multigated acquisition (MUGA) scan: echocardiogram or MUGA will be evaluated in patients with previous history of anthracycline treatment. For these patients, an echocardiogram or MUGA will be performed at screening and every 3 months whilst on treatment and when clinically indicated. An echocardiogram or MUGA will be performed at the end of treatment (EOT) visit if not performed within 3 months of discontinuation.
29. End of treatment visit (EOT visit): Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
30. Follow up: At least 28 days and no more than 35 days after discontinuation of treatment, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Late immune related adverse event information will be collected during the 28 to 35 day follow up visit. 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. Independent to time of disease progression, all patients (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor) will be followed for survival for at least 2 years from the time of their first dose of investigational product. After the completion of end of treatment visits, Patients will be contacted every 2 months for survival status. To collect additional late immune related adverse event information, any patient who discontinue from treatment after 1 to 4 or 6 cycles of treatment will also be contacted by phone during the follow up period. For patients who discontinues after receiving 5 cycles of treatment, late immune information will be collected during the 28 to 35 day follow up visit. If the patient discontinues after receiving 6 cycles of treatment, they will be contacted by phone 14 days (±2 days) after EOT. If the patient discontinues after receiving 4 cycles of treatment, they will be contacted by phone 42 days (±2 days) after EOT. If the patient discontinues after receiving 3 cycles of treatment, they will be contacted by phone 56 days (±2 days) after EOT. If the patient discontinues after receiving 2 cycles of treatment, they will be contacted by phone 70 days (±2 days) after EOT. If the patient discontinues after receiving 1 cycle of treatment, they will be contacted by phone 84 days (±2 days) after EOT. If any concern arises, patient will be called in for an inpatient follow up visit within 5 calendar days of initial phone call (assessments will be the same as the assessments performed 28-35 days after end of treatment follow up visit).
31. Subsequent cycles: Day 8 is not required after Cycle 3.

SCHEDULE OF ACTIVITIES: Part B1 Combination Therapy

The schedule of activities table provides 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.

Part B1 Combination Therapy		**Treatment Period**											**Post Treatment**					
		Cycle 1 Only (Days 1 to 14)			**Cycle 2 (Days 1 to 14)**		**Cycle 3 (Days 1 to 14)**		**Cycles 4 to 6 (Days 1 to 14)**	**Cycle 7 (Days 1 to 14)**	**Subsequent Cycles (Days 1 to 14)[32]**	**End of Treatment (EOT)[30]**	**Follow Up (Days after EOT visit)[31]**					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Informed Consent[2]	X																	
Tumor History[3]	X																	
Medical History[4]	X																	
Complete Physical Examination	X	X										X		X				
Abbreviated Physical Examination[5]			X	X	X	X	X	X	X	X	X							
Baseline Signs and Symptoms[6]		X																
Height	X																	
Weight[7]	X	X			X		X		X	X	X	X		X				
Vital signs (BP/PR/Temp)[8]	X	X	X	X	X	X	X	X	X	X	X	X		X				
Eastern cooperative oncology group (ECOG) Performance Status[9]	X								X (Cycle 4 only)			X		X				
Triplicate 12 Lead ECG[10]	X (single ECG only)	X	X	X	X	X	X	X	X	X	X	X						

Part B1 Combination Therapy		Treatment Period											Post Treatment					
		Cycle 1 Only (Days 1 to 14)			Cycle 2 (Days 1 to 14)		Cycle 3 (Days 1 to 14)		Cycles 4 to 6 (Days 1 to 14)	Cycle 7 (Days 1 to 14)	Subsequent Cycles (Days 1 to 14)[32]	End of Treatment (EOT)[30]	Follow Up (Days after EOT visit)[31]					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Laboratory																		
Hematology[11]	X	X		X	X	X	X	X	X	X	X	X		X				
Blood Chemistry[12]	X	X		X	X	X	X	X	X	X	X	X		X				
Coagulation[13]	X	X		X	X	X	X	X	X	X	X	X		X				
Urinalysis[14]	X			X	X	X	X	X	X	X	X	X		X				
Pregnancy Test[15]	X	X			X		X		X	X	X	X						
Hepatitis B, C and HIV tests[16]	X																	
Cardiac enzymes[17]	X	X					X		X (Cycle 5 only)	X	X (Cycle 9 and every other cycle)	X						
Registration and Treatment																		
Registration[18]		X																
Utomilumab Treatment[19]		X					X		X (Cycle 5 only)	X	Cycle 9 and every other cycle							
PF-04518600 Treatment[20]		X			X		X		X	X	X							
Tumor Assessments																		
CT or MRI scan or equivalent[21]	X	Every 6 weeks until confirmed progressive disease. Scans may be moved to every 12 weeks after 24 weeks until confirmed progressive disease.																
Other samplings																		
[redacted] CCI	[redacted]								[redacted]			[redacted]						
[redacted]		[redacted]																
[redacted]																		

Part B1 Combination Therapy		Treatment Period											Post Treatment					
		Cycle 1 Only (Days 1 to 14)			Cycle 2 (Days 1 to 14)		Cycle 3 (Days 1 to 14)		Cycles 4 to 6 (Days 1 to 14)	Cycle 7 (Days 1 to 14)	Subsequent Cycles (Days 1 to 14)[32]	End of Treatment (EOT)[30]	Follow Up (Days after EOT visit)[31]					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Blood Samples for PK[24]		See Pharmacokinetic and Pharmacodynamic Sampling Schedule Table below.																
Blood Sample for Anti-Drug antibodies[25]		See Pharmacokinetic and Pharmacodynamic Sampling Schedule Table below.																
CCI [redacted]		[redacted]																
Other clinical assessments																		
Adverse Events[27]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication and non-drug supportive interventions[28]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram or MUGA[29]	X	Every 3 months										X						

Except for safety assessments, all other activities performed during Cycle 1 can be performed ±1 day, and for Cycle 2 onwards ±2 days. Safety assessments must be performed prior to dosing (see footnotes for details). All cycles are relative to PF-04518600 administration.

Footnotes

1. Screening: to be obtained within 28 days prior to treatment start.
2. Informed Consent: must be obtained prior to undergoing any study specific procedures. For Japan Part B1 only: after completion of 2 treatment cycles and prior to initiation of Cycle 3, a follow up consent must be obtained to confirm patient's willingness to continue on study.
3. Tumor History: will be collected within 28 days during screening prior to treatment start. Includes history of disease under study including details of primary diagnosis and treatment history.
4. Medical History: Includes history of disease process other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
5. Abbreviated Physical Examination (PE): Abbreviated PEs should be performed as appropriate at each visit where complete physical exams are not required. Refer to Section 7.1 Assessments for further details.
6. 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. During the study, any new or worsened conditions since baseline will be recorded on the Adverse Events (AE) case report form (CRF) page.
7. Weight: Patient's body weight will be measured prior to the preparation of investigational product (PF-04518600) and patient's dose of PF-04518600 for that cycle will be based on the patient's body weight (see Administration Section 5.4).
8. Vital signs: includes temperature (oral, tympanic, temporal or axillary), blood pressure (BP), and pulse rate to be recorded in the sitting position after 5 minutes of rest. On Day 1 of each cycle, vital signs should be measured prior to infusion start (pre-dose) and 1 hour after the start of the infusion.
9. Performance status: use Eastern Cooperative Oncology Group (ECOG) scale in Appendix 1.
10. Triplicate 12-leads electrocardiogram (ECG): Triplicate ECGs will be collected at times specified in the Schedule of Activities. At each time point, at least a 10 second strip, three consecutive 12-lead ECGs will be performed 1-5 minutes apart to determine mean QTcF interval. The Screening ECG will be a single, 12-lead ECG. 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-04518600. Additional ECGs will be collected on Cycle 1 Day 2 (C1D2), Cycle 1 Day 8 (C1D8), Cycle 2 Day 8 (C2D8), and Cycle 3 Day 8 (C3D8). 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. All ECGs will be reviewed by a centralized ECG vendor. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. Refer to Section 7.1.5 (12-Lead) ECG for further details.
11. Hematology: complete blood count (CBC) to include hematocrit, hemoglobin, platelets, white blood cells (WBC), absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Assessments conducted on Cycle 1 Day 1 (C1D1) must be completed within 48 hours prior to dosing. If screening 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 Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for Laboratory Tests list.
12. Blood Chemistry: Tests for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (Alk Phos), gamma-glutamyltransferase (GGT), sodium, potassium, magnesium, chloride, total calcium, total bilirubin, blood urea nitrogen (BUN) or urea, creatinine, uric acid, glucose (non-fasted), albumin, phosphorous or phosphate, amylase, lipase and thyroid stimulating hormone (TSH) will be performed. Assessments conducted on Cycle 1 Day 1 (C1D1) must be completed within 48 hours prior to dosing. If screening assessments are performed within 72 hours prior to C1D1, there is no need to repeat assessments on C1D1. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. If abnormalities are observed in TSH values, a T4 Thyroxine test will be performed.

13. Coagulation Assays: prothrombin time (PT) and partial thromboplastin time (PTT). Assessments conducted on Cycle 1 Day 1 (C1D1) must be completed within 48 hours prior to dosing. If screening assessments are performed within 72 hours prior to C1D1, there is no need to repeat assessments on C1D1. Assessments performed on C1D2 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for laboratory tests list.
14. Urinalysis: Dipstick is acceptable. Microscopic analyses required if dipstick abnormal. If ≥2+ protein on urine dipstick, then collect 24 hr urine. Assessments conducted on C1D1 must be completed within 48 hours prior to dosing. No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for Laboratory Tests list.
15. Pregnancy Test (Serum/Urine): For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at C1D1, before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle prior to dosing during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Results will be obtained prior to initiating therapy at all times. Additional pregnancy tests may also be undertaken if requested by institutional review board (IRB)/institutional ethics committee (IEC)s or if required by local regulations.
16. 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. History of human papilloma virus (HPV) will be recorded for HNSCC patients.
17. Cardiac enzymes: Troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) will be evaluated in patients with previous history of anthracycline treatment. Assessments must be performed prior to dosing. No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment performed within 72 hours prior to that date. Assessments performed on Cycle 3 Day 1 (C3D1) and Day 1 of each subsequent odd number cycles should be performed within 48 hours prior to dosing. Assessments should also be performed when clinically indicated. See Assessments Section 7.1.3 for Laboratory Tests list.
18. Registration: Patient number and dose level allocation provided by Pfizer Inc. Treatment should begin no longer than four days from registration.
19. Utomilumab Treatment: utomilumab will be administered once every 28 days as an IV infusion over 60 minutes (-5 to +15 minutes) and should include the time needed to flush the infusion line. Day 1 safety labs (blood chemistry, hematology, coagulation, and urinalysis) need to be reviewed by a physician prior to dosing at the beginning of each cycle. On cycles whereby both PF-04518600 and utomilumab are to be administered on the same day, PF-04518600 will be administered no sooner than 30 minutes after completion of the utomilumab infusion and after post- utomilumab and pre- PF-04518600 pharmacokinetic blood draws. Furthermore, separate infusion bags and filters must be used for each investigational product. Treatment with investigational product will continue until disease progression by irRECIST, patient refusal, unacceptable toxicity occurs, or the end of the study, whichever occurs first.
20. PF-04518600 Treatment: PF-04518600 will be administered once every 2 weeks as an IV infusion over 60 minutes (-5 to +15 minutes) and should include the time needed to flush the infusion line. Utomilumab will be administered first, and PF-04518600 will be administered no sooner than 30 minutes after completion of utomilumab infusion and after post- utomilumab and pre- PF-04518600 pharmacokinetic blood draws. Day 1 safety labs (blood chemistry, hematology and urinalysis) need to be reviewed by a physician prior to dosing at the beginning of each cycle. Treatment with investigational product will continue until disease progression by irRECIST, patient refusal, unacceptable toxicity occurs, or the end of the study, whichever occurs first.

21. Tumor Assessments: Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans. Brain scans and bone scans will be performed at baseline and on-study 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. CT or MRI scans to be done every 6 weeks (±5 days) from the start of study treatment until confirmed disease progression by RECIST (1.1), irRECIST or death, or patient begins a different anti-cancer therapy. Scans may be moved to every 12 weeks after 24 weeks until confirmed progressive disease. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Confirmation of response (complete response (CR)/partial response (PR)) is not required. CT or MRI scans should be completed before tumor biopsy samples are collected.

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24. PK Sampling: Specific timing for collection of pharmacokinetic samples can be found in the pharmacokinetic and pharmacodynamic sampling schedule table below.
25. Anti-drug antibodies: Specific timing for collection of anti-PF-04518600 and anti-utomilumab antibody samples can be found in the Pharmacokinetic and Pharmacodynamic Sampling Schedule table below.

CCI [redacted]

27. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.03. Patients must be followed for adverse events (AEs) for 60 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. However, late immune-related DLTs that are not SAEs need to be collected consistent with Section 3.2.1. 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 98 calendar days from first administration of the investigational product, or up to 60 days after last administration of investigational product, whichever is later. Serious adverse events 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 serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

28. 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), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
29. Echocardiogram or multigated acquisition (MUGA) scan: echocardiogram or MUGA will be evaluated in patients with previous history of anthracycline treatment. For these patients, an echocardiogram or MUGA will be performed at screening and every 3 months whilst on treatment and when clinically indicated. An echocardiogram or MUGA will be performed at the end of treatment (EOT) visit if not performed within 3 months of discontinuation.
30. End of treatment visit (EOT visit): Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
31. Follow up: At least 28 days and no more than 35 days after discontinuation of treatment, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Late immune related adverse event information will be collected during the 28 to 35 day follow up visit. 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. Independent to time of disease progression, all patients (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor) will be followed for survival for at least 2 years from the time of their first dose of investigational products. After the completion of end of treatment visits, Patients will be contacted every 2 months for survival status. To collect additional late immune related adverse event information, any patient who discontinue from treatment after 1 to 4 or 6 cycles of treatment will also be contacted by phone during the follow up period. For patients who discontinues after receiving 5 cycles of treatment, late immune information will be collected during the 28 to 35 day follow up visit. If the patient discontinues after receiving 6 cycles of treatment, they will be contacted by phone 14 days (±2 days) after EOT. If the patient discontinues after receiving 4 cycles of treatment, they will be contacted by phone 42 days (±2 days) after EOT. If the patient discontinues after receiving 3 cycles of treatment, they will be contacted by phone 56 days (±2 days) after EOT. If the patient discontinues after receiving 2 cycles of treatment, they will be contacted by phone 70 days (±2 days) after EOT. If the patient discontinues after receiving 1 cycle of treatment, they will be contacted by phone 84 days (±2 days) after EOT. If any concern arises, patient will be called in for an inpatient follow up visit within 5 calendar days of initial phone call (assessments will be the same as the assessments performed 28-35 days after end of treatment follow up visit).
32. Subsequent cycles: Day 8 is not required after Cycle 3.

SCHEDULE OF ACTIVITIES: Part A2 Monotherapy and B2 Combination Therapy

The schedule of activities table provides 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.

Part A2 Monotherapy & B2 Combination Therapy		**Treatment Period**										**Post Treatment**					
		Cycle 1 Only (Days 1 to 14)		**Cycle 2 (Days 1 to 14)**		**Cycle 3 (Days 1 to 14)**		**Cycles 4 to 6 (Days 1 to 14)**	**Cycle 7 (Days 1 to 14)**	**Subsequent Cycles (Days 1 to 14)[31]**	**End of Treatment (EOT)[29]**	**Follow Up (Days after EOT visit)[30]**					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Informed Consent[2]	X																
Tumor History[3]	X																
Medical History[4]	X																
Complete Physical Examination	X	X									X		X				
Abbreviated Physical Examination[5]			X	X	X	X	X	X	X	X							
Baseline Signs and Symptoms[6]		X															
Height	X																
Weight[7]	X	X									X		X				
Vital signs (BP/PR/Temp)[8]	X	X	X	X	X	X	X	X	X	X	X		X				

Part A2 Monotherapy & B2 Combination Therapy		**Treatment Period**										**Post Treatment**					
		Cycle 1 Only (Days 1 to 14)		**Cycle 2 (Days 1 to 14)**		**Cycle 3 (Days 1 to 14)**		**Cycles 4 to 6 (Days 1 to 14)**	**Cycle 7 (Days 1 to 14)**	**Subsequent Cycles (Days 1 to 14)[31]**	**End of Treatment (EOT)[29]**	**Follow Up (Days after EOT visit)[30]**					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Eastern cooperative oncology group (ECOG) Performance Status[9]	X	X		X		X		X	X	X	X		X				
Triplicate 12 Lead ECG[10]	X (single ECG only)	X	X	X	X	X	X	X	X	X	X						
Laboratory																	
Hematology[11]	X	X	X	X	X	X	X	X	X	X	X		X				
Blood Chemistry[12]	X	X	X	X	X	X	X	X	X	X	X		X				
Coagulation[13]	X	X	X	X	X	X	X	X	X	X	X		X				
Urinalysis[14]	X		X	X	X	X	X	X	X	X	X		X				
Pregnancy Test[15]	X	X		X		X		X	X	X	X						
Hepatitis B, C, D and HIV tests[16]	X																
Hepatitis B or C viral load tests (Part A2 HCV/ HBV+ only)[16]		X							X	X (every 3 months)	X						
Cardiac enzymes[17]	X	X				X		X (Cycle 5 only)	X	X (Cycle 9 and every other cycle)	X						

Part A2 Monotherapy & B2 Combination Therapy		**Treatment Period**										**Post Treatment**					
		Cycle 1 Only (Days 1 to 14)		**Cycle 2 (Days 1 to 14)**		**Cycle 3 (Days 1 to 14)**		**Cycles 4 to 6 (Days 1 to 14)**	**Cycle 7 (Days 1 to 14)**	**Subsequent Cycles (Days 1 to 14)[31]**	**End of Treatment (EOT)[29]**	**Follow Up (Days after EOT visit)[30]**					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Alpha Fetoprotein (**A2 only**)	X	Every 8 weeks for 48 weeks and then every 12 weeks, until confirmed progressive disease															
Registration and Treatment																	
Registration[18]		X															
PF-04518600 Treatment[19]		X		X		X		X	X	X							
Utomilumab Treatment (**B2 Only**)[20]		X				X		X (Cycle 5 only)	X	Cycle 9 and every other cycle							
Tumor Assessments																	
CT or MRI scan or equivalent[21]	X	Every 8 weeks for 24 weeks and then every 12 weeks, until confirmed progressive disease															
Other samplings																	
CCI [redacted]																	
[redacted]																	
[redacted]																	
Blood Samples for PK[23]		See Pharmacokinetic and Pharmacodynamic Sampling Schedule Table below.															

Part A2 Monotherapy & B2 Combination Therapy		Treatment Period										Post Treatment					
		Cycle 1 Only (Days 1 to 14)		Cycle 2 (Days 1 to 14)		Cycle 3 (Days 1 to 14)		Cycles 4 to 6 (Days 1 to 14)	Cycle 7 (Days 1 to 14)	Subsequent Cycles (Days 1 to 14)[31]	End of Treatment (EOT)[29]	Follow Up (Days after EOT visit)[30]					
Visit Identifier	**Screen[1] (≤28 days)**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**		**14 days**	**28 to 35 days**	**42 days**	**56 days**	**70 days**	**84 days**
Visit Window in Days			**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**							
Blood Sample for Anti-drug Antibodies[24]		See Pharmacokinetic and Pharmacodynamic Sampling Schedule Table below.															
CCI [redacted]		[redacted]															
Other clinical assessments																	
Adverse Events[26]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication and non-drug supportive interventions[27]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram or MUGA[28]	X	Every 3 months									X						

Except for safety assessments, all other activities performed during Cycle 1 can be performed ±1 day, and for Cycle 2 onwards ±2 days. Safety assessments must be performed prior to dosing (see footnotes for details).

Footnotes

1. Screening: to be obtained within 28 days prior to treatment start.
2. Informed Consent: must be obtained prior to undergoing any study specific procedures.
3. Tumor History: will be collected within 28 days during screening prior to treatment start. Includes history of disease under study including details of primary diagnosis and treatment history.

4. Medical History: Includes history of disease process other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
5. Abbreviated Physical Examination (PE): Abbreviated PEs should be performed as appropriate at each visit where complete physical exams are not required. Refer to Section 7.1 Assessments for further details.
6. 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. During the study, any new or worsened conditions since baseline will be recorded on the Adverse Events (AE) case report form (CRF) page.
7. Weight. Patient's body weight is not needed prior to the preparation of investigational product.
8. Vital signs: includes temperature (oral, tympanic, temporal or axillary), blood pressure (BP), and pulse rate to be recorded in the sitting position after 5 minutes of rest. On Day 1 of each cycle, vital signs should be measured prior to infusion start (pre-dose) and 1 hour after the start of the infusion.
9. Performance status: use Eastern Cooperative Oncology Group (ECOG) scale in Appendix 1.
10. Triplicate 12-leads electrocardiogram (ECG): Triplicate ECGs will be collected at times specified in the Schedule of Activities. At each time point, at least a 10 second strip, three consecutive 12-lead ECGs will be performed 1 to 5 minutes apart to determine mean QTcF interval. The Screening ECG will be a single, 12 lead ECG. 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-04518600. Additional ECGs will be collected on Cycle 1 Day 8 (C1D8), Cycle 2 Day 8 (C2D8), and Cycle 3 Day 8 (C3D8). 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. All ECGs will be reviewed by a centralized ECG vendor. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. Refer to Section 7.1.5 (12-Lead) ECG for further details.
11. Hematology: complete blood count (CBC) to include hematocrit, hemoglobin, platelets, white blood cells (WBC), absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Assessments conducted on Cycle 1 Day 1 (C1D1) must be completed within 48 hours prior to dosing. If screening 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 Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for Laboratory Tests list.
12. Blood Chemistry: Tests for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (Alk Phos), gamma-glutamyltransferase (GGT), sodium, potassium, magnesium, chloride, total calcium, total bilirubin, blood urea nitrogen (BUN) or urea, creatinine, uric acid, glucose (non-fasted), albumin, phosphorous or phosphate, amylase, lipase and thyroid stimulating hormone (TSH) will be performed. Assessments conducted on Cycle 1 Day 1 (C1D1) must be completed within 48 hours prior to dosing. If screening assessments are performed within 72 hours prior to C1D1, there is no need to repeat assessments on C1D1. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. If abnormalities are observed in TSH values, a T4 thyroxine test will be performed. See Assessments Section 7.1.3 for laboratory tests list.
13. Coagulation Assays: prothrombin time (PT) and partial thromboplastin time (PTT). Assessments conducted on Cycle 1 Day 1 (C1D1) must be completed within 48 hours prior to dosing. If screening assessments are performed within 72 hours prior to C1D1, there is no need to repeat assessments on C1D1. Assessments performed on C1D2 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for laboratory tests list.
14. Urinalysis: Dipstick is acceptable. Microscopic analyses required if dipstick abnormal. If ≥2+ protein on urine dipstick, then collect 24 hr urine. Assessments conducted on C1D1 must be completed within 48 hours prior to dosing. No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Assessments performed on C2D1 and Day 1 of each subsequent cycle should be performed within 48 hours prior to dosing. See Assessments Section 7.1.3 for Laboratory Tests list.

