# A FIRST-IN-HUMAN PHASE 1, DOSE ESCALATION, SAFETY AND PHARMACOKINETIC STUDY OF PF-06647020 IN ADULT PATIENTS WITH ADVANCED SOLID TUMORS

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| **Compound:** | PF-06647020 |
| **Compound Name:** | Not applicable (N/A) |
| **United States (US) Investigational New Drug (IND) Number:** | CCI [redacted] |
| **European Clinical Trials Database (EudraCT) Number:** | 2014-003296-36 |
| **Protocol Number:** | B7661001 |
| **Phase:** | 1 |

[redacted]

## Document History

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| Amendment 8 (United Kingdom only) | 09 November 2017 | The following changes are only for sites in the UK:<br><br>Section 4.3 Lifestyle Guidelines: Clarification added that a condom with or without spermicide is not considered a highly effective method of contraception in the UK.<br><br>Section 4.3 & Appendix 8, Section A6.2 Exclusion Criteria: Additional criteria added to clarify that male patients must use contraception methods for an additional 90 days (120 days for single agent, 150 days for combination) and that female partners of male patients must use a highly effective method of contraception. |
| Amendment 7 | 15 May 2017 | Study Design Section and Section 3.1 Study Overview: Addition of Q2W regimen expansion sub-study, avelumab background/rationale for the Q2W combination cohort, and removal the Japanese PK/Safety sub-study (including revision to objectives/endpoints). Increased number of patients (~190) and sites (~15-20).<br><br>Schedule of Activities for Q3W Regimen: Modified Day 8 assessments for patients beginning at Cycle 8.<br><br>Section 1.2.4 Clinical Safety (PF-06647020): Updated clinical safety, PK and efficacy data.<br><br>Sections 1.9 Rationale for Japanese Sub-Study: This section was deleted and sub-study no longer planned, no patients were enrolled under this sub-study.<br><br>Section 9.1 Analysis Sets: Addition of immunogenicity and [redacted]<br><br>Section 9.5.1 Analysis of Pharmacokinetics: |

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| | | Clarification was made to specific PK parameter to be calculated; $V_{ss}$ was added to replace $V_d$.<br><br>Reference Section: Included new references.<br><br>Appendix 8 Replace Japanese Sub study with Q2W Regimen Expansion Sub-Study: Details provided for Q2W regimen expansion, including a Schedule of Activities tables.<br><br>All other changes are minor in nature added to this amendment to provide clarity and additional information. |
| Amendment 6 | 26 September 2016 | Study Design: Addition of Japan sub-study to evaluate safety and pharmacokinetics (PK) in approximately 12 patients.<br><br>Study Design: Increased number of sites participating in Part 2 (8-12 sites).<br><br>Study Objectives and Endpoints for Part 2: Addition of primary and secondary objectives/endpoints as a result of inclusion of the Japanese sub-study.<br><br>CCI [redacted]<br><br>Section 1.9 Rationale for Japanese Sub-Study and Section 1.9.1 Starting dose in Japanese Patients: Included to provide rationale and information on doses that will be evaluated.<br><br>Section 4.1 Inclusion Criteria 2.c.2 and 2.c.3: Added liposomal doxorubicin as approved agent for second and third prior line of therapy.<br><br>Section 7.5.2 Immunophenotyping: Clarified that Japanese patients will not have immunophenotyping collection/analysis. |

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| | | Section 9.5.1 Analysis of Pharmacokinetics and Section 9.6 Safety Analysis: Clarified that there will be separate summaries of PK and safety parameters for DDI and Japanese patients.<br><br>Appendix 8. Japanese Sub-Study: Details provided for Japanese sub-study, including a Schedule of Activities table. |
| Amendment 5 | 06 July 2016 | Study Design, Section 3.5 Dose Expansion Phase (Part 2), Section 9.3 Sample Size Determination: Additional enrollment of 25 OVCA patients in Part 2 included.<br><br>Section 1.7 Clinical Experience: Updated clinical experience data included.<br><br>Section 5.7.4 Anti Diarrhea, Anti Emetic Therapy: Updated to allow for prophylaxis prior to Cycle 1 and subsequent cycles.<br><br>Section 7.1.3 Laboratory Safety Assessments: Updated to align with current Protocol Template.<br><br>CCI [redacted]<br><br>[redacted]<br><br>Section 7.7 Immunogenicity Evaluations: Revised to be consistent with language in Schedule of Activities footnote.<br><br>Section 7.8.2 Additional Research: Updated to align with current Protocol Template.<br><br>Section 10 Quality Control and Quality Assurance, Section 11 Data Handling and Record Keeping, Section 12 Ethics, Section |

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|---|---|---|
| | | 14 Sponsor Discontinuation Criteria, Section 15 Publication of Study Results: Updated to align with current Protocol Template. |
| Amendment 4 | 20 January 2016 | Study Design, Objectives and Endpoints: Included new requirement for pre-selection of TNBC Part 2 patients. Clarified that all analytes are being analyzed for the DDI sub study.<br><br>Section 1.5 PTK7 IHC Assay for PTK7 Expression, CCI [redacted]<br><br>Section 1.7 Clinical Experience: Updated clinical experience data included.<br><br>CCI [redacted]<br><br>Section 7.2.1 Blood for PK analysis of ADC, Total Antibody, and Unconjugated Payload: Clarified protocol allowed windows for PK sampling.<br><br>Appendix 7 Drug-Drug Interaction Sub-Study and respective Schedule of Activity tables: Clarified that the 1st dose fluconazole will be administered on C1D21. Clarified that Cycles 1 and 4 will have the same PK sampling requirements. |
| Amendment 3 | 03 December 2015 | Background and Rationale: Included ovarian cancer (OVCA) background information.<br><br>Study Design, Objectives, and Endpoints: Included 20 OVCA patients and a drug-drug |