15. Pregnancy Test (Serum/Urine): For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at C1D1, before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle prior to dosing during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Results will be obtained prior to initiating therapy at all times. Additional pregnancy tests may also be undertaken if requested by institutional review board (IRB)/institutional ethics committee (IEC)s or if required by local regulations.
16. 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 at screening. All Part A2 HCC patients with detectable viral load for hepatitis B at screening must also be tested for hepatitis D by antibody (HDV Ab) or polymerase chain reaction (PCR). All Part A2 HCC patients with detectable viral load for HCV or HBV at screening, must be retested every 3 months (ie, Cycle 7 Day 1, Cycle 13 Day 1, Cycle 19 Day 1, etc) and at the EOT visit.
17. Cardiac enzymes: Troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) will be evaluated in patients with previous history of anthracycline treatment. Assessments must be performed prior to dosing. No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment performed within 72 hours prior to that date. Assessments performed on Cycle 3 Day 1 (C3D1) and Day 1 of each subsequent odd number cycles should be performed within 48 hours prior to dosing. Assessments should also be performed when clinically indicated. See Assessments Section 7.1.3 for Laboratory Tests list.
18. Registration: Patient number and dose level allocation provided by Pfizer Inc. Treatment should begin no longer than four days from registration.
19. PF-04518600 Treatment: PF-04518600 will be administered once every 2 weeks as an IV infusion over 60 minutes (-5 to +15 minutes) and should include the time needed to flush the infusion line. Day 1 safety labs (blood chemistry, hematology, and urinalysis) need to be reviewed by a physician prior to dosing at the beginning of each cycle. Treatment with investigational product will continue until disease progression by irRECIST, patient refusal, unacceptable toxicity occurs, or the end of the study, whichever occurs first.
20. Utomilumab Treatment: utomilumab will be administered once every 28 days as an IV infusion over 60 minutes (-5 to +15 minutes) and should include the time needed to flush the infusion line. Day 1 safety labs (blood chemistry, hematology, coagulation, and urinalysis) need to be reviewed by a physician prior to dosing at the beginning of each cycle. On cycles whereby both PF-04518600 and utomilumab are to be administered on the same day, PF-04518600 will be administered no sooner than 30 minutes after completion of the utomilumab infusion and after post-utomilumab and pre- PF-04518600 pharmacokinetic blood draws. Furthermore, separate infusion bags and filters must be used for each investigational product. Treatment with investigational product will continue until disease progression by irRECIST, patient refusal, unacceptable toxicity occurs, the or end of the study, whichever occurs first.

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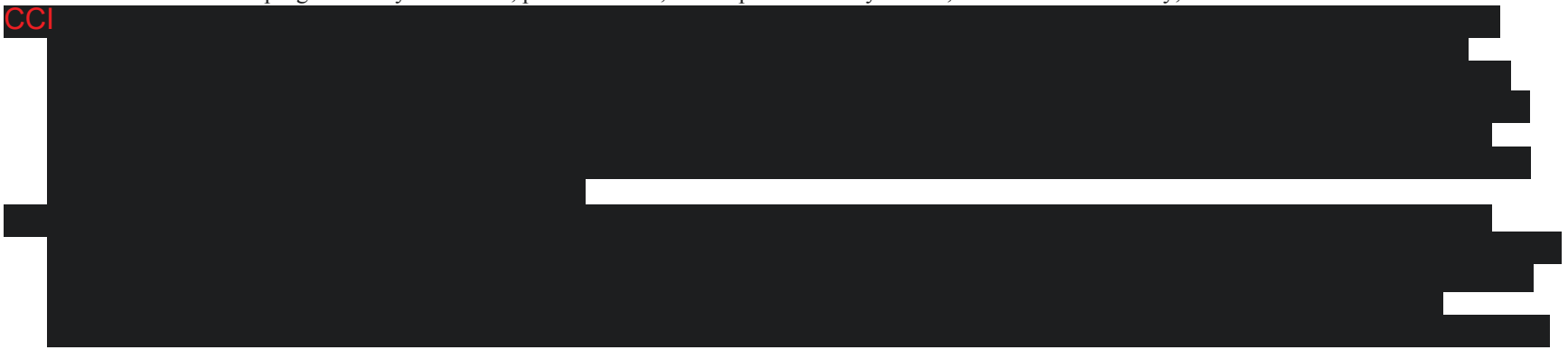

CCI [redacted]

23. PK Sampling: Specific timing for collection of pharmacokinetic samples can be found in the pharmacokinetic and pharmacodynamic sampling schedule table below.
24. Anti-drug Antibodies: Specific timing for collection of anti-drug antibody samples can be found in the Pharmacokinetic and Pharmacodynamic Sampling Schedule table below.

CCI [redacted]

26. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.03. Patients must be followed for adverse events (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. However, late immune-related DLTs that are not SAEs need to be collected consistent with Section 3.2.1. 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 98 calendar days from first administration of the investigational product, or up to 60 days after last administration of investigational product, whichever is later. Serious adverse events 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 serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
27. Concomitant 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), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
28. Echocardiogram or multigated acquisition (MUGA) scan: echocardiogram or MUGA will be evaluated in patients with previous history of anthracycline treatment. For these patients, an echocardiogram or MUGA will be performed at screening and every 3 months whilst on treatment and when clinically indicated. An echocardiogram or MUGA will be performed at the end of treatment (EOT) visit if not performed within 3 months of discontinuation.
29. End of treatment visit (EOT visit): Obtain these assessments if not completed in the last week (last 8 weeks for tumor assessments).
30. Follow up: At least 28 days and no more than 35 days after discontinuation of treatment, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Late immune related adverse event information will be collected during the 28 to 35 day follow up visit. 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. Independent to time of disease progression, all patients (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor) will be followed for survival for at least 2 years from the time of their first dose of investigational product. After the completion of end of treatment visits, Patients will be contacted every 2 months for survival status and subsequent anti-cancer treatment. Subsequent anti-cancer therapy will be documented and recorded for patients who discontinue investigational products and continue in follow up, and during survival follow up. To collect additional late immune related adverse event information, any patient who discontinues from treatment after 1 to 4 or 6 cycles of treatment will also be contacted by phone during the follow up period. For patients who discontinues after receiving 5 cycles of treatment, late immune information will be collected during the 28 to 35 day follow up visit. If the patient discontinues after receiving 6 cycles of treatment, they will be contacted by phone 14 days (±2 days) after EOT. If the patient

discontinues after receiving 4 cycles of treatment, they will be contacted by phone 42 days (±2 days) after EOT. If the patient discontinues after receiving 3 cycles of treatment, they will be contacted by phone 56 days (±2 days) after EOT. If the patient discontinues after receiving 2 cycles of treatment, they will be contacted by phone 70 days (±2 days) after EOT. If the patient discontinues after receiving 1 cycle of treatment, they will be contacted by phone 84 days (±2 days) after EOT. If any concern arises, patient will be called in for an inpatient follow up visit within 5 calendar days of initial phone call (assessments will be the same as the assessments performed 28-35 days after end of treatment follow up visit).

31. Subsequent cycles: Day 8 is not required after Cycle 3.

Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part A1 Monotherapy

Part A1 Monotherapy	Cycle 1 (Days 1 to 14)					Cycle 2 and 3 (Days 1 to 14)				Cycle 4 (Days 1 to 14)		Cycles 5 and 6 (Days 1 to 14)		Cycle 7 (Days 1 to 14)	Every Other Cycle Thereafter	End of Treatment
Visit Identifier	Day 1				Day 8	Day 1			Day 8	Day 1		Day 1		Day 1	Day 1	
	Pre-dose*	1 hr*	4 hr*	24 hr*		Pre-dose*	1 hr*	4 hr*		Pre-dose*	1 hr*	Pre-dose	1 hr	Pre-dose	Pre-dose*	
Visit Window in Days					±1	±2			±2	±2		±2		±2	±2	
Blood PK sample for PF-04518600	X	X	X	X	X	X	X	X (Cycle 3 only)	X	X	X	X	X	X	X[3]	X[3]
Blood sample for anti-PF-04518600-antibodies[1]	X					X				X		X (Cycle 5 only)		X	X	X
CCI	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]				[redacted]		[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]				[redacted]		[redacted]
	[redacted]				[redacted]	[redacted]				[redacted]				[redacted]		[redacted]
	[redacted]				[redacted]	[redacted]			[redacted]	[redacted]				[redacted]		[redacted]
	[redacted]									[redacted]				[redacted]		[redacted]
	[redacted]									[redacted]						

***Sampling times are related to the start of infusion; 1 hr samples should be collected immediately before the infusion ends. All sample time windows, except 1 hr samples will be ±10% of nominal time. Therefore, a 4 hr sample will have a ±24 minutes collection window. Similarly, a Day 4 sample will have a ±9.6 hrs collection window.**

1. Blood sample for anti-PF-04518600-antibodies and NAb: Samples for anti-PF-04518600-antibodies and NAb will be collected pre-dose on Day 1 of Cycle 1 to 5, 7 and every other cycle after ie, Cycle 9, 11, 13, 15 etc. and again at end of treatment visit. Patients having an unresolved adverse event that is possibly related to ADA formation will be asked to return for ADA and drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator, and sponsor concurs with that the investigator's assessment, up to 6 months from the EOT or the day of early withdrawal (see Section 3.1 Study Overview).

[redacted]

3. Companion blood sample for the determination of drug concentration will be collected in conjunction with the ADA sample collection to facilitate ADA assessment.

Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part B1 Combination Therapy

Part B1 Combination Therapy	Cycle 1 (Days 1 to 14)					Cycle 2 (Days 1 to 14)			Cycle 3 (Days 1 to 14)			Cycle 4 (Days 1 to 14)		Cycle 5 (Days 1 to 14)		Cycle 6 (Days 1 to 14)		Cycle 7 (Days 1 to 14)	Every Other Cycle There-after	EOT
Visit Identifier	Day 1				Day 8	Day 1		Day 8	Day 1		Day 8	Day 1		Day 1		Day 1		Day 1	Day 1	
	Pre-dose*	1 hr*	4 hr*	24 (±4) hr*		Pre-dose*,3	1 hr*,		Pre-dose*	1 hr*		Pre-dose*,3	1 hr*,	Pre-dose*	1 hr*	Pre-dose*	1 hr*	Pre-dose*	Pre-dose*	
Visit Window in Days					±1	±2		±2	±2		±2	±2		±2		±2		±2	±2	
Blood PK sample for PF-04518600	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X[3]	X[3]
Blood sample for anti-PF-04518600-antibodies[1]	X					X			X			X		X				X	X	X
Blood PK sample for utomilumab	X	X	X	X	X	X[4]			X	X	X	X[4]		X	X			X	X[3]	X[3]
Blood sample for anti-utomilumab antibodies[2]	X								X					X				X	X	X
CCI	[redacted]																			

***Sampling times are related to the start of infusion of the corresponding investigational product; 1 hr samples should be collected immediately before the infusion of the corresponding investigational product ends. Each cycle is 2 weeks and is relative to PF-04518600 dosing.**

1. Blood sample for anti-PF-04518600-antibodies and NAb: Samples for anti-PF-04518600-antibodies and NAb will be collected pre-dose on Day 1 of Cycle 1 to 5, 7 and every other cycle after ie, Cycle 9, 11, 13, 15 etc. and again at end of treatment visit. Patients having an unresolved adverse event that is possibly related to ADA formation will be asked to return for ADA and drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator, and sponsor concurs with that the investigator's assessment, up to 6 months from the EOT or the day of early withdrawal (see Section 3.1 Study Overview).
2. Blood sample for anti-utomilumab-antibodies and NAb: Samples for anti-utomilumab-antibodies and NAb will be collected pre-dose on Day 1 of Cycle 1, 3, 5, 7 and every other cycle after ie, Cycle 9, 11, 13, 15 etc. and again at end of treatment visit. Patients having an unresolved adverse event that is possibly related to ADA formation will be asked to return for ADA and drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator, and sponsor concurs with that the investigator's assessment, up to 6 months from the EOT or the day of early withdrawal (see Section 3.1 Study Overview).
3. Companion blood sample for the determination of drug concentration will be collected in conjunction with the ADA sample collection to facilitate ADA assessment.

[redacted]

Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part A2 and B2 Combination Therapy

Part A2 Monotherapy & B2 Combination Therapy	**Cycle 1 (Days 1 to 14)**				**Cycle 2 (Days 1 to 14)**			**Cycle 3 (Days 1 to 14)**			**Cycle 4 (Days 1 to 14)**		**Cycle 5 (Days 1 to 14)**		**Cycle 6 (Days 1 to 14)**		**Cycle 7 (Days 1 to 14)**	**Every Other Cycle Thereafter**	**EOT**
Visit Identifier	**Day 1**			**Day 8**	**Day 1**		**Day 8**	**Day 1**		**Day 8**	**Day 1**		**Day 1**		**Day 1**		**Day 1**	**Day 1**	
	Pre-dose*	**1 hr***	**4 hr***		**Pre-dose*,3**	**1 hr*,**		**Pre-dose***	**1 hr***		**Pre-dose*,3**	**1 hr*,**	**Pre-dose***	**1 hr***	**Pre-dose***	**1 hr***	**Pre-dose***	**Pre-dose***	
Visit Window in Days				**±1**	**±2**		**±2**	**±2**		**±2**	**±2**		**±2**		**±2**		**±2**	**±2**	
Assessments for Both A2 and B2																			
Blood PK sample for PF-04518600	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X[5]	X[5]
Blood sample for anti-PF-04518600-antibodies[1]	X				X			X			X		X				X	X	X
CCI [redacted]	[redacted]																		
Assessments for Part B2 only																			
Blood PK sample for utomilumab	X	X	X	X	X[6]			X	X	X	X[6]		X	X			X	X[5]	X[5]
Blood sample for anti-utomilumab antibodies[2]	X							X					X				X	X	X

Part A2 Monotherapy & B2 Combination Therapy	**Cycle 1 (Days 1 to 14)**				**Cycle 2 (Days 1 to 14)**			**Cycle 3 (Days 1 to 14)**			**Cycle 4 (Days 1 to 14)**		**Cycle 5 (Days 1 to 14)**		**Cycle 6 (Days 1 to 14)**		**Cycle 7 (Days 1 to 14)**	**Every Other Cycle There-after**	**EOT**
Visit Identifier	**Day 1**			**Day 8**	**Day 1**		**Day 8**	**Day 1**		**Day 8**	**Day 1**		**Day 1**		**Day 1**		**Day 1**	**Day 1**	
	Pre-dose*	**1 hr***	**4 hr***		**Pre-dose*,3**	**1 hr*,**		**Pre-dose***	**1 hr***		**Pre-dose*,3**	**1 hr*,**	**Pre-dose***	**1 hr***	**Pre-dose***	**1 hr***	**Pre-dose***	**Pre-dose***	
Visit Window in Days				**±1**	**±2**		**±2**	**±2**		**±2**	**±2**		**±2**		**±2**		**±2**	**±2**	
Serum sample for soluble 4-1BB (s4-1BB)[8]	X		X	X	X		X	X		X	X						X		X

***Sampling times are related to the start of infusion of the corresponding investigational product; 1 hr samples should be collected immediately before the infusion of the corresponding investigational product ends. Each cycle is 2 weeks and is relative to PF-04518600 dosing.**

1. Blood sample for anti-PF-04518600-antibodies and NAb: Samples for anti-PF-04518600-antibodies and NAb will be collected pre-dose on Day 1 of Cycle 1 to 5, 7 and every other cycle after ie, Cycle 9, 11, 13, 15 etc. and again at end of treatment visit. Patients having an unresolved adverse event that is possibly related to ADA formation will be asked to return for ADA and drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator, and sponsor concurs with that the investigator's assessment, up to 6 months from the EOT or the day of early withdrawal (see Section 3.1 Study Overview).
2. Blood sample for anti-utomilumab-antibodies and NAb (Part-B2 only): Samples for anti-utomilumab-antibodies and NAb will be collected pre-dose on Day 1 of Cycle 1, 3, 5, 7 and every other cycle after ie, Cycle 9, 11, 13, 15 etc. and again at termination visit. Patients having an unresolved adverse event that is possibly related to ADA formation will be asked to return for ADA and drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator, and sponsor concurs with that the investigator's assessment, up to 6 months from the EOT or the day of early withdrawal (see Section 3.1 Study Overview).

[redacted]

6. During Cycles 2 and 4 when utomilumab will not be infused, PK and pharmacodynamic samples for utomilumab/4-1BB will be collected within 1 hour before start of PF-04518600 infusion (Part B2 only).

[redacted]

8. Sampling of sOX40 and s4-1BB (Part B2 only) will be relative to the infusion of PF-04518600 on cycles whereby PF-04518600 is administered alone, or to utomilumab on cycles whereby PF-04518600 is administered in combination with utomilumab.

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APPENDICES

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-04518600 is a fully human IgG2 monoclonal antibody (mAb) specific for human OX40 (CD134). OX40 is a member of the tumor-necrosis factor receptor (TNFR) superfamily that is expressed primarily on activated T cells.[2,3] By acting as a co-stimulatory receptor, OX40 plays a key role in the regulation of antigen-specific T-cell expansion, differentiation and function. Mechanistically, PF-04518600 has been shown to costimulate OX40, thereby inducing a T cell mediated anti-tumor response in vivo. In this clinical study, PF-04518600 as a monotherapy (Part A), and PF-04518600 in combination with utomilumab (Part B) will be evaluated for the treatment of adult patients with select locally advanced or metastatic cancers who are unresponsive to current available therapies, or for whom no standard therapy is available.

1.2. Background and Study Rationale

Additional pre-clinical and clinical information for PF-04518600 may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure for PF-04518600.

1.2.1. OX40 (CD134)

The ability to escape immune recognition is a hallmark of cancer progression. By manipulating the immune system and restoring immune surveillance, immunotherapy offers the opportunity to not only eradicate or stop tumor growth, but also the opportunity to decrease the rate of recurrence.[1] One strategy for increasing tumor immunity would be to activate and expand tumor-associated antigen T cells. It has long been recognized that T cell activation is not mediated by antigen stimulation alone. Indeed, tumor antigens may induce T-cell anergy, rendering T cells unable to proliferate in response to antigen, and hypo-responsive to further antigen encounter.[8] Instead, co-stimulatory receptors are required to complete the process of T cell activation and expansion. Thus, co-stimulatory receptors may have the potential to prevent tumor-induced immune tolerance.[9,10]

OX40 (CD134) is a co-stimulatory receptor that acts on antigen stimulated T cells but not native T cells.[1,3] OX40 expression is transient, and peaks 48 to 72 hours following T cell receptor (TCR) stimulation. High numbers of OX40 positive infiltrating T cells have been found within tumor biopsies, and lymph nodes of primary melanoma, breast, colon and head and neck cancer patients.[11-14] OX40 plays a key role in T cell survival, proliferation, and activation. Upon binding to OX40 ligand (also known as OX40L, CD252 or TNFSF4), OX40 signaling activates both the canonical and noncanonical NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) survival pathways, leading to an upregulation of anti-apoptotic molecules including Bcl-2, Bcl-xL, and surviving.[4] Furthermore, OX40 engagement may enhance IL-2, IL-4, IL-5, IFN-γ cytokine secretion by activated CD4 T cells. It is interesting to note that OX40 activation has been shown to not require co-stimulation from other co-stimulatory receptors.[15] OX40L is usually expressed on activated B cells and dendritic cells, but due to the immunosuppressive environment within a tumor, OX40L was not detected in the tumor mass of several syngeneic mouse models.[16] Mechanistically, it is therefore possible that an agonistic mAb to

OX40 may reverse T cell's anergic state, and enhance tumor immunity. Indeed, eradication of tumor growth has been observed by using agonistic OX40 mAbs and OX40 agonists in preclinical models of melanoma, sarcoma, and glioma, and colon, breast, prostate and renal cancers.[3,12,17,18] Given the potential for OX40 agonistic mAbs to enhance anti-tumor T cell responses, and induce tumor regression, a Phase 1 clinical trial with a murine anti-OX40 antibody has been completed.[19] In this study, tumor regression was observed in 12 of 30 advance cancer patients, as well as an acceptable toxicity profile. To date, two additional combination Phase 1/2 studies with cyclophosphamide and radiation have been initiated.[21] Pfizer has generated a fully human IgG2 monoclonal antibody specific for the human OX40 (PF-04518600). PF-04518600 has been demonstrated to be an agonistic antibody against OX40. Furthermore, PF-04518600 can selectively and reversibly bind to human OX40 with a high affinity, and in conjunction with TCR signals, is able to functionally co-stimulate T cells as measured by IL-2, IL-6, tumor necrosis factor (TNF) and IFNγ release in vitro. In a syngeneic mouse model, a murine surrogate anti-OX40 agonistic antibody (OX86) demonstrated growth inhibition of colon tumors (see Section 1.2.1.1 Nonclinical Efficacy).

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1.2.1.3. PF-04518600 Clinical Safety

PF-04518600 as monotherapy has been well-tolerated in doses from 0.01 to 10 mg/kg. As of a data cut-off date of 24 May 2017, 52 patients (43 male and 9 female, mean ages of 60.0 years) were treated with PF-04518600 across 6 dose levels (0.01, 0.1, 0.3, 1.5, 3 and 10 mg/kg) in B0601002 Part A1.

The most frequent treatment-emergent adverse events (TEAEs) regardless of causality that occurred in ≥10% of patients were: fatigue (46.2%), nausea (28.8%), decreased appetite (23.1%), pruritus (23.1%), anemia (21.2%), aspartate aminotransferase increase (21.2%), abdominal pain (19.2%), constipation (19.2%), dyspnea (19.2%), headache (17.3%), alanine aminotransferase increase (15.4%), chills (15.4%), cough (15.4%), diarrhea (15.4%), pyrexia (15.4%), vomiting (15.4%), back pain (13.5%), blood bilirubin increase (11.5%), and insomnia (11.5%).

A total of 30 (57.7%) patients out of 52 experienced treatment-related AEs. The most frequent treatment-related AE experienced by ≥10% of patients was fatigue (25.0%). Most treatment-related events reported were Grade 2 or below. There was 1 Grade 3 treatment-related event of gamma-glutamyltransferase increased reported. There did not appear to be a dose-dependent increase in any treatment-related AEs. No dose-limiting toxicities (DLTs) were observed.

The only treatment-related Serious Adverse Event (SAE) reported to date was Grade 2 congestive heart failure (CHF) in an HCC patient receiving the 0.1 mg/kg dose. This patient had a prior history of anthracycline exposure. There were no treatment-related deaths in study B0601002.

As B0601002 is an ongoing study, the available data are preliminary in nature and are subject to further review and quality control and may therefore change.

1.2.1.4. PF-04518600 Clinical Efficacy

As of data cutoff date of 24 May 2017, 2 confirmed partial responses (PRs) were reported in Study B0601002 Part A1; 1 PR was reported in a cutaneous melanoma patient treated at 0.1 mg/kg dose level who had a duration of response of 10.3 weeks, and a second PR was reported in a hepatocellular carcinoma (HCC) patient treated at 0.3 mg/kg dose level who had a duration of response of 44.1+ weeks and is still on study drug. A total of 27 (51.9%) patients, of the 49 evaluable patients treated in Part A1, experienced a best overall response of stable disease (SD).

As B0601002 is an ongoing study, the available data are preliminary in nature and are subject to further review and quality control and may therefore change.

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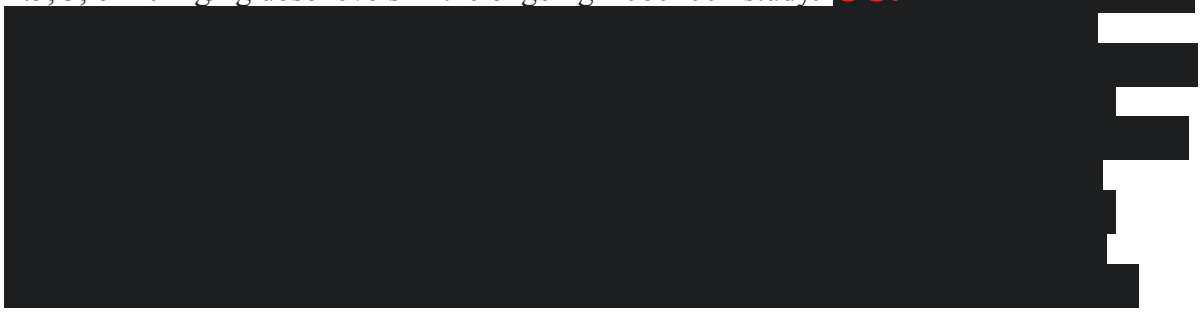
1.2.1.6. PF-04518600 Clinical Anti-Drug Antibodies

As of 17 November 2016, preliminary data were available for 46 patients who had the baseline and at least one ADA sample after treatment initiation analyzed from Part A1 of B0601002. A total of 3 patients (6.5%) tested positive for ADA at baseline. A total of 16 patients (35%) were ADA positive at a minimum of one time point post treatment initiation. The majority of ADA responses were transient with no noticeable effect on the PK of PF-04518600, except for 3 patients at the 0.1 mg/kg dose level; these 3 patients had the highest titers in that group and the C_{trough} of PF-04518600 appeared to be lower compared to the expected profiles.

As B0601002 is an ongoing study, the available data are preliminary in nature and are subject to further review and quality control and may therefore change.

1.2.1.7. PF-04518600 Clinical Pharmacodynamics

As of 30 January 2017, preliminary data were available for ~52 patients at the 0.01, 0.1, 0.3, 1.5, 3, or 10 mg/kg dose levels in the ongoing B0601002 study. CCI



As B0601002 is an ongoing study, the available data are preliminary in nature and are subject to further review and quality control and may therefore change.

1.2.2. 4-1BB (CD137)

4-1BB (CD137, tumor necrosis factor receptor superfamily 9 [TNFRSF9]), first identified as an inducible costimulatory receptor expressed on activated T cells, is a membrane spanning glycoprotein of the tumor necrosis factor receptor superfamily (TNFRSF). Current understanding of 4-1BB indicates that expression is generally activation dependent and encompasses a broad subset of immune cells including activated natural killer (NK and natural killer T (NKT) cells; regulatory T cells; dendritic cells (DC) including follicular DC; stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils and activated B cells.[22,23] The ligand that stimulates 4-1BB (4-1BB Ligand [4-1BBL]) is expressed on activated antigen-presenting cells (APCs), myeloid progenitor cells and hematopoietic stem cells.

4-1BB is undetectable on the surface of T cells but expression increases upon activation. Based on homology to other members of the TNFRSF, ligand binding is expected to induce receptor trimerization resulting in activation.[24] Some members of the TNFRSF can cleave the extracellular domain from the cell surface and exist in a soluble form. Soluble 4-1BB and soluble 4-1BBL have been demonstrated in the serum of some patients with autoimmune diseases and cancers.[25-27]

Upon 4-1BB activation, TNFR-associated factor (TRAF) 1 and TRAF 2, pro-survival members of the TNFR-associated factor (TRAF) family are recruited to the 4-1BB cytoplasmic tail resulting in downstream activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and the Mitogen Activated Protein (MAP) Kinase cascade including extracellular signal-regulated kinases (Erk), c-Jun

N-terminal kinases (Jnk), and p38 MAP kinases. NFkB activation leads to up regulation of Bfl-1 and Bcl-XL, pro-survival members of the Bcl-2 family. The pro-apoptotic protein Bim is downregulated in a TRAF1 and Erk dependent manner.[5]

Numerous studies of murine and human T cells indicate that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production.[28] Reports have shown that 4-1BB agonist mAbs increase costimulatory molecule expression, and markedly enhance cytolytic T lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings and both monotherapy and combination therapy tumor models and have established durable anti-tumor protective T cell memory responses.[29] 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models.[30] This dual activity of 4-1BB offers the potential to provide anti-tumor activity while dampening autoimmune side effects that can be associated with immunotherapy approaches that break immune tolerance.

1.2.2.1. Utomilumab Clinical Efficacy

As of the data cut-off date of 06 June 2016, the safety and efficacy of utomilumab are being evaluated in 3 ongoing studies either as a single agent (B1641001 Portion A) or in combination with other anti-cancer treatments (B1641001 Portion B, B1641003, and B1641004).

For these ongoing studies, the available data are preliminary in nature and are subject to change.

Study B1641001

For B1641001, safety and efficacy data were recorded for 86 patients in Portion A treated with utomilumab in dose levels between 0.006 and 10 mg/kg and 47 patients in Portion B treated with utomilumab in dose levels between 0.03 and 10 mg/kg in combination with rituximab at 375 mg/m^2.

As of the data cut-off date 06 June 2016, in Portion A, 1 confirmed complete response (CR) and 1 confirmed PR in Merkel cell carcinoma (MCC) were reported in patients who were treated at 0.24 mg/kg and 0.6 mg/kg respectively. In addition, 1 patient with anti-PD-1 refractory melanoma treated at 0.24 mg/kg had a PR that was not yet confirmed at the time of data cut-off date; however, this response was confirmed at a subsequent assessment. In addition, 1 patient with anti-PD-1 refractory melanoma treated at 0.24 mg/kg had a greater than 30% reduction in the diameters of multiple target tumors but was considered to have stable disease (irSD) per Immune-related Response Criteria Derived from RECIST version 1.1.

In Portion B, 8 patients with follicular lymphoma (7 patients were refractory to prior rituximab-containing regimen) achieved an objective response: 4 patients achieved a CR (2 treated at 1.2 mg/kg, 1 at 0.12 mg/kg, and 1 at 0.03 mg/kg) and 4 patients achieved a PR (2 treated at treated at 0.18 mg/kg, 1 treated at 1.2 mg/kg, and 1 treated at 5.0 mg/kg). One (1) patient with CD20 + Hodgkin's lymphoma treated at 1.2 mg/kg achieved a PR and 1 patient with Mantle Cell Lymphoma (MCL) treated at 2.4 mg/kg achieved a PR.

Study B1641003

For B1641003, safety and efficacy data were recorded for 23 patients treated with utomilumab in dose levels between 0.45 and 5.0 mg/kg in combination with 2 mg/kg of pembrolizumab.

Among the 23 patients treated, 6 had confirmed objective response providing an objective response rate (ORR) of 26.0%. Two (2) patients had a confirmed CR (1 patient with renal cell carcinoma (RCC) treated at 1.8 mg/kg and 1 patient with small cell lung cancer (SCLC) treated at 5.0 mg/kg). Four (4) patients achieved a PR: 1 patient with RCC and 1 patient with non-small cell lung cancer (NSCLC) treated at 0.45 mg/kg; 1 patient with anaplastic thyroid disease treated at 3.6 mg/kg, and 1 patient with Squamous Cell Carcinoma of the Head and Neck (SCCHN) treated at 5 mg/kg.

Study B1641004

For B1641004, safety and efficacy data were recorded for 11 patients treated with utomilumab in dose levels between 1.2 and 5 mg/kg, in combination with 1 mg/kg of mogamulizumab.

Efficacy assessments are ongoing for Study B1641004. Out of 11 patients evaluated during the utomilumabdose escalation phase of the study, no RECIST-defined responses were observed. Four (4) patients achieved a best overall response of SD of ≤4 months duration. Response was not determined in 2 patients (2.4 mg/kg) and 5 patients had a best overall response of progressive disease (PD).

1.2.2.2. Utomilumab Clinical Safety

Based on a data cut-off date of 06 June 2016 for B1641001, B1641003 and B1641004, utomilumab has been administered to 167 patients, and the amount of safety data collected are beginning to create a picture of the overall safety profile up to the 10 mg/kg in both single agent and in combination with rituximab, and 5.0 mg/kg in combination with pembrolizumab and mogamulizumab.

There were no specific AEs of note in patients treated up to 10 mg/kg utomilumab.

Study B1641001

The most frequently reported TEAEs in Portion A (≥10% of patients, all grades) regardless of causality were fatigue (24.4%), nausea (18.6%), decreased appetite (16.3%), vomiting (16.3%) abdominal pain (15.1%), diarrhea (11.6%), dizziness (11.6%), constipation (10.5%), and pyrexia (10.5%).

The most frequently observed treatment-related TEAE in Portion A (≥10% of patients; all grades) was fatigue (11.6%).

The most frequently reported TEAEs in Portion B (≥10% of patients; all grades) regardless of causality were fatigue (31.9%), infusion-related reaction (21.3%), upper respiratory tract infection (14.9%), diarrhoea (12.8%), pyrexia (12.8%), chills (10.6%), cough (10.6%), and headache (10.6%).

The most commonly reported treatment-related TEAEs in Portion B (≥10% of patients; all grades) that were considered treatment-related were fatigue (23.4%) and infusion-related reaction (21.3%).

One event each of enterocolitis, alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) increased, decreased appetite and pneumonitis were reported as treatment-related in 3 patients. After the data cut-off date, the causality of the ALT and AST elevations were re-assessed by the Investigator as not related to utomilumab. One (1) SAE of infusion-related reaction was considered related to rituximab but not to utomilumab, per Investigator assessment.

There were no DLTs reported in either Portion A or Portion B and no deaths were attributed to study treatment.

In summary, the observed safety profile, based on a data cut-off date of 06 June 2016 for B1641001, support the use of utomilumab both as a single agent and in combination with rituximab.

Study B1641003

The most frequently reported TEAEs (≥10% of patients; all grades) regardless of causality, were fatigue (43.5%), cough (34.8%), decreased appetite (30.4%), nausea (30.4%), constipation, pruritus, rash maculo-papular (26.1% each), pyrexia and vomiting (21.7% each), anaemia, dyspepsia, rash, and upper respiratory tract infection (17.4%, each), arthralgia, asthenia, back pain, dry mouth, dry skin, dyspnoea, fall, haemoptysis, hypokalaemia, hyponatraemia, muscle spasms, oedema peripheral, pleural effusion, pneumonia, sinusitis, and stomatitis (13.0% each).

The most frequently observed treatment-related TEAEs (≥10% of patients; all grades) were fatigue (34.8%), rash maculo-papular (26.1%), pruritus (21.7%), pyrexia (17.4%), nausea, decreased appetite, dry skin, and dry mouth (13.0% each).

No SAEs were considered related to utomilumab per Investigator assessment.

There were no DLTs reported and no deaths were attributed to study treatment.

In summary, the observed safety profile, based on a data cut-off date of 06 June 2016 for B1641003, supports utomilumab use in combination with pembrolizumab.

Study B1641004

The most frequently observed TEAEs (≥10% of patients; all grades) regardless of causality, were rash (36.4%), abnormal dreams, constipation, fatigue and nausea (27.3% each),

decreased appetite, diarrhoea, dyspnoea, infusion related reaction, pruritus, and rhinorrhoea (18.2% each).

The most frequently observed treatment-related TEAEs (≥10% of patients; all grades) were abnormal dreams, nausea, rash, (27.3% each), decreased appetite, diarrhoea, fatigue, infusion-related reaction and pruritus (18.2% each).

No SAEs were considered related to utomilumab per Investigator assessment.

There were no DLTs reported and no deaths were attributed to study treatment.

In summary, the observed safety profile, based on a data cut-off date of 06 June 2016 for B1641004, supports utomilumab in combination with mogamulizumab.

Please refer to the Investigator's Brochure for utomilumab, Section 6.2.1 for the analysis of common adverse events for patients treated with utomilumab.[6]

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1.2.2.4. Utomilumab Immunogenicity

Study B1641001

In Portion A (monotherapy), 9 out of 61 (14.8%) patients exhibited positive ADA prior to treatment with utomilumab. Thirty-five out of 61 patients (57.4%) were positive for ADA for at least one time point regardless of baseline ADA status. Among 35 ADA-positive patients, 7 (20%) exhibited positive neutralizing antibody (NAb) against utomilumab.

In Portion B, 2 out of 41 (4.9%) patients exhibited positive ADA against utomilumab prior to treatment with utomilumab plus rituximab. Three out of 41 patients (7.3%) were positive for

ADA for at least 1 time point regardless of baseline ADA status when administered in combination with rituximab. Among 3 ADA-positive patients, 1 (33.3%) exhibited positive NAb against utomilumab. The impact of ADA on PK of utomilumab was characterized. ADA negative patients were defined as those with negative antibody status for all samples collected during the study including baseline (pre-treatment). ADA positive patients were defined as those with at least 1 positive ADA sample anytime during the study including baseline (pre-treatment). Utomilumab clearance (CL) was similar in ADA negative and ADA positive patients suggesting that ADA status had minimal impact on the PK of utomilumab.

Study B1641003

Two out of 23 (8.7%) patients exhibited positive ADA against utomilumab prior to treatment with utomilumab plus MK-3457. Seventeen out of 23 patients (73.9%) were positive for ADA for at least 1 time point regardless of baseline ADA status when administered in combination with MK-3457. Among 14 ADA-positive patients who were tested for NAb analysis, 5 (35.7%) patients exhibited positive NAb against utomilumab.

Study B1641004

Among 10 patients tested for ADA analysis, none of them exhibited positive ADA against utomilumab prior to treatment with utomilumab plus mogamulizumab. Five out of 10 patients (50%) were positive for ADA against utomilumab for at least 1 time point when administered in combination with mogamulizumab.

Additional pre-clinical and clinical information for utomilumab, including PK data in patients, may be found in the SRSD, which for this study is the utomilumab IB.[6]

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1.2.4. Clinical Combination of PF 04518600 and Utomilumab

As of the data cut-off date of 24 May 2017, 42 patients (23 male and 19 female, mean ages of 58.6 years) were treated with PF-04518600 across 5 dose levels of PF-04518600 (0.1, 0.3, 1 or 3 mg/kg) in combination with 20 or 100 mg of utomilumab in Part B of B0601002.

The most frequent all-causality TEAEs that occurred in ≥10% of patients include: decreased appetite (23.8%), nausea (21.4%), fatigue (19.0%), anemia (16.7%), pyrexia (16.7%), abdominal pain (14.3%), constipation (14.3%), diarrhea (14.3%), and pain (11.9%).

A total of 15 (32.1%) patients out of 42 experienced treatment-related TEAEs. The most frequent treatment-related TEAE experienced in ≥5% of patients include fatigue (9.5%) and nausea (7.1%). All treatment-related events reported were Grade 1 or 2, with the exception of a Grade 3 amylase and a Grade 4 lipase elevation in a single subject receiving 0.3 mg/kg PF-04518600 and 100 mg utomilumab. No DLTs have been reported.

The only treatment-related SAE, which occurred on 19 June 2017, was a Grade 3 infusion reaction in a 67 year old patient with bladder cancer who was receiving 1 mg/kg PF-04518600 and 100 mg utomilumab.

Preliminary efficacy data as of 24 May 2017, indicated that there were 2 ongoing partial responses (PR) in the 10 melanoma patients enrolled: 1 confirmed in a cutaneous melanoma patient at 0.3 mg/kg PF-04518600 and 20 mg utomilumab and 1 unconfirmed in an ocular melanoma patient at 0.3 mg/kg PF-04518600 and 100 mg utomilumab. Both patients are still ongoing in the study. The cutaneous melanoma patient had received prior pembrolizumab plus ipilimumab and had a partial response (PR), then progressed on pembrolizumab maintenance. The ocular melanoma patient had progressed after prior radiotherapy.

As B0601002 is an ongoing study, the available data are preliminary in nature and are subject to further review and quality control and may therefore change.

1.2.5. Tumor Type Rationale

Anti-tumor immune response is the ability for a tumor to elicit an adaptive immune response and prevent tumor growth. It has long been understood that immunodepressed patients have a higher incidence of cancer,[34] and immunodeficient murine models have increased levels of tumor growth.[35] Central to the adaptive defense against tumor cells are the tumor infiltrating lymphocytes (TILs) that include CD8+ effector T cells, and CD4+ T helper (Th) cells. For a number of tumor types, including melanoma, head and neck cancers, hepatocellular carcinoma (HCC), bladder urothelial cell carcinoma and colorectal cancer, a favorable prognosis has been associated with a high number of TILs.[22,36-39] High numbers of OX40 positive infiltrating T cells have been found within tumor biopsies, and lymph nodes of primary melanoma, breast, colon and head and neck cancer patients.[11-14] Thus, for these tumor types, the abundance of activated TILs has been suggested to be a surrogate marker for anti-tumor immune response.[40] Indeed, it has been postulated that the host response to immunotherapeutics may be dependent on the anti-tumor immune response for a given tumor.[40] Nonetheless, a combination of immunotherapeutics may elicit a robust immune response even in a poorly immunogenic tumor type.[41] In the study by Chen et at (2015),[41] a combination of anti-4-1BB/anti-PD-1 demonstrated that it was possible to elicit an effective antitumor response in a poorly immunogenic mouse model. Furthermore, Lee et al[31] demonstrated that a combination of OX40 and 4-1BB agonists induced tumor growth inhibition in an immunologically resistant fibrosarcoma model.

This clinical protocol will be the first to study PF-04518600 as monotherapy, and in combination with utomilumab in patients with advanced or metastatic select tumor types who are unresponsive to existing therapies, or for whom no standard treatment is available.

1.2.5.1. Melanoma

Melanoma is considered to be one of the most immunogenic tumor types due to its ability to undergo spontaneous regression. Worldwide, an estimated 232,000 new cases are diagnosed each year.[42] It is a highly aggressive tumor; 5 year survival rate for patient with regional metastasis is expected to be 63%, whilst survival for a patient with distant metastasis is expected be 16%.[43] Recent Food and Drug Administration (FDA) approval of immune checkpoint inhibitors ipilimumab (a fully human IgG1 anti- cytotoxic T-lymphocyte antigen 4 [CTLA-4] antibody), nivolumab and pembrolizumab (both humanized IgG4 an anti-PD-1 antibodies) provide compelling evidence that melanoma is amenable to immunotherapeutic approaches. In clinical Phase 3 studies, metastatic melanoma patients treated with ipilimumab demonstrated median overall survival of 10.1 months, compared to 6.4 months among patients receiving glycoprotein 100 (gp100) peptide vaccine alone.[44] Notably, durable tumor control was observed, with overall survival (OS) noted for 18% of patients at 5 years and 17% at 7 years, with no deaths reported after 7 year.[45] Historically, 3% Stage IV M1c, 6% Stage IV M1b and 16% of Stage IV M1a patients are expected to survive 10 years.[46] For pembrolizumab, clinical studies showed tumor shrinkage in 24% of treated advance melanoma patients that lasts from 1.4 to 8.5 months, overall median progression-free survival of longer than 7 months and an overall response rate of 26%.[47] Responses were durable.[48] With a median follow-up of 11 months, though the median duration of response had not been reached for all advance melanoma patients, the fast majority (88%) of responders were still on treatment at time of database lock.[47] In patients refractory to ipilimumab treated with pembrolizumab, objective response rate (ORR) by RECIST was 28%, and again durable response was observed.[48] Combining checkpoint inhibitors nivolumab and ipilimumab in previously untreated melanoma yields a greater response rate of 57.6% versus nivolumab alone (43.7%) or ipilimumab alone (19%). However, greater frequency of Grade 3 or 4 treatment-related adverse events are seen in patients treated with nivolumab and ipilimumab (55.0%) vs nivolumab (16.3%) or ipilimumab (27.3%).[95] In 2015 the FDA approved two BRAF and MEK inhibitor combinations to treat patients with unresectable or metastatic BRAF-mutated melanoma: cobimetinib with vemurafenib and dabrafenib with trametinib. The Phase 3 Cobimetinib combined with vemurafenib in advanced $BRAF^{V600}$-mutant melanoma (coBRIM) study showed that vemurafenib with cobimetinib improved OS at 9 months of 81% vs 73% for vemurafenib with placebo, PFS 11.3 vs 6.0 months, ORR of 68% vs 45%.[123] The Phase 3 COMBI-d study showed that dabrafenib with trametinib improved overall survival with a median survival of 25.1 months vs 18.7 months for dabrafenib alone, PFS 11.0 vs 8.8 months, ORR of 69% vs 53%.[124]

The most common melanoma subtype is cutaneous, which arises from melanocytes located in the basal layer of the epidermis, and was the subtype of melanoma primarily evaluated in the clinical trials described above.[107] Ocular melanoma located anywhere in the uveal tract is the most common primary intraocular malignancy in adults, representing ~85% of cases.[108] The remaining ocular melanomas arise from the conjunctiva (~5%) or other sites

(~10%).[108] The molecular profile of ocular melanoma is different from those of cutaneous or mucosal melanomas and is composed of a number of chromosomal abnormalities and somatic gene alterations. As a result of these differences, no effective adjuvant systemic therapy has been demonstrated to reduce the risk of metastasis of ocular melanoma, as recently reviewed by Triozzi and Singh.[109] And for those patients with ocular melanoma who do develop metastatic disease, there is no proven standard of care. Dacarbazine, a chemotherapeutic option for treatment of cutaneous melanoma, has been used for ocular melanoma; however, activity has been limited.[110,111,112] Other chemotherapeutic regimens including temozolomide, cisplatin, treosulfan, fotemustine and various combinations have been investigated in ocular melanoma with disappointing results to date.[113,114,115] Immune checkpoint inhibitors evaluated in several small prospective and/or retrospective studies have rarely demonstrated responses and no overall survival benefit.[125] Ipilimumab has shown response rates of ~5%–10% in metastatic ocular melanoma, but evidence of a median overall survival (OS) of 6.0–9.7 months in these trials suggests that responses could be delayed and durable in only a minority of patients.[116,117,118,119] Additionally, ipilimumab demonstrated very limited clinical activity in treatment-naïve or pre-treated patients with metastatic ocular melanoma in the Phase II German Dermatologic Cooperative Oncology Group (DeCOG) trial; median progression-free survival (PFS) was 2.8 months and median OS was 6.8 months.[120] Initial assessment of pembrolizumab in seven patients with metastatic ocular melanoma who had progressed on ipilimumab reported a median PFS of ~3 months.[121]

1.2.5.2. Head and Neck Squamous Cell Carcinoma (HNSCC)

Approximately 650,000 new cases of head and neck cancers are diagnosed globally each year, and head and neck squamous cell carcinoma (HNSCC) is the most common form.[42,49,50] HNSCC is an aggressive tumor type with a 10.1 month overall survival rate for patients with recurrent and/or metastatic disease.[51] HNSCC is considered to be an immunosuppressive tumor,[52] circulating and tumor-infiltrating T cells of HNSCC patients have signaling defects,[53] and immune effector cell anergy is well described. This, together with TILs' ability to act against HNSCC tumor antigens, makes HNSCC a good candidate for immunotherapy. Cetuximab, an anti-EGFR (epidermal growth factor receptor) antibody targets, EGFR, which is expressed on >90% of all HNSCC tumors. In Phase 3 studies, recurrent and metastatic HNSCC treated with cetuximab plus chemotherapy increased overall survival from 7.4 months to 10.1 months, when compared with HNSCC patients treated with chemotherapy alone.[51] 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 ORR of 16% and CR rate of 5%.[97] The FDA approved nivolumab for HNSCC that has progressed during chemotherapy with a platinum-based drug or that has recurred or metastasized after platinum-based chemotherapy in 2016. Nivolumab improved overall survival with a median survival of 7.5 months vs 5.1 months for standard therapy, ORR of 13.3% vs 5.8%, PFS was approximately the same 2.0 vs 2.3 months.[131]

1.2.5.3. Hepatocellular Carcinoma (HCC)

An estimated 782,000 cases of HCC are diagnosed worldwide each year; it is the third leading cause of tumor deaths, with an expected 5-year survival rate of 5-6%.[42,54] Sorafenib, a multikinase inhibitor, was the first approved systemic therapy for unresectable HCC with

overall survival of 10.7 vs 7.9 months, PFS 5.5 vs 2.8 months, ORR of 2% vs 1%, disease control rate of 43% vs 32% compared to placebo.[96] Recently, regorafenib, another multikinase inhibitor, was approved for HCC patients who have progressed during sorafenib treatment. Regorafenib improved overall survival with a median survival of 10.6 months vs 7.8 months for placebo, PFS 3.1 vs 1.5 months, ORR of 11% vs 4%, disease control rate of 49% vs 23%.[105] Additionally, a Phase II study evaluating lenvatinib, a multi-tyrosine kinase receptor inhibitor, for HCC treatment showed promising outcomes, with median survival of 18.7 months, TTP of 7.4 months, an ORR of 37%, and a disease control rate of 78%.[106] There is evidence to suggest that HCC is amenable to immunotherapy. Firstly, HCC tumor recurrence has been linked to immunosuppression. Secondly, HCC patients treated with autologous lymphocytes activated in vitro with recombinant interleukin-2 and antibody to CD3 had significantly improved recurrence-free survival and disease-specific survival. Thirdly, CD4+ regulatory T cells and immunosuppressive T regulatory cells (Tregs) that may suppress T cell responses have been identified in tumors of HCC patients, and it has been demonstrated that engagement of another T cell co-stimulatory receptor GITR can reverse the suppressive effect of Tregs.[55,56] It should however be noted that the liver has a unique intrinsic tolerogenic and intra-hepatic immunosuppressive environment, with mechanisms that preferentially inactivate T cells, as well as mechanisms that increase T cell tolerance, and apoptosis.[57] As such, for the limited number of immunotherapeutic trials completed to date involving therapeutic vaccination and cell therapy strategies, only modest results have been observed.[54] There are data that suggest that immune checkpoint inhibition with anti-PD1 may have anti-tumor efficacy in HCC. In the Checkmate 040 Phase 1/2 study, patients with advanced or metastatic HCC were treated with nivolumab. Objective responses occurred in 16% and CR in 1% of 214 patients, and responses were seen regardless of PD-L1 status, prior sorafenib treatment, or hepatitis C virus (HCV) or hepatitis B virus (HBV) infection.[98]

1.2.5.4. Renal Cell Carcinoma (RCC)

Renal cell carcinoma (RCC) accounts for >90% of all kidney cancers, and approximately 338,000 cases are diagnosed worldwide each year.[42,58] In the US, for the last 30 years, the incidence of RCC has been raising by approximately 3% each year.[59] Clear cell RCC is the most common form of renal adenocarcinomas, representing 70% of all RCC, and the expected 5-year survival rate for these patients are 55%.[60,61] There is nonetheless other compelling evidence for an immunotherapeutic approach for this disease.[64] Increased expression of immune checkpoint PD-1 receptor and PDL-1 ligand have been identified on TILs and tumor cells from RCC patients, and this correlated with patient survival.[64] Lastly, results of a Phase 3 trial of nivolumab versus (vs) everolimus in metastatic RCC patients who failed prior (anti-VEGF [Vascular endothelial growth factor]) treatment found improved ORR of 21.5 vs 5%, and median overall survival of 25.0 vs 19.6 months.[104]

1.2.5.5. Bladder Cancer

For bladder cancer, tumor infiltration of CD3+ and CD8+ T cells has been associated with better overall survival.[22,65] Bladder 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.[22,65] Worldwide, it is estimated that 386,000 new cases of bladder cancer will occur each year, with approximately 105,000 deaths.[42] Approximately

75% of cases of bladder cancer are non- muscle invasive bladder cancer (NMIBC). While treatment with BCG has been shown to reduce the risk of tumor recurrence,[67] approximately 40% of patient with NMIBC will fail BCG therapy.[68] Atezolizumab, an anti-PD-L1 antibody, has received accelerated approval from the FDA for locally advanced and metastatic urothelial carcinoma that has progressed following treatment with platinum-based chemotherapy following a single-arm multicenter trial with 310 patients that demonstrated an ORR of 14.8% in all patients (5.5% CR, 9.4% PR) and ORR of 26% (12% CR, 14% PR) in patients with PD-L1 expression in ≥5% of immune cells.[99,100]

1.2.5.6. Cervical Cancer

According to published data by the International Association of Research in Cancer (IARC), 528,000 new cases of cervical cancer are diagnosed worldwide each year.[42] It is understood that cervical cancer is caused by high risk human papilloma virus (HPV). There are two main types of cervical cancer. The first one, which accounts for about 90% of diagnosed cervical cancers, is squamous cell carcinoma that covers the cervix.[126] The second type of cervical cancer, located in the gland cells of the endocervix, is called cervical adenocarcinoma. There has been an increase in the incidence of cerival adenocarcinoma in many countries, mainly in women under the age of 40.[127,128,129,130] Whilst vaccination against the HPV oncogenes E6 and E7 have been effective for premalignant lesions, there were no clinical effects on advance or recurrent tumor.[71] Spontaneous regression of premalignant lesions has been associated with circulating HPV specific CD4+ and CD8+ T cells, and a higher ratio of effector T cells to Tregs.[71] The ratio between CD8 T cells and Foxp3+ regulatory CD4 T cells (Tregs), and the number of tumor infiltrating M1 macrophages are also independent prognostic factors.

Currently, there are a number of immunotherapeutics in development for cervical cancer. They include T cell adoptive therapy,[72] and therapies that target immune checkpoints.[73,74] In a Phase 1 study of HPV infused TILs, out of 9 metastatic cervical cancer patients CR with long term durability (22 to 15 months) was observed in 2 patients, and PR was observed in 1 patient.[72] In a Phase 1/2 study of ipililumab in recurrent or metastatic cervical cancer patients, preliminary results revealed 3 PR (1 PR and 2 unconfirmed PR) and 8 SD in 34 patients.[73] In a Phase 1b study KEYNOTE-028 pembrolizumab had a 17% ORR in 24 patients with PD-L1 positive advanced cervical cancer.[74]

1.2.5.7. Gastric Adenocarcinoma

Gastric cancer is the 5th most common cancer in the world, with 952,000 new cases reported in 2012.[42] Approximately 50% these cases were reported in Eastern Asia. It is also the third leading cause of cancer deaths, with 723,000 deaths recorded in 2012. Except in countries like Japan and Korea, gastric cancer often presents with advanced disease upon diagnosis. The principle treatment method is still surgical resection; whilst 20-30% patients will have resectable disease, those with lymph node metastasis will be deemed inoperable. Even for those patients treatable with surgical resection, the recurrence rate remains high and the five-year survival rate is 29%.[43]

It is understood that gastric cancer is a histologically diverse disease, and the majority is associated with infectious agents such as helicobacter pylori and Epstein–Barr virus (EBV). Recently, the Cancer Genome Atlas (TCGA) Research Network analyzed the molecular characteristics of gastric adenocarcinoma (TCGA 2014) and identified 4 distinct subtypes: tumors positive for EBV, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability. Each distinct subtype may therefore require a different therapeutic option.

Immunotherapy may offer an alternative treatment strategy for gastric cancer patients. Gastric cancer patients with increased numbers of CD3, CD8, and CD45RO positive TILs have improved survival rates compared to patients with lower numbers of TILs.[75]

A limited number of immunotherapy approaches are currently being evaluated in gastric cancer. Checkpoint inhibitors, including CTLA-4, PD-L1 and PD-1 are currently being evaluated. In the Phase 2 study with Tremelimumab (CTLA-1 mAb), a 5% response rate was observed in 18 gastric cancer patients.[84] In the KEYNOTE-012 study, a multicenter open-label Phase 1b trial pembrolizumab for positive recurrent or metastatic adenocarcinoma of the stomach of gastro-esophageal junction, 36 patients evaluable for response 8 (22%) had overall response (all PR).[101]

1.2.5.8. Non-Small Cell Lung Cancer (NSCLC)

Lung cancer remains to be the most common cancer worldwide, with 1.8 million cases reported in 2012.[42] In the US, non-small cell lung cancer (NSCLC) accounts for over 85% of these cases, and with a 17.1% 5-year survival rate.[84] NSCLCs represent a heterogeneous set of diseases with diverse pathological, genetic and cellular features, with three NSCLC histological sub-types: adenocarcinoma (~50% of cases), squamous cell carcinoma (~40% of cases), and large cell carcinoma.[132,133] There are differences in mutation burden between smokers and non-smokers: 1) smokers have significantly higher mutation frequencies; 2) point mutations in smokers are predominantly C:G->A:T, but non-smokers are predominantly C:G->T:A; and 3) the distinctive sets of mutations identified in non-smokers are EGFR mutations and ROS proto-oncogene 1 (ROS1) and anaplastic lymphoma kinase (ALK) fusions, while smokers have Kirsten rat sarcoma proto-oncogene (KRAS), tumor protein p53 gene (TP53), BRAF, Janus kinase 2 (JAK2), Janus kinase 3 (JAK3), and mismatch repair gene mutations.[133] For NSCLC with specific genetic alterations, including epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) translocations (2-8%), molecular targeted therapies with erlotinib and crizotinib, have improved median overall survival (OS).[84] However, the majority of NSCLC patients do not harbor these genetic mutations, since only 15-18% of NSCLC has EGFR genetic alterations and 2-8% have ALK translocations.

In October 2015, nivolumab and pembrolizumab (PD-1 mAbs) were approved for the treatment of metastatic NSCLC. In the pivotal studies for nivolumab,[84] overall survival of 12.2 months was observed for nivolumab treated patients, whilst overall survival for docetaxel treated patients was 9.4 months. Furthermore, PR/CR was observed in 19% of nivolumab treated patients. In the 495 patient study for pembrolizumab, an overall response rate of approximately 20% was observed for previously treated and treatment-naive advanced or metastatic NSCLC patients.[84] Patients with high PD-L1-expressing NSCLC had an even

more impressive overall response rate of 45.2%. Median overall survival for all patients treated with pembrolizumab was 12.0 months. An open-label Phase 3 study randomizing 305 patients with previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells to pembrolizumab versus investigator's choice platinum-based chemotherapy demonstrated superior PFS (10.3 vs 6 months, hazard ratio 0.5), response rate (44.8 vs 27.8%), duration of response (1.9+ to 14.5+ vs 6.3 months), and overall survival at 6 months (80.2% vs 72.4%, HR for death = 0.6) for pembrolizumab.[102] In 2016, another checkpoint inhibitor targeting program death-ligand 1 (PD-L1), atezolizumab was approved for the same indication.[134] Moreover, pembrolizumab also received approval in 2016 for first-line NSCLC treatment in patients with high PD-L1 expressing tumors (≥50% of tumor cells).[135,136] More recently, in May 2017, FDA approved pembrolizumab as First-Line Combination Therapy with Pemetrexed and Carboplatin, irrespective of PD-L1 Expression.[137] Other inhibitors of PD-1/PD-L1 pathway, such as avelumab (Avelumab in Non-Small Cell Lung Cancer/JAVELIN LUNG 200; ClinicalTrials.gov, National Clinical Trial (NCT)02395172) and durvalumab (ClinicalTrials.gov, NCT02087423), are also being assessed in phase 3 trials.[138,139,140]

CTLA-4 inhibitors are being evaluated too. Ipilimumab appeared to show improved efficacy for squamous histology but not for non-squamous histology.[141] A phase III trial (ClinicalTrials.gov, NCT01285609) is currently ongoing to compare the standard carboplatin and paclitaxel chemotherapy with concomitant administration of ipilimumab specifically in patients with squamous NSCLC. Ipilimumab is also being studied empirically in combination with targeted inhibitors (erlotinib or crizotinib) for EGFR and ALK translocation-positive NSCLC (ClinicalTrials.gov, NCT01998126), and PD-1 antibody. Tremelimumab did not demonstrate strong efficacy as single agent.[142] The combination of durvalumab and tremelimumab is tested as well in third-line (A Global Study to Assess the Effects of MEDI4736, Given as Monotherapy or in Combination With Tremelimumab Determined by PD-L1 Expression Versus Standard of Care in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer (ARCTIC) ClinicalTrials.gov, NCT02352948) and in first-line (Phase III Open Label First Line Therapy Study of MEDI 4736 (Durvalumab) With or Without Tremelimumab Versus SOC in NSCLC (MYSTIC) ClinicalTrials.gov, NCT02453282) and Study of 1st Line Therapy Study of Durvalumab With Tremelimumab Versus Standard of Care in NSCLC (NEPTUNE) (ClinicalTrials.gov, NCT02542293).

1.2.5.9. Selection of Tumor Types for Combination Studies Using The Cancer Genome Atlas (TCGA)

RNA-seq data generated by the cancer genome atlas (TCGA) research network (http://cancergenome.nih.gov/) across multiple tumor types was used as a guide for the selection of tumor types for Part B PF-04518600/utomilumab combination phase. Given that the RNA-seq data is generated from bulk tumor, spearman correlations of mRNA expression of target of interest (4-1BB or OX40) to mRNA expression of markers of specific immune cell subsets was completed. This correlation was used as a guide for the determination of OX40 or 4-1BB expression levels within different immune cells. For 4-1BB, since an anti-4-1BB agonist is expected to stimulate cytotoxic T-cells (see Section 1.2.2 4-1BB [CD137]), correlation of 4-1BB expression to expression of granzyme A and

perforin 1 (enzymes indicative of a cytotoxic [CYT] signature)[75] was completed. For OX40, since anti-OX40 agonist is expected to stimulate CD4 cells, correlation of OX40 expression to CD4 expression was completed.

Based on the results from this analysis, the combination of PF-04518600 and utomilumab will be conducted in patients with locally advanced or metastatic HNSCC, melanoma, urothelial bladder carcinoma, NSCLC, gastric cancer or squamous cell carcinoma of the uterine cervix that is either resistant to standard therapy or for which no standard therapy is available.

1.2.5.10. Summary of Benefit Risk Assessment

Overall, the nonclinical package and the preliminary clinical experience with PF-04518600 support the safety and design of Protocol B0601002 for both single agent treatment and in combination with utomilumab.

1.3. Starting Dose Rationale

1.3.1. Monotherapy Starting Dose Rationale

The objective for this first-in-patient (FIP) study is to assess safety, tolerability, pharmacokinetics, and pharmacodynamics (immune-modulatory or IM effects) of PF-04518600 in patients with advanced or metastatic HCC, melanoma, clear cell RCC or HNSCC.

The selected starting dose for PF-04518600, 0.01 mg/kg, represents approximately 60% of a theoretical receptor occupancy calculated by the Duff equation.[84]

The starting dose and subsequent PF-04518600 doses of 0.01, 0.1, 0.3, 1.5, and 3 mg/kg were proposed based on:

1. Published clinical trial results of a similar agonist monoclonal antibody (9B12) against OX40, the same target as PF-04518600, which was studied in patients with advanced cancer at 3 dose levels, 0.1, 0.4, and 2 mg/kg.[12,19]
2. Differences between PF-04518600 and 9B12 in terms of co-stimulatory potency on T cell proliferation.
3. Expected differences in PK properties.
4. Preclinical toxicology data on PF-04518600.

The proposed doses have been studied in an ascending order, please refer to Section 3.1.5 Criteria for Dose Escalation). As MTD was not reached up to 3 mg/kg, and there was evidence for a pharmacodynamic response at 3 mg/kg, a 10 mg/kg additional cohort has been added (see Section 3.1.1 Part A1 Monotherapy).

1.3.2. Combination Starting Dose Rationale

1.3.2.1. PF-04518600

The initial proposed PF-04518600 dose is 0.1 mg/kg based on safety information obtained in Part A monotherapy. Subsequently, the doses to be evaluated for combination are 0.3, 1.0, and 3 mg/kg. If preliminary data suggest that 10 mg/kg may be effective and safe, an additional 10 mg/kg dose may be studied in combination as well. Except at 10 mg/kg, a given dose of PF-04518600 will not be tested in combination with utomilumab until at least an one-half-log higher dose of PF-04518600 monotherapy has been deemed to be safe and well tolerated. Please refer to Section 3.1.5.2 (Criteria for Dose Escalation Part B Combination Therapy) for dose combination level information.

1.3.2.2. Utomilumab

The proposed starting dose of utomilumab to be tested in Part B combination therapy is 20 mg. The starting dose takes into account potential safety findings for OX40 monotherapy study (Part A) but also the possible overlap in safety profiles between utomilumab and PF-04518600. Subsequently the other dose to be evaluated for combination is 100 mg.

In the ongoing First-In-Human Phase 1 Study B1641001, utomilumab as single agent has been well tolerated up to the dose of 10 mg/kg (the highest planned dose level). To date, no DLTs have been observed in Study B1641001, either for utomilumab as a monotherapy or utomilumab in combination with rituximab. The safety profile of utomilumab either as single agent or in combination with rituximab was manageable without occurrence of treatment related life threatening (>Grade 4) adverse events (AEs).

Activities of utomilumab were observed at doses as low as 0.24 mg/kg (approximately 20 mg) in MCC as a single agent. It is not clear if higher doses might be active as limited number of MCC patients (5 of 15 patients) were treated at higher doses. Responses were also observed with the combination of utomilumab and rituximab in R-refractory Non-Hodgkin's Lymphoma (NHL) as low as 0.03 mg/kg with highest active dose of 2.4 mg/kg. These data suggest that the active dose range of utomilumab is quite broad, spanning an approximate 100-fold dose range. Flat utomilumab doses of 20 (approximately 0.2 mg/kg), 100 (approximately 1.2 mg/kg), and 500 mg (approximately 6 mg/kg) are being tested in Study B9991004.

1.4. Rationale for Flat Dosing in Part A2 and Part B2

Based on the population PK/PD analysis using preliminary data from Part A1 (monotherapy dose escalation) of this study, the predicted median and 5^{th} and 95^{th} percentiles of PF-04518600 exposure parameters, particularly the trough concentrations of PF-04518600, over the weight range of the patient population are expected to be comparable between body-weight based and flat dosing. Therefore, PF-04518600 will be given as a flat dose in the dose expansion cohorts (Part A2 and Part B2) to simplify the dosage preparation procedure.

1.5. Rationale for Pre-Treatment and On-Treatment Biopsies

PF-04518600 as a monotherapy and in combination with utomilumab is hypothesized to elicit its anti-tumor clinical activity by activating and enhancing anti-tumor T cell response. The effect on TILs in the tumor microenvironment will provide important data to estimate the optimal biological dose (OBD) of the PF-04518600 (see Section 3.4 Optimal Biological Dose). It has been shown that OX40 has negligible expression on resting T cells in peripheral blood, but is much higher in TILs and in tumor draining lymph nodes in patients with melanoma and head and neck cancer.[11] Similarly, 4-1BB is expressed on activated immune cells including activated CD8 cells, activated NK and natural killer T (NKT) cells; regulatory T cells; dendritic cells (DC) including follicular DC; stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils and activated B cells.[5] This difference in receptor expression suggests potential differences between pharmacodynamic (immune modulatory) effects of OX40 and 4-1BB agonist in tumor verses peripheral blood. All patients will be required to provide an archival biopsy sample, which will be shipped to the central lab after Cycle 1 Day 1 (C1D1). Except for the first 2-4 patients in the each dose level in Parts A1 and B1, all other patients in this study will be required to provide tumor biopsy samples before, and on Cycle 4 Day 1 (C4D1) after PF-04518600 or PF-04518600/utomilumab combination treatment. Any CT or MRI scans for tumor assessments should be completed before tumor biopsy samples are collected. In Part A1, a second on treatment biopsy is mandatory on C7D1 for melanoma patients. This second on treatment biopsy is optional for all other patients in Parts A1. In Part A2 and B2, all patients will provide an archival biopsy sample. Additionally, there will be 2 to 3 mandatory biopsy collections: 1) fresh pre-treatment biopsy (ie, collected during screening), 2) on-treatment biopsy on Cycle 4 Day 1 (C4D1), 3) at time of initial response or initial progression (whichever occurs first), provided the biopsy is not within 4 weeks of the C4D1 biopsy. If a patient terminates study drug treatment before the scheduled on treatment biopsy at C4D1, the patient will be asked to provide a fresh biopsy at the termination visit. If tissue is collected from clinically indicated procedures at other time points, a portion may be submitted to the Sponsor. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted. Part B1 patients will not be required to provide a second on treatment biopsy.

The number, type and location of TILs can present large heterogeneity among different tumor types and among patients. Furthermore, it is hypothesized that pharmacodynamic effects may vary widely from patient to patient. Therefore, each dose level in Part A1 will be expanded to approximately 10 patients following safety and peripheral pharmacodynamic assessments in the first 2-4 patients. Patients who are part of the expansion of any dose level will undergo mandatory pre- and on-treatment biopsies. To better estimate the OBD, tumor pharmacodynamic data from all patients will be evaluated at the end of Part A1.

While the decision to dose escalate will depend on the adjudication of the safety data from the initial data set of 2 to 4 patients, safety information provided by additional patients within each cohort will be taken into account for RP2D determination.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the PF-04518600 and PF-utomilumab IBs.[6,20]

1.6. Biomarker Rationale

The aim of biomarker collections and analyses is to provide evidence of target engagement (TE), pharmacodynamic activity and immune-modulatory (IM) activity for PF-04518600 and utomilumab. This will provide data to guide dose selection, and allow characterization of the relationship between PF-04518600/utomilumab TE, pharmacodynamic activity and any observed anti-tumor effects. Furthermore, this may enable the identification of patients and/or tumor types most responsive to PF-04518600 alone or in combination with utomilumab.

TE by PF-04518600 will be assessed by using a flow cytometry assay to measure unbound (free) OX40 receptor expressed on peripheral blood T cells. The relationship between TE and the pharmacokinetics of PF-04518600 will provide guidance for dose selection for PF-04518600. The measurement of TE by utomilumab has been shown to be problematic due to receptor down-modulation upon antibody binding and the lack of an appropriate antibody (Ab) reagent; therefore only total 4-1BB receptor expression on peripheral blood T cells will be assessed as a measure of target load. Other pharmacodynamic measures will be used to inform utomilumab dose selection. The goal of this analysis will be to select doses that result in full TE and pharmacodynamic activity while exhibiting an acceptable safety profile, and potentially providing evidence of anti-tumor activity.

The pharmacodynamic effect of OX40 or OX40 plus 4-1BB agonism will be investigated in peripheral blood for all patients and in tumor tissues for patients enrolled into the expansion cohorts in Parts A1 and B1, and in expansion Phases A2 and B2. Potential effects of PF-04518600 or PF-04518600 plus utomilumab on relative proportions and phenotypes of T cells (including memory and regulatory subsets) and on T cell activation status will be assessed by flow cytometry. In the tumor tissue samples, the phenotype, quantity and tissue localization of TILs will be assessed by immunohistochemistry (IHC). These evaluations of peripheral blood and tumor infiltrating T cell subsets will be undertaken in an effort to identify components of cell-based immunity responsive to dosing with PF-04518600 or PF-04518600 plus utomilumab, and potentially serve as a guide for tumor or patient selection.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Objectives for Part A Monotherapy

2.1.1.1. Objectives for Part A1 Monotherapy Dose Escalation

Primary Objective:

- To assess safety, and tolerability at increasing dose levels of PF-04518600 in patients with selected advanced or metastatic solid tumors in order to establish the MTD.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in patients with selected advanced or metastatic solid tumors solid tumors.
- To characterize the single dose and multiple dose PK of PF-04518600 following IV administration.
- To evaluate the immunogenicity of PF-04518600 following IV administration.
- To characterize the degree of target engagement (TE) by PF-04518600 at multiple doses by measuring unbound (free) cell surface OX40 in peripheral blood.

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

2.1.1.2. Objectives for Part A2 Monotherapy Dose Expansion

Primary Objectives:

- To establish the RP2D of PF-04518600 in patients with selected advanced or metastatic HCC.
- To further characterize the safety and tolerability of PF-04518600 in patients with selected advanced or metastatic HCC.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in patients with selected advanced or metastatic HCC.
- To characterize the single dose and multiple dose PK of PF-04518600 following IV administration.
- To evaluate the immunogenicity of PF-04518600 following IV administration.

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2.1.2. Objectives for Part B Combination Therapy

2.1.2.1. Objectives for Part B1 Combination Therapy Dose Escalation

Primary Objective:

- To assess safety and tolerability at increasing dose levels of PF-04518600 in combination with utomilumab in patients with selected advanced or metastatic solid tumors and to estimate MTD of the combination.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in combination with utomilumab.
- To characterize single and multiple dose pharmacokinetics of PF-04518600 and utomilumab when given in combination.
- To evaluate immunogenicity of PF-04518600 and utomilumab when given in combination.

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2.1.2.2. Objectives for Part B2 Combination Therapy Dose Expansion

Primary Objective:

- To further assess safety and tolerability of PF-04518600 in combination with utomilumab in patients with melanoma or NSCLC in order to establish RP2D for the combination.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in combination with utomilumab.
- To characterize single and multiple dose pharmacokinetics of PF-04518600 and utomilumab when given in combination.
- To evaluate immunogenicity of PF-04518600 and utomilumab when given in combination.

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2.2. Endpoints

2.2.1. Endpoints for Part A Monotherapy

2.2.1.1. Endpoints for Part A1 Monotherapy Dose Escalation

Primary Endpoints:

- Dose limiting toxicities (DLTs) observed in each patient during the first 98 days in order to determine the MTD.
- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to study therapy PF-04518600.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 years.
- Pharmacokinetic parameters of PF-04518600:
  SDo - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit. MD (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, and R_{ac} ($AUC_{ss,\tau}/AUC_{sdo,\tau}$) as data permit.
- Incidence of ADA and NAb against PF-04518600.
- Levels of free OX40 receptor expressed on T cells in peripheral blood.

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- Levels of serum cytokines (including, but not limited to IFNγ, IL-2, IL-6, IL-10, and TNF-α), chemokines (including, but not limited to MIP-1 α, MIP-1β and MCP-1) and soluble OX40.

2.2.1.2. Endpoints for Part A2 Monotherapy Dose Expansion

Primary Endpoints:

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to study therapy PF-04518600.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 years.
- Pharmacokinetic parameters of PF-04518600:
  SDo - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit. MD (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, and R_{ac} ($AUC_{ss,\tau}/AUC_{sdo,\tau}$) as data permit.
- Incidence of ADA and NAb against PF-04518600.

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2.2.2. Endpoints for Part B Combination Therapy

2.2.2.1. Endpoints for Part B1 Combination Therapy Dose Escalation

Primary Endpoints:

- DLTs observed in each patient during the first 98 days in order to determine the MTD.
- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to PF-04518600/utomilumab combination.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 years.
- Pharmacokinetic parameters of PF-04518600 and utomilumab:
  SDo - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit. MD (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, and R_{ac} ($AUC_{ss,\tau}/AUC_{sdo,\tau}$) as data permit.
- Incidence of ADA against PF-04518600 and utomilumab.

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- [redacted]

2.2.2.2. Endpoints for Part B2 Combination Therapy Dose Expansion

Primary Endpoints:

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to PF-04518600/utomilumab combination.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 year.
- Pharmacokinetic parameters of PF-04518600 and utomilumab:
  SDo - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit. MD (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, and R_{ac} ($AUC_{ss,\tau}/AUC_{sdo,\tau}$) as data permit.
- Incidence of ADA against PF-04518600 and utomilumab.

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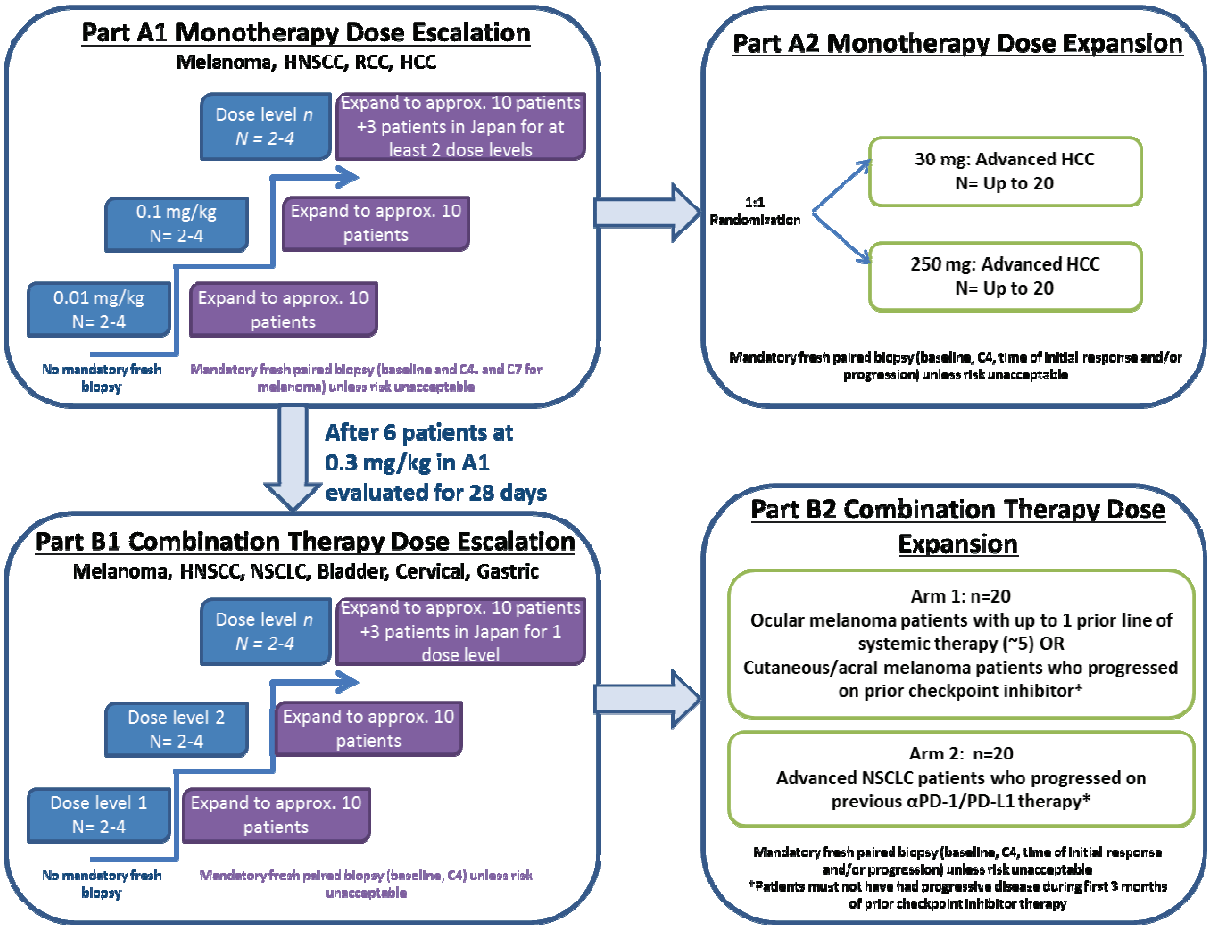
3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open label, multi-center, multiple dose, dose escalation, safety, pharmacokinetic, and pharmacodynamic study of PF-04518600 monotherapy (Part A) and PF-04518600 plus utomilumab combination therapy (Part B). Both Part A and Part B will be further divided into a dose escalation phase, and a dose expansion phase (see Figure 4).

Figure 4. Study Schematic



A maximum of approximately 210 patients are expected to be enrolled into the study. Patients will complete up to 4 weeks of screening. Patients in Parts A1 and B1 who are part of the expansion of any dose level and all patients in Parts A2 and B2 will undergo mandatory pre- and on-treatment biopsies. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted (see Section 1.4 Rationale for Pre Treatment and On Treatment Biopsies). Patients will receive doses of PF-04518600 intravenously (IV) over 60 minutes (-5 to +15 minutes) every 2 weeks. Patients in Part B will also receive doses of utomilumab intravenously (IV) over 60 minutes (-5 to +15 minutes) every 28 days. Following the initial dose, treatment with investigational product will continue until disease progression by irRECIST (see Section 0 Treatment after Initial Evidence of Radiological Disease Progression), patient refusal, unacceptable toxicity occurs, or the end of the study, whichever comes first. Patients will be allowed to stay on study, if the treating physician feels that it is in the patient's best interest, in the case of radiological progression and in the absence of clear clinical progression. A follow-up visit after approximately 4 weeks after the last dose for AE and SAE collection will be conducted. Assessment of late immune related responses will be evaluated up to 98 days after the first dose of Cycle 1. Because atypical tumor responses after growth of pre-existing lesions or appearance of new lesions have been observed with immune checkpoint inhibitors, study B0601002 will assess tumor response based on both response evaluation criteria in solid tumor (RECIST) and Immune-related Response Criteria Derived from RECIST v1.1 (irRECIST). Survival data will be collected (by phone, every 8 weeks, see Section 6.3 Follow-up Visit, Section 7.4 Tumor Response Assessments and Appendix 5).[85-87] The time on study can vary depending on the observed toxicity and potential benefit an individual patient derives. It is estimated that patients will remain on treatment for approximately 12-18 weeks, making total study duration approximately 20-26 weeks (exclusive of 2-year survival follow-up). Actual duration can be longer, if a patient derives benefit from study treatment. However, 2 years from the time of the first dose of investigational product of the last patient enrolled or last surviving patient (whichever is later) the study will be closed.

Patients having an unresolved adverse event that is possibly related to ADA formation will be asked to return for ADA and drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator, and sponsor concurs with that the investigator's assessment, up to 6 months from the end of treatment (EOT) or the day of early withdrawal.

3.1.1. Part A Monotherapy

3.1.1.1. Part A1 Dose Escalation

Part A1 will study doses of PF-04518600 in sequential dose levels (0.01, 0.1, 0.3, 1.5, 3 and 10 mg/kg) of adult patients with advanced or metastatic HCC, melanoma, clear cell RCC or HNSCC who are unresponsive to currently available therapies or for whom no standard therapy is available. Each dose level will include an initial cohort of 2-4 patients that may be expanded to approximately 10 patients based on peripheral pharmacodynamic data. Approximately 3 patients enrolled in Japan will be included for at least 2 dose levels for safety evaluation (see Section 3.1.1.3 Japan Only).

Approximately 58 patients will be enrolled into Part A1, which includes the 48 patients already enrolled in Cohorts 1-5 (see Section 1.2.1.3 for details), and ~10 patients enrolled into Cohort 7. The actual number of patients enrolled will therefore depend on the observed safety and tolerability profile of PF-04518600 monotherapy, the number of dose levels that will be explored or expanded to characterize the pharmacodynamic effects, the number of dose levels required to identify the MTD or OBD. All Japanese patients in Part A1 should be hospitalized until 2nd dosing.

A modified toxicity probability interval (mTPI) method, targeting a DLT rate of 25% and an acceptable DLT interval (20%-30%),[88] will be utilized.

When a dose level is deemed safe following a DLT observation period of 28 days or 2 cycles for the initial cohort of 2 to 4 patients, escalation will occur to the next dose level. The study may be stopped if the drug is deemed not tolerable at the lowest dose level. For safety reasons, a staggered start will be employed at all dose levels; 1 patient in each cohort of 2-4 patients will be dosed, and observed for 48 hours before subsequent patients can be dosed. If no safety concerns arise during this 48 hr period, a second patient will be enrolled into the same dose level. A staggered start will not be implemented for the expansion phase of a dose level; that is, the first patient within the expansion cohort will not need to be observed for 48 hours before additional patients are enrolled into the same dose level.

Peripheral pharmacodynamic assessments of any given dose may be completed after the dose is deemed safe, and escalation to the next dose level has already occurred. When peripheral monitoring indicates immune modulation in the first 2-4 patients, the dose level will be expanded to approximately 10 patients allowing better characterization of pharmacodynamic effects and reducing variability due to small sample size. If no peripheral pharmacodynamic effects are observed for the first 2-4 patients in any dose level, the dose level will not be expanded.

Patients who are part of the expansion of any dose level will undergo mandatory pre- and on-treatment biopsies (See Schedule of Activities for specifics). To better estimate the OBD, tumor pharmacodynamic data from all patients will be evaluated at the end of Part A1.

Safety information provided by additional patients enrolled into each dose expansion cohort will be taken into account for RP2D determination. If the DLT rate is estimated to reach 30% or more at any dose level, enrollment at that level and all higher levels will be temporarily stopped and the safety data will be analyzed. Decision on moving forward will follow the same DLT target as described previously. Dose escalation will continue until an MTD has been established, maximum dose level (20 mg/kg, please see Section 3.1.5 Criteria for Dose Escalation) has been reached or until three sequential dose levels show a similar pharmacodynamic signal.

Late immune related DLTs that occur during the first 98 days (or first 7 cycles if patient remains on treatment) will be taken into account for MTD determination (see Section 3.2.1 Late Immune Related DLTs and Section 6.3 Follow-up Visit). If late immune related DLTs occur, all safety data will be reviewed and a decision will be made whether or not to permanently stop enrollment in the higher cohorts and declare the MTD, to continue enrollment in the cohort, to increase the number of patients evaluated in that cohort or to stop the study.

Dose levels selected for Part A2 are based on data from Part A1.

The proposed doses, schedule(s) and PK time points may be reconsidered and amended during the study based on the emerging safety and pharmacokinetic data. Lower, intermediate and higher dose cohorts (maximum of 20 mg/kg, refer to Section 3.1.5 Criteria for Dose Escalation) can be added. Higher dose cohorts can only be initiated if the next lowest level is deemed safe.

3.1.1.2. Part A2 Dose Expansion

Part A2 monotherapy dose expansion phase will randomize HCC patients 1:1 to flat dose levels of either 30 mg (Arm 1) or 250 mg (Arm 2) of PF-04518600 given every 2 weeks up to 20 patients per arm. These are doses chosen based on the following preliminary data from Part A1.

1. Partial responses were observed in 1 melanoma and 1 HCC patient at 0.1 (n=10) and 0.3 mg/kg (n=11) dose levels. Full receptor occupancy in peripheral T cells was observed in both responders.

2. Full receptor occupancy was achieved for all patients at doses ≥0.3 mg/kg.

The flat dose that is equivalent to 0.3 mg/kg was determined to be 25 mg in terms of matching the center of the distributions based on the population PK/PD analysis using preliminary data from Part A1 of this study. However, 30 mg was chosen as the low dose (Arm 1) for Part A2 to ensure the 5th percentile of trough concentrations (C_{trough}) to be at or above which the full receptor occupancy was observed.

Although no responses were observed in the 3 mg/kg cohort, increases in peripheral blood central memory CD4 T cell proliferation and activation similar to the increases found at the 0.1 mg/kg were observed at 3 mg/kg. Therefore, Arm 2 will evaluate a 3 mg/kg flat dose equivalent of 250 mg.

An additional flat dose level of 800 mg, approximately equivalent to 10 mg/kg, may be added after initiation of enrollment into Arms 1 and 2 if this is supported by emerging data from the 10 mg/kg cohort of Part A1.

All patients in A2 will undergo mandatory pre- and on-treatment biopsies (See Schedule of Activities for specifics).

If preliminary sign of efficacy from Part A1, or emerging data from other OX40 agonist programs indicate a rationale for exploration of a different tumor type, these may be added or substituted for HCC patients.

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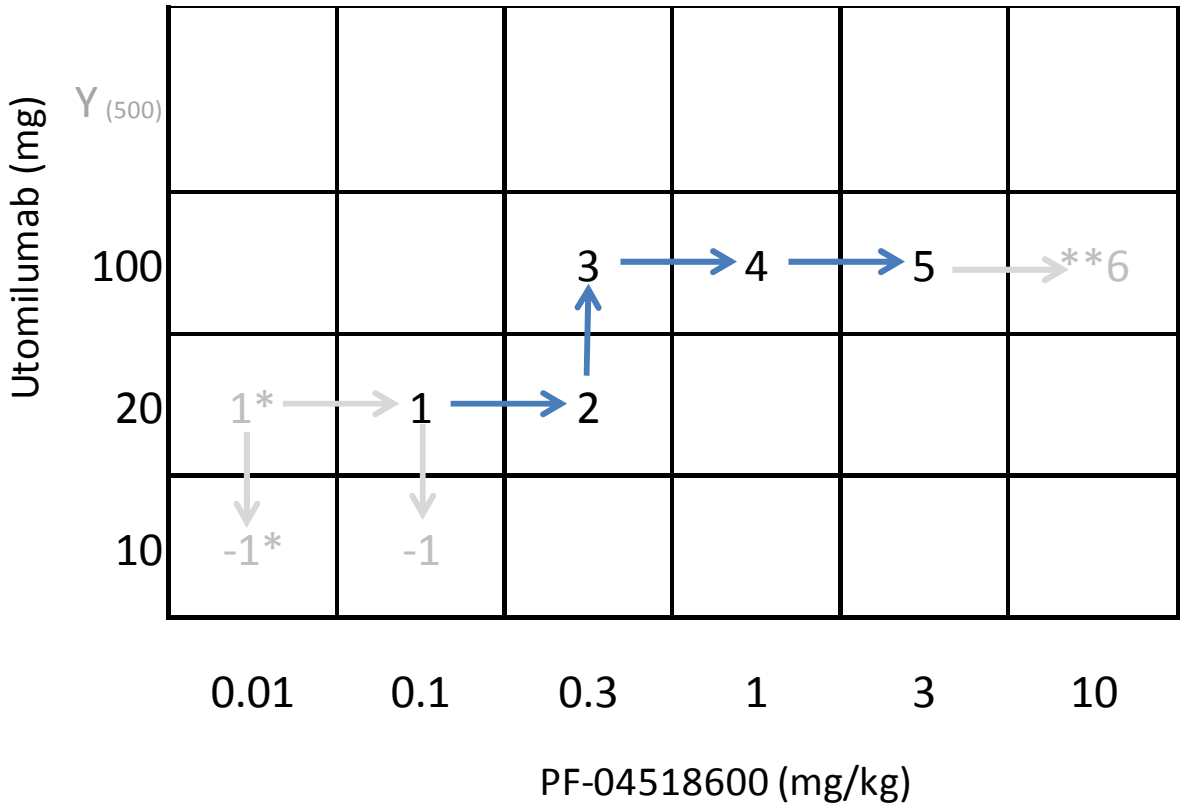
3.1.2. Part B Combination Therapy

3.1.2.1. Part B1 Dose Escalation

After initial safety data have been evaluated and deemed safe for the first 3 dose levels in Part A1, Part B will be initiated. Part B1, the combination therapy dose escalation phase, will enroll approximately 55 patients. At least 6 patients must have been evaluated for the 28 day DLT observation period at the 0.3 mg/kg dose level in Part A1 OX40 monotherapy before Part B1 can be initiated. Part B1 will study sequential dose levels of PF-04518600 (0.1, 0.3, 1.0 and 3 mg/kg, with an option of 10 mg/kg pending data from Part A1) combined with 20 mg or 100 mg of utomilumab in adult patients with NSCLC, HNSCC, melanoma, bladder, gastric or cervical cancer who are unresponsive to currently available therapies or for whom no standard therapy is available. The starting dose level will be 0.1 mg/kg of PF-04518600 and 20 mg of utomilumab, given no sooner than 30 minutes apart (for dosing schedule, please see Section 5.4.2 Administration Part B Combination Therapy). Based on emerging data in the 10 mg/kg Part A1 cohort, an optional cohort of 10 mg/kg PF-04518600 in combination with 100 mg of utomilumab may be evaluated. If patients at the 0.3 mg/kg dose level in Part A1 OX40 monotherapy experiences ≥ Grade 2 immune related toxicities or cytokine release syndrome, starting dose of PF-04518600 will be 0.01 mg/kg combined with 20 mg of utomilumab.

The mTPI method for dose escalation adopted for PF-04518600 monotherapy in Part A1 will also be used in PF-04518600/utomilumab combination therapy in Part B1, and targets a dose limiting toxicities (DLT) rate of 25% and an acceptable DLT interval (20%-30%),[7] will be utilized for dose escalation (see Section 3.1.5 Criteria for Dose Escalation).[88]

Figure 5. Dose Escalation Scheme based on the Proposed Doses for PF-04518600 and Utomilumab



* If first 6 patients at the 0.3 mg/kg dose level in Part A1 OX40 monotherapy experience ≥ Grade 2 immune related toxicities or cytokine release syndrome, starting dose of PF-04518600 will be 0.01 mg/kg combined with 20 mg of utomilumab in Part B1.

** Based on emerging data in the 10 mg/kg Part A1 cohort, an optional cohort of 10 mg/kg PF-04518600 in combination with 100 mg of utomilumab may be evaluated.

An initial 2 to 4 patient may be enrolled initially into each dose level combination. Fresh biopsies will not be required for these patients. The mTPI model performs dose escalation by increasing or decreasing the dose of either PF-04518600, utomilumab or both based on the observed number and/or nature of DLTs at the current dose combination level (see Figure 5). The starting dose combination level will be 0.1 mg/kg PF-04518600 combined with 20 mg of utomilumab. If no DLTs are observed, the next dose combination level will be 0.3 mg/kg PF-04518600 combined with 20 mg of utomilumab. If no toxicity is observed, the dose of PF-04518600 will continue to be increased (see Figure 5). If toxicity is observed at the starting dose combination level, 0.1 mg/kg PF-04518600 combined with 10 mg of utomilumab will be evaluated. Subsequent to the initial dose, if dose de-escalation is recommended after evaluation, intermediate dose levels between the previous dose combination and current dose combination may be studied. Using the observed data, 1 or more dose combination levels of PF-04518600 and utomilumab with toxicity rate closest to,

but not exceeding, the predefined target rate of 25% will be identified. If the starting dose is deemed not tolerable, the next dose combination level will be 0.1 mg/kg PF-04518600 combined with 10 mg of utomilumab.

When a dose combination level is deemed safe following a DLT observation period of 28 days or 2 cycles (of PF-04518600), escalation will occur to the next dose combination level. A staggered start will be employed for all dose combination levels; that is, the first patient for any dose combination level will be dosed, and observed for 48 hours before subsequent patients can be dosed. If no safety concerns arise during this 48 hr period, a second patient will be enrolled into the same dose combination level.

Peripheral pharmacodynamic assessments of any given dose combination level may be completed after the dose combination level is deemed safe, and escalation to the next dose combination level has already occurred. When peripheral monitoring indicates immune modulation in the first 2-4 patients, the dose level will be expanded to approximately 10 patients allowing better characterization of pharmacodynamic effects and reducing variability due to small sample size. To allow for better characterization of pharmacodynamic effects, these additional patients will undergo mandatory pre-treatment and on treatment biopsies (See Schedule of Activities for specifics). If no peripheral pharmacodynamic effects are observed for the first 2-4 patients in any dose combination level, the dose combination level will not be expanded.

3.1.2.2. Part B2 Dose Expansion

Part B2 combination therapy dose expansion phase will further evaluate safety and anti-tumor activity of the combination with a dosing regimen selected based on results of Part B1 with flat dose equivalents of PF-04518600.

From the results of Part B1, the selected dose for PF-04518600 in the B2 combination therapy dose expansion cohorts is 30 mg (a flat dose equivalent to 0.3 mg/kg) intravenously (IV) Q2W in combination with PF-05082566 20 mg IV every 28 days.

Part B2 will be divided into 2 arms:

Arm 1 will enroll melanoma patients who have either:

a. Ocular melanoma patients with advanced/metastatic disease; or,

b. Cutaneous/acral melanoma patients with advanced/metastatic disease who have received checkpoint inhibitor (anti-PD-L1, anti-PD-1, or anti-CTLA4) based treatment on which disease progressed. [Note: Checkpoint inhibitor may have been part of a combination therapy, as long as the combination did not contain OX40 or 4-1BB agonist.] Any questions on prior treatment may be discussed with the Sponsor.

Arm 2 will enroll NSCLC patients who have:

a. Histological or cytological diagnosis of NSCLC with advanced/metastatic disease. Patients must have previously received prior anti-PD-L1 or anti-PD-1 mAb on which disease progressed. [Note: Previous anti-PD-L1 or anti-PD-1 mAb may have been part of a combination therapy, eg in combination with chemotherapy, as long as the combination did not contain OX40 or 4-1BB agonist.]

Part B2 will initially enroll up to 20 patients in each arm (including approximately 5 ocular melanoma patients in Arm 1), and all patients will undergo mandatory pre- and on-treatment tumor biopsies. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted (see Section 1.4 Rationale for Pretreatment and On-treatment Biopsies).

The dose level of PF-04518600 and the dose level of utomilumab within the dose combination level will be selected from MTD or OBD established in Part B1. If the MTD is not reached, the maximum administered dose (MAD) maybe selected. A flat dosing strategy for PF-04518600, similar to one implemented for Part A2, will be implemented if supported by PK data.

Based on emerging data from Parts B1 and B2, if no response has been seen by the time the 10th patient enrolls in either arm in B2, enrollment may pause until a patient experiences a response or after the 16 week tumor assessment for the 10th patient, whichever is first. If at least 1 response does not occur in the first 10 patients in an arm, then enrollment may stop in that arm. Enrollment will continue in any arm that has at least 1 responder in the first 10 patients. If there are responders in both arms before the 10th patient enrolls, then enrollment will continue to the full 20 patients for each arm.

3.1.2.3. Japan participation in Part B Combination Therapy

Japan will participate in Part B after safety of PF-04518600 of at least 2 dose levels as a single agent has been evaluated in Japanese patients (See Section 3.1.1.3 Japan Cohorts in Part A Monotherapy). Following the completion of the safety assessment of at least 2 dose levels for Japanese patients in Part A1, and if deemed acceptable by the local health authorities, the combination of PF-04518600 with utomilumab may also be tested in order to evaluate the safety of the combination therapy in patients enrolled in Japan.

3.1.3. Enrollment Prioritization

3.1.3.1. Dose Escalation Phase

For both Part A1 monotherapy and Part B1 combination therapy dose escalation phases (except for Japan), once a monotherapy dose level or combination dose level is open for enrollment, first priority will be given to the recruitment of the first 2-4 patients into that dose level. If a DLT occurs in the first 2-4 patients at a dose level, second recruitment priority will be given to the expansion of that dose level. Third recruitment priority will be given to the expansion of any dose level (monotherapy or combination) based on pharmacodynamic assessment trigger. During expansion of multiple dose levels for pharmacodynamic assessments, patients will be recruited into the lowest available dose level first.

3.1.4. Starting Dose

The initial starting dose for monotherapy PF-04518600 (Part A1) is 0.01 mg/kg. In Part B1, the starting dose combination level will be 0.1 mg/kg PF-04518600 combined with 20 mg of utomilumab. PF-04518600 will be given once in 2 week cycles, and utomilumab will be given once every other cycle.

3.1.5. Criteria for Dose Escalation

3.1.5.1. Part A Monotherapy

A mTPI method, targeting a DLT rate of 25% and an acceptable DLT interval (20%-30%),[88] will be utilized in Part A1 dose escalation phase. Initial 2 to 4 patients will be enrolled in each cohort with a target size of 3 patients. In dose cohorts with 2 patients enrolled, an additional patient may be enrolled for dose escalation assessment if one of the two patients has a DLT event observed. Decisions to escalate to the next dose level will be determined using safety assessments obtained from these initial 2-4 patients.

The dose levels to be evaluated are listed in Table 2. Beginning with the starting dose of 0.01 mg/kg, if either a DLT related to PF-04518600 or a grade ≥2 cytokine release syndrome, infusion reaction, or allergic reaction is observed, subsequent dosages will not be increased by more than 3-fold, or one- half a log (eg, increases from 0.01 mg/kg will be to 0.03 mg/kg, and increases from 0.3 mg/ kg will be to 1.0 mg/kg). If dosages greater than 3 mg/kg are evaluated, if DLTs are absent, subsequent dose levels may include a maximum of 5-fold increase. If a DLT considered related to PF-04518600 is observed, the next dose level will not be greater than 3-fold the previous dose level. Up to a maximum of 20 mg/kg may be evaluated. If a high DLT rate is observed at the starting dose, the study may be stopped.

Table 2. Table of Potential Dose Levels

Cohort	Dose (mg/kg)
1	0.01
2	0.1
3	0.3
4	1.5
5	3
6	TBD: maximum 6.0 (optional)
7	10

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level to determine where future cohorts should be on dose escalation, no change in dose, or dose de-escalation.

The algorithm will stop if any of the following criteria is met:

1. The maximum sample size has been achieved (approximately 58 patients total).

2. A minimum of 9 patients have been accumulated on a dose that is predicted to be the MTD or MAD; or,

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

All clinically relevant AEs and SAEs will be reviewed by the sponsor and investigators to determine if the dose allocation schedule requires modification.

Table 3. Decision Rules

	Number of Patients Treated at a Dose level										
Number of Patients Having DLT	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12
0	E	E	E	E	E	E	E	E	E	E	E
1	n/a	S	S	S	E	E	E	E	E	E	E
2	U	D	D	S	S	S	S	S	S	S	S
3		U	U	D	D	S	S	S	S	S	S
4			U	U	U	D	D	D	D	D	S
5				U	U	U	U	U	D	D	D
6					U	U	U	U	U	U	D
7						U	U	U	U	U	U

D: De-escalate the dose; E: Escalate the dose; S: Stay at the dose;
U: Unacceptable toxicity; n/a: Not applicable

Patients experiencing a DLT may be managed with dose modification (after dose interruption) or discontinuation. Subsequent dose levels may not be opened until the first 2-4 patients entered at the current dose level have been treated and observed for at least two complete cycles and the number of DLTs among those patients in their first two cycles has been determined.

If a patient withdraws from the study before Day 28 for reasons other than investigational product-related toxicity (see Section 3.2 DLT Definition), another patient may be enrolled to replace that patient at the current dose level. In principle, all patients must be evaluated for 28 days. However, if a patient withdraws close to Day 28 for reasons other than toxicity and is due to a clear unrelated drug event (eg, traffic accident, clear disease progression), the patient may be deemed evaluable for safety if safety assessments have been unremarkable,

and the investigator and sponsor's medical monitor both agree that the patient is evaluable for DLT safety observation.

The dose escalation portion of the study is completed when at least 9 evaluable patients have been treated at the highest dose associated with a mean DLT rate of 25%.

3.1.5.2. Part B Combination Therapy

The dose escalation scheme based on mTPI method described in Section 3.1.5.1 will also be used in Part B Combination Therapy. The potential dose combination level of PF-04518600 and utomilumab are depicted in Figure 5.

Similar to Part A, the dose escalation portion of Part B is completed when at least 9 evaluable patients have been treated at the highest dose combination level(s) associated with a DLT rate of 25%.

Selected dose for PF-04518600 in the B2 combination therapy dose expansion cohorts is 30 mg (a flat dose equivalent to 0.3 mg/kg) intravenously (IV) Q2W in combination with PF-05082566 20 mg IV every 28 days.

3.2. DLT Definition

Severity of adverse events will be graded according to CTCAE version 4.03 (see Appendix 2). For the purpose of dose escalation, any of the following adverse events occurring in the first two cycle of treatment (28 days) will be classified as DLTs, unless there is a clear alternative explanation (eg, related to underlying disease/progression):

Hematologic:

- Grade 4 neutropenia lasting >7 days.
- Febrile neutropenia (defined as absolute neutrophil count (ANC) <1000/mm3 with a single temperature of >38.5°C (101.3°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
- Grade ≥3 neutropenic infection.
- Grade ≥3 thrombocytopenia with clinically significant bleeding or requiring medical intervention [eg, transfusion].
- Grade 4 thrombocytopenia.
    - any <10.000;
    - 10.000-25.000 for >5 days*.
- Grade 4 anemia.

- Grade ≥3 anemia related to hemolysis or autoimmune disease (>2 g/dL decrease in hemoglobin requiring medical intervention [transfusion or steroids]).

- Non-hematologic:

- Grade ≥3 toxicities that are considered clinically significant, including cytokine release syndrome, infusion reactions and allergic reactions, except those that have not been maximally treated (eg, nausea, vomiting, diarrhea) or can be easily treated (eg, electrolyte abnormalities).

In addition, clinically important or persistent toxicities (eg, toxicities responsible for significant dose delay as described in Section 5.4.5.5 Dose Delay) that are not included in the above criteria may be considered a DLT following review by Pfizer and the investigators. All DLTs need to represent a clinically significant shift from baseline.

*Specifically for HCC patients entering with a lower baseline value of platelets, change from baseline needs to be taken into consideration.

Information regarding DLT observation period can be found in Section 3.1.5 (Criteria for Dose Escalation). Whilst DLT observation for 28 days is required for dose escalation, safety and tolerability assessment for the first 98 days (or completion of 7 cycles) will be taken into account for MTD and RP2D selection (see Section 3.3, MTD definition). During the 98 day assessment period, specific attention will be paid to late immune-related AEs (see Section 3.2.1 Late Immune Related DLTs). Late immune-related AE information will be collected from patients who withdraw after 1 to 6 cycles of treatment during follow up visits (see Section 6.3 Follow-up Visit).

3.2.1. Late Immune Related DLTs

Late immune related DLTs are immune-related AEs that meet the same grading criteria as DLT criteria and occur from Day 29 through the 98 day assessment period (or completion of first 7 cycles if patient remains on treatment). If late immune related DLTs occur, enrollment into any higher dose level cohorts will be placed on temporarily hold. All safety data will be reviewed, and a decision will be made to either:

- Continue enrollment in higher dose level cohorts.

- Increase the number of patients in the cohort in which the immune-related DLT occurred to 6 total patients. If the cohort has already recruited 6 patients, the number of patients should be increased to 9 total patients. All patients will be followed for at least 98 days to reassess safety at this dose level. If no other late immune-related DLTs are observed (total late immune-related DLT rate is 1 out of 6 or 1 out of 9), enrollment in higher dose level cohorts may resume. If after the enrollment of additional patients the late immune-related DLT rate increases to 2 or more patients out of 6, this dose level will be considered above the MTD. In this case, the next lower dose level cohort will be expanded to 6 then 9 total patients to reassess safety at that dose level.

- Permanently stop enrollment in higher dose level cohorts, and declare the dose level to be above MTD. Increase the number of patients in the next lowest dose level cohort to 6 then 9 total patients and follow all patients for at least 98 days to reassess safety at this dose level.

- Stop the study.

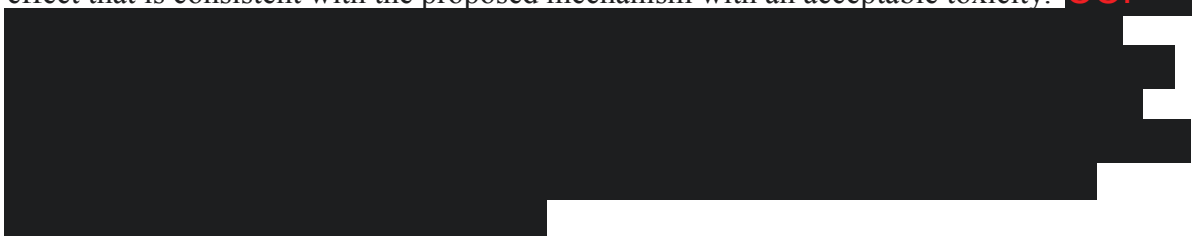
For any given patient that is on-treatment at dose levels that are subsequently considered to be above the MTD, the option to dose reduce will be discussed (see Section 5.4.5.6 Dose Reductions, Interruptions and Discontinuation Criteria). If a patient tolerated the above MTD dose level well and is benefiting, continuation of treatment at the above MTD dose level will require re-consenting.

3.3. Maximum Tolerated Dose (MTD) Definition

The estimated MTD is the dose level associated with approximately 25% of patients experiencing DLT. The target interval for the DLT rate is 20%-30%. Due to the discreteness of the dose levels and in the interest of safety of patients, the estimated MTD is the highest tested dose level with mean DLT rate ≤0.25 in at least 9 DLT evaluable patients. This is with the exception of Grade 4 and 3 cytokine release syndrome, infusion reaction or allergic reaction. If ≥1 patient out of 6 (or ≥17%) experiences a Grade 4 cytokine release syndrome, infusion reaction or allergic reaction, or if 2 patients out of 6 (33%) experiences Grade 3 cytokine release syndrome, infusion reaction or allergic reaction, the dose level will be considered to be above the MTD. All safety data will be evaluated and a decision will be made whether or not to permanently stop enrollment in the higher cohorts and declare the MTD, to continue enrollment in the cohort, to increase the number of patients evaluated in that cohort or to stop the study (see Section 3.2.1 Late Immune Related DLTs). The cumulative incidence of all late immune related DLTs will be taken into account for determination of the MTD/RP2D. An interim safety analysis will be triggered if the overall cumulative incidence of late immune related DLTs increases above 25% across all dose levels. If a clear dose response is observed, the study may resume enrollment at the lowest dose level with incidence in 1 or less patients out of 6. If the incidences of late immune related DLTs do not appear to have a dose response relationship (ie, consistently observed in all dose levels), the option to terminate the study will be considered.

3.4. Optimal Biological Dose (OBD) Definitions

The Optimal Biological Dose (OBD) is the lowest dose that can produce a pharmacodynamic effect that is consistent with the proposed mechanism with an acceptable toxicity. CCI



3.5. Maximum Administered Dose (MAD)

The Maximum Administered Dose (MAD) is the highest dose administered.

3.6. Recommended Phase 2 Dose (RP2D) Definition

The Recommended Phase 2 Dose (RP2D) is the dose chosen for further study based on Phase 1 results. If the MTD proves to be clinically feasible for long term administration in a reasonable number of patients, such dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD. Next to safety assessment, careful consideration will be given to pharmacodynamic effects. If an OBD can be determined, this will be a key factor in the determination of the RP2D.

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 protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

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

4.1. Inclusion Criteria

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

4.1.1. Part A Monotherapy

1. Part A1 only: Patients with histological or cytological diagnosis of HNSCC, HCC, melanoma, or clear cell RCC who progressed on or are intolerant to standard therapy, for which no standard therapy is available or who decline standard therapy.

2. Part A2 only: Patients with histological or cytological diagnosis of advanced/metastatic HCC who are treatment naïve and have declined standard of care, or have had at least 1 prior line of systemic therapy. Prior anti-PD-L1/PD-1 therapy is allowed.

3. Patients must have at least one measurable lesion as defined by RECIST version 1.1, be willing to undergo the mandatory biopsies and there is no excessive risk from biopsy as judged by the Investigator.

4. Adults (men and women) age ≥18 years (for Japan only: ≥20 years of age).

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

6. Adequate Bone Marrow Function, including:

   - ANC ≥1,500/mm^3 or ≥1.5 x 10^9/L.
   - ANC for HCC only ≥1,000/mm^3 or 1.0 x 10^9/L.
   - Platelets ≥100,000/mm^3 or ≥100 x 10^9/L.

- Platelets for HCC only: ≥60,000/mm^3.

- 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 (approximately 3 month) past.

7. Adequate Renal Function, including:

   - Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥60 ml/min as calculated using the method standard for the institution. If an estimated creatinine clearance is believed to be inaccurate for a patient, 24 hr urine collection with actual assessment of creatinine clearance is allowed.

8. Adequate Liver Function (all patients, except HCC, see Inclusion Criteria 9), including:

   - Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome.

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

9. Inclusion for HCC patients only:

   - Child-Pugh Class A or B with a score of 7 (see Appendix 3) and no prior history of hepatic encephalopathy.

   - Serum bilirubin ≤3 mg/dL.

   - Serum Albumin ≥2.8 g/dL.

   - AST and ALT ≤5.0 x ULN.

   - International Normalized Ratio (INR) ≤2.3 or Prothrombin Time (PT) ≤6 seconds above control.

10. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTCAE except for AEs not constituting a safety risk by investigator judgment.

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

12. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective method(s) of contraception throughout the study and for at least 90 days after the last dose of assigned treatment.

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.

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

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

4.1.2. Part B Combination Therapy

1. Part B1 only: Patients with histological or cytological diagnosis of NSCLC, HNSCC, melanoma, urothelial bladder carcinoma (including renal pelvis, ureters, urinary bladder, and urethra), gastric or squamous cell carcinoma of the uterine cervix who progressed on or are intolerant to standard therapy, for which no standard therapy is available, or who decline standard therapy.

2. Part B2 Arm 1 only:

   a. Ocular melanoma patients with advanced/metastatic disease; or,

   b. Cutaneous/acral melanoma patients with advanced/metastatic disease who have received checkpoint inhibitor (anti-PD-L1, anti-PD-1, or anti-CTLA4) based treatment on which disease progressed. [Note: Checkpoint inhibitor may have been part of a combination therapy, as long as the combination did not contain OX40 or 4-1BB agonist.] Any questions on prior treatment may be discussed with the Sponsor.

3. Part B2 Arm 2 only: Histological or cytological diagnosis of NSCLC with advanced/metastatic disease. Patients must have previously received prior anti-PD-L1 or anti-PD-1 mAb on which disease progressed. [Note: Previous anti-PD-L1 or anti-PD-1 mAb may have been part of a combination therapy, eg, in combination with chemotherapy, as long as the combination did not contain OX40 or 4-1BB agonist.]

4. Patients must have at least one measurable lesion as defined by RECIST version 1.1, be willing to undergo the mandatory biopsies and there is no excessive risk from a biopsy as judged by the Investigator.

5. Adults (men and women) age ≥18 years (for Japan only: ≥20 years of age).

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

7. Adequate Bone Marrow Function, including:

   - ANC ≥1,500/mm^3 or ≥1.5 x 10^9/L.

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

   - Hemoglobin ≥9 g/dL. 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 (approximately 3 month) past.

8. Adequate Renal Function, including:

   - Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥60 ml/min as calculated using the method standard for the institution. If an estimated creatinine clearance is believed to be inaccurate for a patient, 24 hr urine collection with actual assessment of creatinine clearance is allowed.

9. Adequate Liver Function including:

   - Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome.

   - Aspartate and alanine aminotransferase (AST & ALT) ≤2.5 x ULN.

10. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTCAE except for AEs not constituting a safety risk by investigator judgment.

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

12. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective method(s) of contraception throughout the study and for at least 90 days after the last dose of assigned treatment.

    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.

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

14. 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 A Monotherapy

1. Patients with known symptomatic brain metastases requiring systemic corticosteroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to the start of study medication, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable. Mild neurological deficits are allowed, if they do not interfere with the ability to judge the safety profile of PF-04518600.

2. History of or active autoimmune disorders (including but not limited to: Crohn's Disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave's disease) and other conditions that compromise or impair the immune system.

3. Active bacterial, fungal or viral infection including hepatitis B (HBV, see exception below for patients with HCC), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) -related illness.

   For Part A1 patients with HCC only: after the safety profile of a cohort has been established in 2-4 patients, and escalation to the next higher dose level has taken place, HCC patients enrolled into the expansion lower dose cohort meeting the following criteria can be enrolled: patients infected with the HBV or HCV but with minimal viral load (<20 IU/ml) at the moment of screening and who are being treated with either entecavir or tenofovir during the full study period.

   For Part A2 HCC patients: patients with chronic HCV infection are allowed; however, patients with chronic HBV infection must be receiving effective antiviral therapy (viral load <100 IU/ml). Patients with active coinfection with HBV and HCV, active coinfection with HBV and hepatitis D virus are excluded. The following HCC subtypes are also exclusionary: fibrolamellar HCC, sarcomatoid HCC, and mixed cholangiocarcinoma.

4. Bleeding esophageal or gastric varices <2 months prior to informed consent document (ICD) date.

5. Unmanageable ascites (limited medical treatment to control ascites is permitted, but all patients with ascites will require review by sponsor's medical monitor).

6. Major surgery within 4 weeks of starting study treatment.

7. Patients who have undergone solid organ or hematopoietic transplant.

8. Systemic anti-cancer therapy within 4 weeks of starting study treatment (6 weeks for mitomycin C or nitrosoureas). If systemic anti-cancer therapy was given within 4 weeks, patient may be included if 4-5 times elimination half-life of drug has passed.

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

10. Previous high dose chemotherapy requiring stem cell rescue.

11. Prior treatment with an OX40 agonist.

12. Currently require doses of systemic immune suppressive medication [eg, ≥10 mg of prednisone or equivalent (≥1.5 mg of dexamethasone)].

13. History of Grade 3 or higher immune-mediated adverse event (including AST/ALT elevations that where considered drug related and cytokine release syndrome) that was considered related to prior immune-modulatory therapy (eg, checkpoint inhibitors, co-stimulatory agents etc.) or any grade immune-related AEs that required immune suppressive therapy.

14. Patients with intolerance to or who have had a severe (≥ Grade 3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins, or patients who have had a severe allergic or anaphylactic reaction to any of the substances included in the investigational product (including excipients).

15. Patients with a previous history of anthracycline treatment and are at risk of cardiac failure (New York Heart Association [NYHA] Class II or above).

16. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, torsade's de points, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), 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 and trypsin-like serine protease (factor Xa) inhibitors only, no vitamin-K antagonists) will be allowed if indicated.

17. Participation in other interventional studies within 28 days before the current study begins and/or during study participation. Before joining Study B0601002, at least 28 days must have passed from last systemic study therapy administration. Participation in long term follow up is allowed if no procedures which may interfere with the interpretation of study results will be performed.

18. Patients in the 0.01 mg/kg cohort must not be ≤50 kg in weight.

19. Pregnant female patients; breastfeeding female patients (including patients who are weaning their infants).

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

21. 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 B Combination Therapy

1. Patients with known symptomatic brain metastases requiring systemic corticosteroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to the start of study medication, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable. Mild neurological deficits are allowed, if they do not interfere with the ability to judge the safety profile of PF-04518600/utomilumab.

2. History of or active autoimmune disorders (including but not limited to: Crohn's Disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave's disease) and other conditions that compromise or impair the immune system.

3. Active bacterial, fungal or viral infection including HBV, HCV, known human HIV or AIDS -related illness.

4. Bleeding esophageal or gastric varices <2 months prior to ICD date.

5. Unmanageable ascites (limited medical treatment to control ascites is permitted, but all patients with ascites will require review by sponsor's medical monitor).

6. Major surgery within 4 weeks of starting study treatment.

7. Patients who have undergone solid organ or hematopoietic transplant.

8. Systemic anti-cancer therapy within 4 weeks of starting study treatment (6 weeks for mitomycin C or nitrosoureas). If systemic anti-cancer therapy was given within 4 weeks, patient may be included if 4-5 times elimination half-life of drug has passed.

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

10. Previous high dose chemotherapy requiring stem cell rescue.

11. Prior treatment with an OX40 agonist or a 4-1BB agonist.

12. Currently require doses of systemic immune suppressive medication [eg, ≥10 mg of prednisone or equivalent (≥1.5 mg of dexamethasone)].

13. History of Grade 3 or higher immune-mediated adverse event (including AST/ALT elevations that where considered drug related and cytokine release syndrome) that was considered related to prior immune-modulatory therapy (eg, checkpoint inhibitors, co-stimulatory agents etc.) or any grade immune-related AEs that required immune suppressive therapy.

14. Patients with intolerance to or who have had a severe (≥ Grade 3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins, or patients who have had a severe allergic or anaphylactic reaction to any of the substances included in the investigational products (including excipients).

15. Patients with a previous history of anthracycline treatment and are at risk of cardiac failure (NYHA Class II or above).

16. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, torsade's de points, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), 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 and factor Xa inhibitors only, no vitamin-K antagonists) will be allowed if indicated.

17. Participation in other interventional studies within 28 days before the current study begins and/or during study participation. Before joining Study B0601002, at least 28 days must have passed from last systemic study therapy administration. Participation in long term follow up is allowed if no procedures which may interfere with the interpretation of study results will be performed.

18. Pregnant female patients; breastfeeding female patients (including patients who are weaning their infants).

19. Patients that will receive 0.01 mg/kg PF-04518600 must not be ≤50 kg in weight.

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

21. 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.

4.3. Lifestyle Guidelines

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive PF-04518600 or PF-04518600 in combination with utomilumab, which is a compound for which the teratogenic risk is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for 90 days after the last dose. The investigator or his/her designee, in consultation with the patient will confirm the patient has selected two appropriate methods of contraception for the individual patient 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 or her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the Schedule of Activities 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 a selected contraception method is discontinued or if pregnancy is known or suspected in the patient or the 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 the following:

1. Established use of oral, inserted, injected (not available in Japan), implanted (not available in Japan) or transdermal hormonal (not available in Japan) 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 (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available (for example in Japan) 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; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for 90 days after the last dose.

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 International Conference on Harmonization (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). Eligible patients will be enrolled to receive PF-04518600 (and utomilumab for Part B patients) in an open-labeled, unblinded manner. Patients will be registered and successively assigned to the next available treatment slot at a dose level or dose combination level decided on after the previous cohort's safety evaluation and ongoing observations of earlier enrolled patients. For monotherapy, patients will be dosed at 0.01 mg/kg PF-04518600 in the first cohort. For combination therapy, patients will be dosed at 0.1 mg/kg PF-04518600 and 20 mg utomilumab in the first dose combination level. Selected dose for PF-04518600 in the B2 combination therapy dose expansion cohorts is 30 mg (a flat dose equivalent to 0.3 mg/kg) intravenously (IV) Q2W in combination with PF-05082566 20 mg IV every 28 days.

5.1. Allocation to Treatment

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will e-mail 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 Form (CRF) pages and other study-related documentation or correspondence referencing that patient and e-mail 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.

5.2. Patient Compliance

The site will complete required dosage Preparation Record located in the study manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Pfizer monitor.

At each study visit, the Investigator, or designee, will assess the patient's compliance with the study requirements. The assessment will include checks of protocol compliance and concomitant mediation use.

5.3. Investigational Product Supplies

PF-04518600 and utomilumab will be supplied for the study by Pfizer. No patients or third-party payers will be charged for investigational product.

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 Study Manual. The study monitor should be contacted for any issues related to drug supplies.

5.3.1. Dosage Forms and Packaging

5.3.1.1. PF-04518600

PF-04518600 10 mg/mL injection is presented as a sterile solution for intravenous administration. Each vial contains 108 mg of PF-04518600 in 10.8 mL of aqueous buffered solution, with a nominal volume of 10 mL, is sealed with a coated stopper and an overseal, and labeled according to local regulatory requirements. The vial is designed for single use.

PF-04518600 will be shipped under refrigerated conditions (2-8°C) and should be stored under refrigerated conditions (2-8°C).

5.3.1.2. Utomilumab

Utomilumab drug product will be supplied in glass vials at a 10 mg/mL concentration and labeled as open supplies. Each vial is packed in an individual carton.

5.3.2. Preparation and Dispensing

See the investigational product (IP) Manual located in the Study Manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. 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. Part A1 Monotherapy

PF-04518600 will be administered intravenously with adjustment for body weight at every cycle. A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 2 weeks in duration. PF-04518600 will be administered on Day 1 of each 2 week cycle per the IP Manual as an intravenous (IV) infusion over 60 minutes (-5 to +15 minutes and should include the time needed to flush the infusion line) on an outpatient basis. If infusion reaction occurs, infusion rate maybe reduced (refer to Section 5.4.5.1 Infusion Reactions and Appendix 4 for management of infusion reactions).

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.

Each patient may receive PF-04518600 until disease progression by irRECIST (see Section 5.4.6 Treatment After Initial Evidence of Radiological Progression), patient refusal, or unacceptable toxicity occurs, or end of study, whichever occurs first.

The dose level will be assigned by the sponsor (Section 5.1 Allocation to Treatment). 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. All patients should be weighed within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of PF-04518600 required for dose preparation. Decision to recalculate PF-04518600 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 >10% compared to the weight used to calculate the initial dose, the amount of PF-04518600 required for investigational product preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

5.4.2. Part A2 Monotherapy

PF-04518600 will be administered intravenously as a flat dose. A cycle is defined as the time from current Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 2 weeks in duration. PF-04518600 will be administered on Day 1 of each 2 week cycle per the IP Manual as an intravenous (IV) infusion over 60 minutes (-5 to +15 minutes and should include the time needed to flush the infusion line) on an outpatient basis. If infusion reaction occurs, infusion rate maybe reduced (refer to Section 5.4.5.1 Infusion Reactions and Appendix 4 for management of infusion reactions).

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. Please refer to the IP manual for infusion rate and duration.

Each patient may receive PF-04518600 until disease progression by irRECIST (see Section 5.4.6 Treatment After Initial Evidence of Radiological Progression), intolerability, death, or until end of study, whichever comes first.

The dose level will be assigned by the sponsor (Section 5.1 Allocation to Treatment).

5.4.3. Part B1 Combination Therapy

In Part B1, utomilumab will be administered on Day 1 of every other cycle (every 28 days) per IP Manual as an intravenous (IV) infusion over 60 minutes (-5 to +15 minutes and should include the time needed to flush the infusion line). Utomilumab will be administrated intravenously using a flat dose.

Per monotherapy, PF-04518600 will be administered on Day 1 of each 2 week cycle per the IP Manual as an intravenous (IV) infusion over 60 minutes (-5 to +15 minutes and should include the time needed to flush the infusion line) on an outpatient basis. PF-04518600 will be administered intravenously with adjustment for body weight at every cycle. On cycles whereby both PF-04518600 and utomilumab are to be administered on the same day, PF-04518600 will be administered after, but no sooner than 30 minutes after completion of the utomilumab infusion in absence of infusion reaction and after post-utomilumab and pre-PF-04518600 pharmacokinetic blood draws (see Section 5.4.5.6.2 Dose Reductions, Interruptions, and Discontinuation Criteria Part B Combination). All blood draws should be taken from the contra-lateral arm of the infusion. Furthermore, separate infusion bags, infusion lines, and filters must be used for each investigational product. Indwelling catheters should be flushed prior to infusion of each investigational product.

A cycle is defined as the time from Day 1 dose of PF-04518600 to the next Day 1 dose. If there are no treatment delays, a cycle will be 2 weeks. Each patient may receive PF-04518600 and utomilumab until disease progression by irRECIST (see Section 5.4.6 Treatment After Initial Evidence of Radiological Progression), intolerability, death, or until end of study, whichever comes first.

If infusion reaction occurs, refer to Section 5.4.5.1 Infusion Reactions and Appendix 4 for management of infusion reactions. If premedication is required for the management of infusion reactions, administration of PF-04518600 not sooner than 30 minutes before utomilumab administration may be considered.

5.4.4. Part B2 Combination Therapy

In Part B2, utomilumab will be administered on Day 1 of every other cycle (every 28 days) per IP Manual as an intravenous (IV) infusion over 60 minutes (-5 to +15 minutes and should include the time needed to flush the infusion line). Utomilumab will be administrated intravenously using a flat dose.

PF-04518600 will be administered intravenously as a flat dose on Day 1 of each 2 week cycle per the IP Manual as an intravenous (IV) infusion over 60 minutes (-5 to +15 minutes and should include the time needed to flush the infusion line). On cycles whereby both PF-04518600 and utomilumab are to be administered on the same day, PF-04518600 will be administered after, but no sooner than 30 minutes after completion of the utomilumab infusion in absence of infusion reaction and after post-utomilumab and pre- PF-04518600 pharmacokinetic blood draws (see Section 5.4.5.6.2 Dose Reductions, Interruptions, and Discontinuation Criteria Part B Combination). All blood draws should be

taken from the contra-lateral arm of the infusion. Furthermore, separate infusion bags, infusion lines, and filters must be used for each investigational product. Indwelling catheters should be flushed prior to infusion of each investigational product.

A cycle is defined as the time from Day 1 dose of PF-04518600 to the next Day 1 dose. If there are no treatment delays, a cycle will be 2 weeks. Each patient may receive PF-04518600 and utomilumab until disease progression by irRECIST (see Section 5.4.6 Treatment After Initial Evidence of Radiological Progression), intolerability, death, or until end of study, whichever comes first.

If infusion reaction occurs, refer to Section 5.4.5.1 Infusion Reactions and Appendix 4 for management of infusion reactions. If premedication is required for the management of infusion reactions, administration of PF-04518600 not sooner than 30 minutes before utomilumab administration may be considered.

5.4.5. Recommended Dose Modifications

Every effort should be made to administer study treatment on the planned dose and schedule.

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

Dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle.
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

5.4.5.1. Infusion Reactions

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

In the case of infusion reaction, characterized by fever and chills, and less commonly hypotension, either experienced by a particular patient or if seen in other patients, pretreatment medication should be administered to reduce the incidence and severity. A regimen is suggested here; however, if local standard of care is a different regimen, this will be allowed. In cases of infusion reactions, patients should be pretreated with acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before investigational product administration. The pretreatment medications will not be supplied by Pfizer. Suggested starting doses are 650 to 1000 mg acetaminophen and 50 mg

diphenhydramine (or equivalent for other antihistamines) either IV or oral. Two (2) additional doses of acetaminophen may be administered approximately every 4-6 hours after the initial pretreatment or as needed.

5.4.5.2. 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 adverse events (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 and monitoring for clinical signs of a systemic reaction will continue thereafter for clinical signs of allergic reactions/hypersensitivity.

In the case of a hypersensitivity reaction, the patient will be treated symptomatically with supportive care, further monitoring, and treatment with anti-histamines and/or corticosteroids. Study infusions may be stopped and the patient will be followed until the end of the study.

Detailed guidance on treatment, dose interruptions and potential retreatment is provided in Appendix 4.

5.4.5.3. Extravasation

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

5.4.5.4. Immune-Related Adverse Events (irAEs)

Although the mechanism of OX40 and 4-1BB are different from check point inhibitors, both OX40 and 4-1BB do stimulate the immune system and thus immune-related AEs (irAEs) can occur. Immune mediated etiology of an AE will be adjudicated by the investigator. Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v4.03):

- Grade 1 or 2: treat symptomatically or with moderate-dose steroids, more frequent monitoring;
- Persistent Grade 2: manage similar to Grade 3 to 4 AE;
- Grade 3 or 4: treat with high-dose corticosteroids.

Treatment of irAEs should follow guidelines set forth in Table 4.

Table 4. Management of Immune-Related Adverse Events (irAEs)

Gastrointestinal irAEs		
Diarrhea / Colitis (NCI CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	Continue investigational product therapy Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: Treat as Grade 2 or 3/4
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	Delay investigational product therapy Symptomatic treatment	If improves to Grade 1: Resume investigational product therapy If persists >5-7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume investigational product therapy per protocol. If worsens or persists >3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs **Grade 4:** life-threatening, perforation	Discontinue investigational product therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone 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 If persists >3 to 5 days, or recur after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Rash (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤30% body surface area	Symptomatic therapy (eg, antihistamines, topical steroids) Continue investigational product therapy	If persists >1 to 2 weeks or recurs: Consider skin biopsy Delay investigational product therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume investigational product therapy If worsens: Treat as Grade 3 to 4

Table 4. Management of Immune-Related Adverse Events (irAEs)

Grade 3 to 4 Covering >30% body surface area; life threatening consequences	Delay or discontinue investigational product therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume investigational product therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of investigational product therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay investigational product therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near baseline, taper steroids over at least 1 month and then resume investigational product therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue investigational product therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Liver Function Tests (LFT) Increase (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue investigational product therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4

Table 4. Management of Immune-Related Adverse Events (irAEs)

Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Delay investigational product therapy Increase frequency of monitoring to every 3 days	If returns to baseline: Resume routine monitoring, resume investigational product therapy If elevations persist >5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume investigational product therapy
Grade 3 to 4 AST or ALT >5 x ULN and /or total bilirubin >3 x ULN	Discontinue investigational product therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: 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
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue investigational product therapy If TSH <0.5 x LLN, or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary MRI scan Symptomatic with abnormal lab / pituitary scan: Delay investigational product therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume investigational product therapy Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Table 4. Management of Immune-Related Adverse Events (irAEs)

Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue investigational product therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, irAE=immune-related adverse event, IV=intravenous, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs, T4=thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

5.4.5.5. Dose Delay

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

- ANC ≥1,000/mm^3.
- Platelets count ≥50,000/mm^3. HCC only: based on investigator judgment, after consultation with sponsor's medical monitor, change from baseline will be considered, and levels of ≥25,000/mm^3 may be acceptable.
- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator discretion, Grade ≤2 if not considered a safety risk for the patient).

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated. Patients experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment interrupted/delayed. Appropriate follow-up assessments should be done until adequate recovery (or until deemed irreversible) occurs as assessed by the Investigator.

If these conditions are met within 2 weeks of treatment interruption or cycle delay, PF-04518600 or PF-04518600/utomilumab may be resumed. For monotherapy, please refer to Section 5.4.5.6.1 (Dose Reductions, Interruptions and Discontinuation Part A Monotherapy) for adverse events requiring dose reduction at the time of treatment resumption. For combination therapy, intrapatient dose reduction will not be permitted (see Section 5.4.5.6.2 Dose Reductions, Interruptions and Discontinuation Part B Combination Therapy).

If these conditions are not met, treatment resumption must be delayed up to a maximum of 4 weeks. If these parameters have not been met after 4 weeks of dose interruption or 4 weeks of new cycle delay, permanent discontinuation of treatment with PF-04518600 or PF-04518600/utomilumab should be considered. 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 14 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

5.4.5.6. Dose Reductions, Interruptions and Discontinuation Criteria

5.4.5.6.1. Part A Monotherapy

Following dose interruption, cycle delay due to toxicity, or observation of late immune related DLTs such that the current dose of treatment is now considered to be above the MTD (see Section 3.2.1 Late Immune Related DLTs), the PF-04518600 dose may need to be reduced when treatment is resumed.

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

Dose reduction of PF-04518600 by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity observed. Patients enrolled in the first (0.01 mg/kg) cohort should be discontinued from the study if dose reduction is required. Patients requiring more than 2 (or 1 for the first cohort) dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. For example, if a patient has clear signs of clinical benefit, and if the investigator considered it to be in the best interest of the patient, they may be allowed to stay on study at a further reduced dose after recovery and appropriate dose interruption. All dose modifications/adjustments must be clearly documented in the patient's source notes and CRF.

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

Patients experiencing a DLT may resume dosing at the next lower dose level once adequate recovery is achieved. No dose reductions are planned for patients experiencing toxicities other than those listed as DLTs. However, patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to ≤ Grade 1 or baseline is achieved.

Recommended dose reductions are illustrated in Table 5.

Table 5. Dose Modification for Drug Related Toxicity at Start of Subsequent Cycle in Part A

Event	Action
Grade 3 or 4 non-hematologic toxicity considered **related** to PF-04518600 per investigator judgment (including persistent nausea, vomiting, diarrhea despite optimal medical therapy), excluding clinically manageable electrolyte abnormalities.	• Hold PF-04518600 infusion until recovery to Grade 0-1 or baseline and reduce by 1 dose level. • If toxicity (Grade 3-4) reoccurs despite reduction, patient may be dose reduced again by 1 more dose level upon recovery to Grade 0-1 or baseline. • Prompt palliative and supportive measures mandated per local standard of care (eg, antiemetic). • Patients who experience Grade 4 non hematologic toxicities despite intervention should be discontinued from the study, unless restarting treatment at reduced dose level is in the patient's best interest per investigator judgment and after consultation with Pfizer's medical monitor (eg, clear clinical benefit and no alternative treatment options).
Hematologic toxicity considered related to PF-04518600 per investigator judgment • Grade 4 neutropenia, ie, ANC <500 mm^3 (1.0 x 10^9/L) for more than 7 days; or, • Febrile neutropenia, ie, fever >38.3°C or a sustained temperature of ≥38°C (100.4°F) with ANC <1000/mm^3; or, • Grade 4 Thrombocytopenia, ie, PLTS <25,000 mm^3 (25.0 x 10^9/L); or, • Grade 3 Thrombocytopenia, ie, PLTS <50,000 mm^3 (50.0 x 10^9/L) with bleeding.	• Hold PF-04518600 until recovery of ANC to ≥1.0 x 10^9/L (1,000 cells/mm^3) and platelets ≥75 x 10^9/L (75,000 cells/mm^3). For HCC patients, a lower threshold for platelets can be considered after discussion with the sponsor's medical monitor (eg, 40,000 cells/mm^3), depending on the shift from baseline. • Reduce PF-04518600 by 1 dose level. • If toxicity reoccurs (grades a described on the left side) despite dose reduction, patient may either be held until recovery and continuation at same dose, or undergo further dose reduction by 1 more dose level.
Other grade 4 hematologic toxicity considered **related** to PF-04518600 per investigator judgment.	• Hold PF-04518600 until recovery to Grade 0-1 or baseline and reduce PF-04518600 dose by 1 dose level. • If toxicity reoccurs (Grade 4) despite dose reduction, patient may either be held until recovery and continuation at same dose, or undergo further dose reduction by 1 more dose level.
No recovery of toxicities within 4 weeks of scheduled PF-04518600 infusion.	• Discontinue treatment, unless restarting treatment at reduced dose level (either lowest dose level tested or more than 2 dose level reduced) is in the patient's best interest per investigator judgment and after consultation with Pfizer's medical monitor (eg, clear clinical benefit and no alternative treatment options).

Please refer to Section 9.6.3 for (12-Lead) Electrocardiogram (ECG) events that may lead to dose reductions or discontinuations.

5.4.5.6.2. Part B Combination Therapy

Intrapatient dose reductions are not permitted during the combination therapy with PF-04518600 and utomilumab unless, in discussion with the sponsor, a dose combination level is deemed to be above the determined MTD for the combination.

Given the expected similarities of side effect profile and mechanism between the two co-stimulation monoclonal antibodies, both treatments must be interrupted or discontinued together. Patients will not be permitted to continue treatment with one agent, while the other agent is either interrupted or permanently discontinued. If infusion related reactions are observed following the administration of the first agent, administration of the second agent will be withheld until symptoms resolve (see Section 5.4.5.1 Infusion Reactions).

Treatment of irAEs should follow guidelines set forth in Table 4 in Section 5.4.5.4 Recommended dose modifications for any other drug-related toxicity are illustrated in Table 6.

Table 6. Treatment Interruptions/ Discontinuations for Drug Related Toxicity at Start of Subsequent Cycle

Toxicity	NCI CTCAE Severity Grade	Treatment Modifications
Hematologic abnormalities.	Grade 3	• Withhold until recovery to Grade 1 or better. • If toxicity does not resolve to Grade 1 or better within 4 weeks of last infusion, consider permanent discontinuation after consultation with the sponsor. • Upon the second occurrence of the same Grade 3 toxicity that does not resolve to Grade ≤1 by the next administration, treatment must be permanently discontinued.
	Grade 4	• Permanent discontinuation. Exceptions are: Single laboratory values out of normal range that are unlikely related to investigational product (s) as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.
Infusion-related reaction.	Grade 1-4	• See Section 5.4.5.1 and Appendix 4.
Hypersensitivity reaction.	Grade 1-4	• See Section 5.4.5.2 and Appendix 4.
Other non-hematologic toxicities and laboratory abnormalities.	Grade 2	• If toxicity resolves to Grade ≤1 by the next administration, treatment may continue. • If toxicity does not resolve to Grade ≤1 by the next administration despite optimal treatment, the next infusion should be omitted. If at the end of 4 weeks of dose holding, the event has not resolved to Grade ≤1, the patient should permanently discontinue treatment (except for hormone deficiencies that can be managed by replacement therapy and for which up to 2 additional subsequent doses may be omitted).

Table 6. Treatment Interruptions/ Discontinuations for Drug Related Toxicity at Start of Subsequent Cycle

Toxicity	NCI CTCAE Severity Grade	Treatment Modifications
	Grade 3	• Permanent discontinuation, Exceptions are: • Transient (≤6 hours) flu-like symptoms or fever, which is controlled with medical management. • Transient (≤24 hours) fatigue, local reactions, headache that resolves to Grade ≤1. • Nausea and vomiting controlled by medical therapy. • Diarrhea, skin toxicity, or liver function test (ALT, AST, or Gamma-glutamyltransferase [GGT]) that resolves to ≤ Grade 1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated. • Amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis. • Tumor flares phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor. • Non hematologic laboratory abnormality that do not require medical intervention or hospitalization. • Single non hematologic laboratory values out of normal range that are unlikely related to treatment as assessed by the Investigator, do not have any clinical correlate, and resolve to ≤ Grade 1 within 7 days with adequate medical management.
	Grade 4	• Permanent discontinuation, Exceptions are: • Non hematologic laboratory abnormality that does not require medical intervention or hospitalization. Single non hematologic laboratory values out of normal range that are unlikely related to treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management. • Amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis.

5.4.6. Treatment after Initial Evidence of Radiological Disease Progression

Immunotherapeutic agents such as PF-04518600 and/or utomilumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression, tumor assessment should be repeated ≥4 weeks later in order to confirm the progression (See Appendix 6). Assigned study treatments may be continued at the Investigator's discretion while awaiting radiologic confirmation of disease progression.

Patients may receive study treatments while waiting for confirmation of progressive disease (PD) if they are clinically stable as defined by the following criteria:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease by radiographic imaging.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If repeat imaging no longer shows PD but rather CR, PR or SD compared to the initial scan, treatment may be continued/resumed. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target as well as non-target lesions (refer to the Appendix 6).

If the repeat imaging confirms PD, patients should be considered for discontinuation from both investigational products. However, according to the Investigator's clinical judgment and after discussion between the Investigator and the Sponsor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with both investigational products. The Investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data.

Patients who stop treatment for reasons other than toxicity with either or both investigational products and then experience radiologic disease progression shortly thereafter will be eligible for re-treatment with either or both investigational products at the discretion of the Investigator and after discussion with the Sponsor.

5.5. Drug Storage

The investigator, or an approved representative, eg, pharmacist will ensure that the investigational products PF-04518600 and utomilumab are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label. See the IP Manual, package insert or equivalent for storage conditions of the product once reconstituted and/or diluted.

Storage conditions stated in the single reference safety document (SRSD) (ie, investigator brochure [IB]) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the labeled 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 while maintaining appropriate storage conditions (2-8°C) 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. The Investigational Product Manual should be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range.

5.6. Drug Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

To ensure adequate records, all PF-04518600 and utomilumab will be accounted for in the case report form 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]). If Pfizer authorizes destruction at the trial 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. Destruction must be adequately documented.

Under no circumstances should the investigator or other site personnel supply investigational product 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 well-being 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).

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

No additional anticancer treatment including chemotherapy, hormonal therapy (see Section 4.2 Exclusion Criteria, and Section 5.7.2 Supportive Care), or experimental anticancer medications will be 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 or local standard of care.

5.7.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors (G-CSF) is not permitted during the first two cycles but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[93] For Japan only: since the indications and dosages of G-CSF compounds approved in Japan may differ, please refer to Japanese guidelines.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia, except during the DLT observation period. Note that use of erythropoietin for the treatment of anemia in cancer patients is not approved in Japan.

5.7.4. Anti Diarrhea, Anti Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is permitted in this study 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 it must be approved by the sponsor.

5.7.5. Anti-inflammatory Therapy

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

5.7.6. Corticosteroids

Chronic, systemic corticosteroid use (prednisone ≥10 mg/day or dexamethasone ≥1.5 mg/day) 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-04518600/utomilumab administration, required to minimize the potential risk of impaired wound healing, risk of infection and bleeding, has not been determined. Stopping PF-04518600/utomilumab administration is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-04518600/utomilumab treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.7.8. Anticoagulation

Anticoagulation (heparin and factor Xa inhibitors only, no vitamin-K antagonists) will be allowed if indicated. However, perioperative anticoagulant use must be in alignment with the institutional standards for perioperative biopsy procedures.

5.7.9. Radiotherapy

There has been tumor regression observed in a non-irradiated tumor following palliative radiotherapy in a melanoma patient treated with 10 mg/kg of PF-04518600 who had initially met criteria for PD by RECIST. It is possible that radiation may have benefited the anti-tumor immune response from PF-04518600 similar to what has been reported in a preclinical study evaluating the anti-tumor activity of OX40 agonist and radiation.[122]

Consideration may be given for optional radiotherapy administered at palliative doses to a tumor between time of first progression by RECIST and when the patient has confirmed disease progression by irRECIST. The irradiated tumor should preferably be a non-target lesion. If a target lesion is selected for irradiation, there should be other target lesions that can be followed for measurements. Palliative radiotherapy on study is permitted (eg, for the treatment of painful bony or skin lesions) if clinically indicated at any time.

In view of the current lack of data about the interaction of PF-04518600 and/or utomilumab with concurrent radiotherapy, study drug treatment should be interrupted during radiotherapy, stopping 1 day before and resuming treatment at least 1 day after. Planned dosing schedule, treatment fields and technique need to be discussed with and approved by the sponsor's medical monitor before start of treatment.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see Schedule of Activities and Section 7 Assessments.

All patients being considered for the study and eligible for screening must sign an informed consent for the study before completing any study-specific procedures. A patient identification number will be assigned. The investigator (or appropriate delegate at the site) will obtain informed consent from each patient in accordance with the procedures described in the Schedule of Activities and Section 12.3 on Patient Information and Informed Consent.

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

The required screening assessments 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 Assessments Section 7.

6.3. Follow-up Visit

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

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. Late immune related DLT information will also be collected during this visit.

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

Independent to time of disease progression, all patients (unless patients are lost to follow up, consent is withdrawn, or study is discontinued by the sponsor) will be followed for survival for at least 2 years from the time of their first dose of investigational product (s). After the completion of end of treatment visits, Patients will be contacted by phone every 2 months for survival status. However, 2 years from the time of the first dose of investigational product of the last patient enrolled or last surviving patient (whichever is later) the study will be closed.

6.3.1. Follow-Up for Late Immune-Related Events

As outlined in Section 3.2.1 (Late Immune Related DLTs), safety and tolerability assessment for the first 98 days (or completion of 7 cycles) will be taken into account for MTD and RP2D selection. To collect late immune related DLT information, any patient who discontinues after 1 to 4 or 6 cycles of treatment will be contacted by phone as part of the follow up visit. For patients who discontinue after receiving 5 cycles of treatment, late immune information will be collected during the 28 to 35 day follow up visit. If the patient discontinues after receiving 6 cycles of treatment, they will be contacted by phone 14 days (±2 days) after end of treatment (EOT). If the patient discontinues after receiving 4 cycles of treatment, they will be contacted by phone 42 days (±2 days) after EOT. If the patient discontinues after receiving 3 cycles of treatment, they will be contacted by phone 56 days (±2 days) after EOT. If the patient discontinues after receiving 2 cycles of treatment, they will be contacted by phone 70 days (±2 days) after EOT. If the patient discontinues after receiving 1 cycle of treatment, they will be contacted by phone 84 days (±2 days) after EOT. 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 follow up visit completed 28 to 35 days after end of treatment. Patients continuing to experience late immune-related toxicity 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.

6.4. 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 28 days after the last dose of investigational product for adverse events.

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.

1. Reasons for withdrawal of study treatment may include:

- Objective disease progression according to irRECIST* (see Appendix 5 and Appendix 6),[85-87]
- 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.

2. Reasons for withdrawal from study follow-up may include:
   - Completed study follow-up;
   - Study terminated by sponsor;
   - Lost to follow-up;
   - Refusal for further follow-up for survival;
   - Death.

*In the case of radiological progression (especially per standard RECIST) but in the absence of clinical deterioration, if investigator deem it is in the best interest of the patient, the patient will be allowed to stay on study.

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

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 the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

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

7.1.1. Pregnancy Testing

For female patients of childbearing potential (that is, patients who are not defined as a patient of non-child bearing potential, see Section 4.3 [Lifestyle Guideline]), a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on 2 occasions prior to starting study treatment-once at the start of screening and once at the baseline (C1D1) visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy 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, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from study medication but may remain in the study. Additional pregnancy tests may also be undertaken if requested by institutional review board (IRB)/institutional ethics committee (IECs) or if required by local regulations.

Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the adverse events 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 human immunodeficiency virus (HIV) serology testing should be conducted at screening. All Part A2 HCC patients with detectable viral load for hepatitis B at screening must also be tested for hepatitis D by antibody (HDV Ab) or polymerase chain reaction (PCR). All Part A2 HCC patients with detectable viral load for HCV or HBV at screening, must be retested for viral load every 3 months (ie, Cycle 7 Day 1, Cycle 13 Day 1, Cycle 19 Day 1, etc) and at the EOT visit. Other tests may be conducted per standard practice to confirm an active hepatitis or HIV infection. In Part B, history of human papilloma virus (HPV) will be recorded for HNSCC patients.

All laboratory safety assessments conducted on Cycle 1 Day 1 (C1D1) must be completed within 48 hours prior to dosing. Prior to dosing a patient, safety assessments (hematology, chemistry, coagulation and urinalysis) must be reviewed by a physician. If screening assessments are performed within 72 hours prior to C1D1, there is no need to repeat hematology, chemistry or coagulation assessments on C1D1. If screening assessments are performed within 7 days of C1D1, there is no need to repeat urinalysis 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.

If abnormalities are observed in Thyroid-stimulating hormone (TSH) values, a T4 thyroxine test will be performed.

For HCC patients, alpha fetoprotein levels will be evaluated at screening and every 6 weeks until confirmed progressive disease in Part A1, every 8 weeks until Week 48 and then every 12 weeks until confirmed progressive disease in Part A2.

For patients with previous history of anthracycline treatment and who are not at high risk of cardiac failure (ie, those patients that have NYHA Class I), troponin I (troponin T is allowed if the assay utilized can be verified to have cardiac specificity) and N-terminal of the prohormone brain natriuretic peptide (Nt-proBNP) levels will be evaluated every other cycle and when clinically indicated.

Hematology	Chemistry	Coagulation	Serology	Urinalysis	Pregnancy Test	Cardiac Enzymes
Hemoglobin	ALT	PT or INR	HBsAg, HBcAb	Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine (to be specified in the protocol)	Troponin I or T (if verified)
Platelets	AST	PTT	HCV Ab			Nt-proBNP
WBC	Alk Phos		HIV serology			
Neutrophils	GGT		HDV Ab or PRC			
Lymphocytes	Sodium		Hepatitis B quantitative test			
Monocytes	Potassium		Hepatitis C quantitative test			
Eosinophils	Magnesium			Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)		
Basophils	Chloride					
Hematocrit	Total Calcium					
	Total Bilirubin***					
	BUN or Urea					
	Creatinine					
	Uric Acid					
	Glucose (non-fasted)					
	Albumin					
	Phosphorous or Phosphate					
	lipase					
	amylase					
	TSH					
	Alpha fetoprotein for HCC patients					

*** For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

7.1.4. Vital Signs and Physical Examination

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

7.1.5. (12-Lead) Electrocardiogram

Electrocardiogram (ECG): A single 12-lead (with at least a 10-second rhythm strip) tracing will be used for the screening ECG. Triplicate 12-lead (with at least a 10-second rhythm strip) tracing will be used for all other scheduled ECGs. Unscheduled visits do not require triplicate ECGs. It is preferable that the machine used has a capacity to calculate the

standard intervals automatically. All 12-lead ECGs will be reviewed by a central laboratory. At each time point (see the Schedule of Activities) three consecutive ECGs will be performed at approximately 1-5 minutes apart to determine the mean QTcF interval. Fridericia's formula (QTcF) is calculated as follows:

$QTcF = QT / (RR)^{0.33}$

If the mean QTcF is prolonged (>501 msec, ie, ≥ CTC AE Grade 3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >501 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 501 msec. If QTcF interval reverts to less than 501 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 501 msec the investigational product will be held until the QTcF interval decreases to 480 msec. Patients will then re-start the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to 480 msec after 2-weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from study drug. Additional triplicate ECGs may be performed as clinically indicated.

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

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

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).

7.1.6. Echocardiogram or Multigated Acquisition (MUGA) Scan

Echocardiogram or multigated acquisition (MUGA) will be evaluated in patients with previous history of anthracycline treatment. For these patients, an echocardiogram or MUGA will be performed at screening and every 3 months whilst on treatment and when clinically indicated. An echocardiogram or MUGA will be performed at the end of treatment (EOT) visit if not performed within 3 months of discontinuation. The following parameters will be evaluated: ventricular function (including left ventricular ejection fraction [LVEF], end systolic volume [ESV] and end diastolic volume [EDV]), qualitative evaluation of chamber size, and wall motion. A Doppler examination will be completed and should include an assessment of mitral valve, atria, right ventricle, tricuspid valve, aortic valve, pulmonic valve, great vessels, and pericardium.

7.2. Pharmacokinetics Assessments

7.2.1. Blood for PK Analysis of PF-04518600 and Utomilumab

For both Part A Monotherapy and Part B Combination Therapy, blood samples for the analysis of PF-04518600 concentrations will be collected into appropriately labeled tubes at times specified in the Schedule of Activities of the protocol. For each analysis, 5 mL of blood samples will be collected to provide approximately 2 mL serum. The PK sampling schedule may be modified based on emerging PK data.

For Part B Combination Therapy only, blood samples (2 mL whole blood at each time point) will be collected to provide serum for PK analysis of utomilumab as outlined in the Schedule of Activities. The PK sampling schedule may be modified based on emerging PK data.

The 1 hr samples should be collected immediately before the infusion ends for the corresponding investigational agent from the contra-lateral arm of the infusion.

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

Where noted in the Schedule of Activities, blood samples for PF-04518600 (both Part A and Part B) and utomilumab (Part B only) concentrations will be collected at approximately the same time as pharmacodynamic samples whenever possible.

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. Samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will be not be captured as a protocol deviation. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor. Additional instructions for sample collection, processing, storage and shipping will be provided in the lab manual.

PK samples will be assayed for PF-04518600 (both Part A and Part B) and utomilumab (Part B only) using validated analytical methods in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases.

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

Anti-tumor clinical activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the applicable Schedule of Activity, whenever disease progression is suspected (eg, symptomatic deterioration), until confirmed progressive disease or start of subsequent anticancer therapy whichever comes first.

Assessment of tumor response will be made using RECIST version 1.1 (Appendix 5)[85] and irRECIST response criteria (Appendix 6).[86,87]

All patients' files and radiologic images must be available for source verification and for potential peer review.

CCI

CCI

[redacted]

7.6. Immunogenicity Evaluations

Bioanalysis to assess for anti-drug (PF-04518600 or utomilumab) antibodies (ADA) will be performed. All samples that are positive in a screening assay will be further characterized in terms of antibody specificity. A tiered approach to screening, confirmation and titer/quantitation will be utilized. The screening assay with competitive confirmatory steps followed by the titer assay will be used. Samples may also be analyzed in neutralization assays (NAb). Patients having an unresolved adverse event that is possibly related to ADA formation will be asked to return for ADA and drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at

a level acceptable to the investigator, and sponsor concurs with that the investigator's assessment, up to 6 months from the EOT or the day of early withdrawal.

Blood samples (10 mL) to provide approximately 5 mL of serum for ADA and NAb analysis will be collected into appropriately labeled tubes at times specified in the Schedule of Activities of this protocol.

Additional instructions for sample collection, processing, storage, and shipping will be provided in the lab manual.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

As part of understanding the immunogenicity of the investigational product, 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.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequela 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 AEs that are 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 98 calendar days from first administration of the investigational product, or up to 60 days after last administration of investigational product, whichever is later. 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 a serious adverse event occurs after informed consent is signed and before investigational product is administered, this information will be reported on a Serious Adverse Event Form and will be recorded in the safety database.

AEs (non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of study treatment through 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later. However, late immune-related DLTs that are not SAEs need to be collected consistent with Section 3.2.1.

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

8.3. Definition of an Adverse Event

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

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);

- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

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

8.4. Medication Errors

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

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

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

Whether or not the medication error 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 adverse event (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 or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see Section 8.8 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 Section 8.14.1 on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug Induced Liver Injury

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

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

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (x ULN) concurrent with a total bilirubin value ≥2 x ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 x ULN or not available;
- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
    - For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 x ULN, or ≥8 x 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 x ULN **or** if the value reaches ≥3 x ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

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

however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

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

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see Section 8.14 on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

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

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant 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 a an SAE report form and an exposure during pregnancy (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 Section 6.4 Patient Withdrawal)

Withdrawal due to AE 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. Sponsor 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

9.1. Analysis Sets

a. Safety analysis set.

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

b. Full analysis set.

   The full analysis set includes all enrolled patients.

c. Per protocol analysis set (evaluable for MTD).

   The per protocol analysis set includes all enrolled patients who receive at least one dose of study medication and who do not have major treatment deviations during first cycle. Patients with major treatment deviations in DLT observation period are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include:

   - Administration of less than 75% of the planned dose of PF-04518600 provided that the reduction is not due to toxicity attributable to PF-04518600.

   - Administration of more than 150% of the planned dose of PF-04518600.

d. PK analysis sets.

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

e. Immunogenicity assessment sets.

The immunogenicity assessment population is defined as all enrolled patients who receive at least one dose of study medication and have ADA results reported for at least one time point.

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose Escalation/De-Escalation

9.2.1.1. Part A Monotherapy

For the monotherapy portion of the study, a mTPI design[88] will be adopted for dose escalation and de-escalation determination. The mTPI design uses a Bayesian statistics framework and a beta-binomial hierarchical model with prior distribution of DLT set as a beta (0.75, 0.65) to compute the posterior probability of three dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT=0.25, where pT is the target probability). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to target probability (pT), the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level.

Decision rules are based on calculating unit probability mass (UPM) of three dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the under dosing interval is defined as (0; pT-e_1), the over-dosing interval (pT+e_2;1), and the proper-dosing interval (pT- e_1, pT+ e_2), where e_1 and e_2 are small fractions. Based on the safety profile of PF-04518600 as a single-agent in Study B0601002, both e_1 and e_2 are selected as 0.05. Therefore, the target interval for the DLT rate is (0.20, 0.30).

The three dosing intervals and the penalty functions are associated with three different dose-escalation decisions. The under-dosing interval corresponds to a dose escalation (E), over-dosing corresponds to dose de-escalation (D), and proper-dosing corresponds to remaining at the current dose (R). Given a dosing interval and a probability distribution, the unit probability mass (UPM) of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the under-dosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Ji et al.[88] have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

The dose-finding portion of the study is terminated when either approximately 40 DLT evaluable patients have been enrolled or when at least 9 evaluable patients have been treated at the highest dose with mean DLT rate ≤30%, whichever comes first. Refer to Table 3 (Decision Rules) in Section 3.1.5.1 (Criteria for Dose Escalation Part A Monotherapy).

9.2.1.2. Part B Combination Therapy

The dose escalation scheme based on mTPI method described in Section 9.2.1.1 will also be used in Part B Combination Therapy.[88]

9.2.2. Statistical Method for Estimating the MTD

9.2.2.1. Part A Monotherapy

As previously described, the estimated MTD is the highest tested dose level with mean DLT rate ≤0.25 in at least 9 DLT evaluable patients. It is also assumed that at the estimated MTD, less than 17% patients will experience Grade 4 cytokine release syndrome, infusion reaction or allergic reaction during the 28 day DLT observation period, and the first 98 days after initial treatment. It is also assumed that at the estimated MTD less than 33% of patients will experience grade 3 cytokine release syndrome, infusion reaction, or allergic reaction during the first 98 days after treatment. We assume that higher doses of either PF-04518600 result in higher toxicity rates. But, due to the relatively low number of patients that may be potentially allocated to any dose combination, this assumption may be violated.

9.2.2.2. Part B Combination Therapy

The estimated MTD is the highest tested dose combination level with mean DLT rate ≤0.25 in at least 9 DLT evaluable patients. It is also assumed that at the estimated MTD the toxicity of PF-04518600/utomilumab combination follows the monotonicity assumption that a higher dose level of either PF-04518600 or utomilumab will result in a higher toxicity rates.

9.3. Sample Size Determination

A maximum of approximately 210 patients are expected to be enrolled into the study. The total sample size is not based on formal hypothesis testing considerations.

9.3.1. Part A Monotherapy

The number of patients to be enrolled in the study will depend upon the observed safety profile, which will determine the number of patients at each dose level and the number of dose levels explored.

At least 9 patients will be treated at the dose declared as the MTD. If MTD was not reached by definition of safety criteria, this statement will apply for highest tested dose level.

The sample size using the mTPI approach cannot be determined in advance. It is estimated the number of DLT evaluable patients to be enrolled in the dose escalation stage will allow a reliable and accurate estimate of the MTD.

The exact sample size of the mTPI design in Part A1 cannot be pre specified in advance because it is a dynamic feature of the design. The maximum sample size after which the Part A1 will be stopped and MTD declared is 58 patients. Also, a minimum of 9 patients is required to establish the MTD. The actual sample size of Part A1 will depend on the underlying dose toxicity profile and variability in actual data realization.

As for the number of patients treated at each dose, it is expected that the typical number will be 2 to 4 patients for the doses actually studied. For the dose declared as MTD at the end of Part A1, this number will be at least 9 patients.

The planned sample size for Part A2 expansion cohort is up to 40 evaluable patients. An evaluable patient will have both a baseline and on-treatment tumor biopsy. Aggregate toxicity will be monitored for patients in Part A2. DLT will continue to be assessed in Part A2, and data acquired in Part A1 dose-escalation phase and Part A2 dose expansion phase will be combined to assess the toxicity (as suggested by Lasonos and O'Quigley, 2014).[89] In the event the observed toxicity exceeds 30%, a revised MTD may be recommended.

Although the A2 sample size is not based on any statistical considerations, the study would have 69% power to assess an overall response rate of 10% with 20 patients assuming the overall response rate of current therapy is 2%,[96] using a one-sample test under a two-sided α level of 0.1. The study would have about 93% power if the true response rate is 20%. A table of 90% confidence intervals based on observed number of responders is provided below for reference:

Table 7. 90% Confidence Intervals of Overall Response Rate

	N=20	90% Confidence Interval	
Observed Responders	ORR	Lower Limit	Upper Limit
0*	0	0	5.6%
1	5%	0	15.5%
2	10%	0	23.5%
4	20%	2.8%	37.2%
6	30%	10.6%	49.4%
8	40%	19.5%	60.5%

*: with 0.005 continuity correction for confidence interval calculation

9.3.2. Part B Combination Therapy

The number of patients to be enrolled in the study will depend upon the observed safety profile, which will determine the number of patients at each dose combination level and the number of dose levels explored. The maximum sample size after which the Part B1 will be stopped and MTD declared is 55 patients. The total planned sample size for Part B2 expansion cohort is approximately 40 evaluable patients.

At least 9 patients each will be treated at the dose combination level(s) identified as MTD. If MTD was not reached by definition of safety criteria, this statement will apply for highest tested dose combination level.

9.4. Efficacy Analysis

In this FIP study, anti-tumor clinical activity is a secondary objective.

Tumor response in terms of time to progression, tumor progression, duration of response, and best objective response by RECIST and irRECIST will be summarized. Summary tables of response rates, median time to progression and corresponding confidence intervals will be provided Summary tables and figures will be generated by dose levels and/or tumor types. Data 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, progression date, death date, date of first response and last tumor assessment date, and date of last contact will be listed.

9.5. Analysis of Pharmacokinetics

9.5.1. PF-04518600 and Utomilumab PK Analysis

Serum pharmacokinetic parameters including the maximum concentration (C_{max}), and area under the concentration versus time curve within a dose interval (AUC_{τ}) for PF-04518600 (Parts A and B) and utomilumab (Part B only) will be estimated using non-compartmental analysis. If data permit or if considered appropriate, minimum concentration (C_{min}), average concentration (C_{av}), AUC from time zero extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), clearance (CL), apparent volume of distribution (V_{ss}), and accumulation ratio (R_{ac}) will be also estimated. The PK parameters will be summarized descriptively by dose, and cycle.

The concentrations of PF-04518600 (Parts A and B) and utomilumab (Part B only) will be summarized descriptively by dose, cycle, and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose and cycle using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

CCI

9.5.3. Immunogenicity

ADA samples will be analyzed for the presence or absence of anti- PF-04518600 and anti-utomilumab antibodies following a tiered approach using screening, confirmation and titer/quantitation using a validated assay. Samples tested positive for ADA will be further analyzed for NAb using a validated assay. Listings and summary tabulations of the time course data on immune response endpoints will be generated. Potential impact of immunogenicity on PK and clinical response including CCI safety/tolerability and efficacy of ADA will be explored, if data is warranted.

9.5.4. Statistical Analysis of Biomarker Endpoint

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 pharmacokinetic parameters and measures of anti-tumor efficacy.

The percentage change from baseline for CCI over the period of the study will be tabulated by individual. The mean change from baseline values over time per cohort will also be tabulated. Data will be presented in tabular and/or graphical format and summarized descriptively.

[redacted]

9.6. Safety Analysis

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

9.6.1. Analysis of Primary Endpoint

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the Study Design Section 3. Adverse Events constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Endpoints

9.6.2.1. Adverse Events

Adverse Events (AEs) will graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study 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).

9.6.2.2. Laboratory Tests Abnormalities

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

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

9.6.3. ECG

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as results collected at C1D1 prior to dosing. ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, response rate (RR), PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate), and by dose. Individual QT` (all evaluated corrections) intervals will be listed by 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 value and changes from baseline in corrected QT after treatment by 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 value across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT value.

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

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.

9.7. Analysis of Anti-drug Antibody (ADA) for PF-04518600 and Utomilumab

Summary of number of patients developed ADA for PF-04518600 and utomilumab will be tabulated by dose group. Subgroup analysis may be performed to assess the PK or pharmacodynamic response if data warrant.

CCI [redacted]

9.9. Interim Analysis

There is no planned formal interim analysis.

9.10. 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.

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 study site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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

10.1. GCP Training

Prior to enrollment of any patients, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the Study will complete the Pfizer GCP Training or equivalent before performing Study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the Study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

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 investigator's 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 International Conference on Harmonization (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

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

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

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

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 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 is 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 their numerical code to the patient's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient 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 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 IRB/EC 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 European Union 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.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as Last Patient Last Visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-04518600 or PF-04518600 plus utomilumab 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 2 business days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), 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 all 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.

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.

EudraCT

Pfizer posts European (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.

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. ECOG Performance Status

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

*As published in Am J Clin Oncol 5:649-655, 1982.[90]

Appendix 2. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 4.03 date June 14, 2010) has been placed in the Study Manual for this protocol. Alternatively, the NCI CTCAE may be reviewed on-line at the following NCI website:

http://ctep.cancer.gov/reporting/ctc.html

Appendix 3. Child-Pugh Score

Factor	1 point	2 points	3 points
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

The total point score will be used to determine the patient's Child-Pugh class outlined below:

	Class A	Class B	Class C
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Appendix 4. Management of Infusion Related Reactions Including Allergic Reactions, Cytokine Release Syndrome or Anaphylaxis

In the event of infusion related reactions, Investigators should institute treatment measures according to best medical and nursing practice.

The following treatment guidelines should be employed:

If chills and fever (>100.4°F/38.0°C) occur, the infusion should be interrupted. Patients may be treated symptomatically (as described in Section 5.4.5.5 Dose Delay) and the infusion should be restarted at 50% of the original rate.

Hypersensitivity reactions:

1. NCI-CTCAE Grade 1 allergic reaction or cytokine release syndrome.
    - Monitor for worsening condition. If the reaction worsens, stop the infusion. Institute premedication for subsequent infusions as per Section 5.4.5.5 Dose Delay.
2. NCI-CTCAE Grade 2 allergic reaction or cytokine release syndrome.
    - Stop PF-04518600 or PF-05082566 infusion.
    - Administer bronchodilators, oxygen, acetaminophen, etc. as medically indicated.
    - 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 per Section 5.4.5.5 Dose Delay.
3. NCI-CTCAE Grade 3 or Grade 4 allergic reaction or cytokine release syndrome or anaphylaxis.
    - A Grade 3 anaphylaxis (hypersensitivity reaction) consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or hypotension.
    - A Grade 4 anaphylaxis (hypersensitivity reaction) is a life-threatening event requiring urgent intervention.
4. Treatment of Grade 3 or Grade 4 allergic reaction, cytokine release syndrome or anaphylaxis.
    - Stop the PF-04518600 or PF-05082566 infusion immediately and disconnect infusion tubing from the patient.

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

- Telephone Sponsor or designated representative to report an SAE as per Section 8 Adverse Event Reporting.

- For a NCI-CTCAE Grade 3 or 4 hypersensitivity reaction, study treatment will be discontinued.

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

    - Once the PF-04518600 or PF-05082566 infusion rate has been decreased due to an allergic reaction or cytokine release syndrome, it will remain decreased for all subsequent infusions.

    - 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-04518600 or PF-04518600/PF-05082566.

    - 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-04518600 or PF-04518600/PF-05082566.

    - 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.

PK, pharmacodynamic and ADA sampling 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.

Appendix 5. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228-247.[85]

A. Categorizing Lesions at Baseline:

1. 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.

2. 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 patientive to other local treatment) is non-measurable unless it has progressed since completion of treatment.

3. 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.

4. 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.

Note: For the patient population being evaluated in this protocol, the baseline assessment may be completed within 6 weeks prior to randomization.

5. 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.

6. Non-target Disease:

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

B. 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.

1. Target Disease:

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

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

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

- Objective Progression (PD): 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.

2. 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.

3. 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.

4. 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.

5. 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 8. 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 will be used:

Table 9. 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 6. Immune-related Response Criteria Derived From RECIST v1.1 (irRECIST)

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

This is particularly true for immunotherapeutic agents such as anti-CTLA-4, anti-PD-1 and anti PD-L1 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.[86,91] 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.[87,92]

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 and designated Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST).[86]

For irRECIST, only target and measurable lesions are taken into account.

In contrast to RECIST 1.1, 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 per 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 responses are 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 longest diameters of target and new measurable lesions decreases ≥30%.

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

- **Overall immune-related progressive disease (irPD)**: Sum of the longest diameters 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.

In order to be selected as new measurable lesions (≤2 lesions per organ, ≤5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively.

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

Table 10. Overall Responses derived from Changes in Index, Non-index, and New Lesions

Measurable Response **Tumor burden**[a]	Non-Measurable Response		Overall Response using irRECIST[b]
	Non-index lesions	New, non-measurable lesions	
↓ 100%	Absent	Absent	irCR
↓ 100%	Stable	Any	irPR
↓ 100%	Unequivocal Progression	Any	irPR
↓≥30%	Absent/ stable	Any	irPR
↓≥30%	Unequivocal Progression	Any	irPR
↓<30% and ↑ <20%	Absent/ Stable	Any	irSD
↓<30% and ↑ <20%	Unequivocal Progression	Any	irSD
↑≥20%	Any	Any	irPD

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