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| | | interaction (DDI) sub-study.<br><br>Schedule of Activities: Modified Day 8 assessments for patients beginning at Cycle 13. Addition of CA-125 serum biomarker for OVCA patients.<br><br>Section 1.7 Clinical Experience: Updated clinical experience data included.<br><br>Section 1.8 Rationale for Drug-Drug Interaction: Rationale provided.<br><br>Section 4.1 Inclusion Criteria: Additional criteria added for OVCA patients.<br><br>Appendix 7 Drug-Drug Interaction Sub-Study: Details provided for DDI study, including a Schedule of Activities table. |
| Amendment 2 | 05 August 2015 | Background and Rationale: Provided Pfizer internal data that PTK7 expression is observed in ~84% of TNBC and NSCLC patients selected by PTK7 expression may be more likely to benefit.<br><br>Study Design: Part 2 patients will be enrolled at the recommended Phase 2 dose, as selected by the Sponsor and Investigators. CCI [redacted]<br><br>Study Design: Increased number of sites participating in Part 2 (8-10 sites).<br><br>Schedule of Activities: Removed requirement that treatment must begin within 3 days of registration.<br><br>CCI [redacted] |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | CCI [redacted]<br><br>Section 1.5 PTK7 Immunohistochemistry (IHC) Assay for PTK7 Expression: Added detail regarding assay to be utilized for Part 2.<br><br>Section 1.6 Triple Negative Breast Cancer and NSCLC in Dose Expansion: Provided rationale for selecting TNBC and NSCLC indications.<br><br>Section 1.7 Clinical Experience: Provided ongoing study information for dose escalation portion.<br><br>CCI [redacted]<br><br>Section 4.2 Exclusion Criteria: Revised Exclusion 2 to exclude anti-cancer therapy |

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| | | within 3 weeks or 5 half-lives.<br><br>Section 4.3 Lifestyle Guidelines: Updated to align with updated Protocol Template.<br><br>Section 5.4.2 Dose Interruptions/Delays: Revised to allow patients more than 2 week delay if discussed and agreed with Sponsor.<br><br>Section 5.7.4 Anti Diarrhea, Anti Emetic Therapy: Revised to clarify that prophylaxis is permitted in subsequent cycles.<br><br>Section 6.4 Patient Withdrawal: Included section covering withdrawal due to disease progression, allowing patients to continue on study due to potential delayed response phenomena.<br><br>Section 7.1.5 12-lead ECG: Clarified measurements to be recorded from ECG.<br><br>CCI [redacted]<br><br>[redacted]<br><br>Section 8 Adverse Event Reporting updated to align with updated Protocol Template.<br><br>Section 15 Publication of Study Results: Updated to align with updated Protocol Template. |
| Amendment 1 | 22 Sep 2014 | Schedule of Activities: Remove language regarding repeat C1D1 coagulation and urinalysis samples. Rationale: it is not applicable for this study.<br><br>CCI [redacted] |

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| | | CCI [redacted]<br><br>Section 3.2 Dose Escalation Phase Table 2: Inclusion of definition for U: unacceptable toxicity. Rationale: previously omitted.<br><br>Section 3.3 DLT Definition: Include ALT or AST ≥3.0 x ULN concurrent with elevation in bilirubin ≥2.0 x ULN as a DLT. Rationale: requested by the FDA.<br><br>Section 3.4 MTD Definition and 9.2 Statistical Method for Estimating the MTD: Revise the definition of the MTD to be the highest dose with a DLT <33%. Rationale: requested by the FDA.<br><br>Section 4.1 Inclusion Criteria: Revision to the inclusion criteria for NSCLC patients. Rationale: Requested by the FDA.<br><br>Section 4.2 Exclusion Criteria: Add language to provide clarity. Rationale: to make criteria more clear.<br><br>Section 4.2 Exclusion Criteria and 5.7 Concomitant Treatment(s): Exclude the use of strong CYP3A inhibitors or inducers for patients enrolled in Part 1. Rationale: Requested by the FDA<br><br>Section 5.4 Administration: Inclusion of language regarding treatment measures for infusion reactions and reference to Appendix 5. Rationale: requested by the FDA.<br><br>Section 5.4.3 Dose Reductions: Add to Table 4: ALT or AST ≥3.0 x ULN concurrent with elevation in bilirubin ≥2.0 x ULN as treatment termination. Rationale: Requested by the FDA. |

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| | | Section 7.1.3 Laboratory Safety Assessments: Add it is acceptable for absolute or % values for lymphocytes, monocytes, eosinophils and basophils. Rationale: provide flexibility to sites.<br><br>CCI [redacted] and<br>7.6 Immunogenicity Evaluations: Revise the amount of serum collected from whole blood samples. Rationale: incorrect conversion provided. |
| Original protocol | 18 Jul 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.

## PROTOCOL SUMMARY

### Background and Rationale:

Antibody-drug conjugates (ADCs) were developed to improve the therapeutic indices of cytotoxic anti-cancer agents. The strategy makes use of an immunoconjugate in which a cytotoxic agent is chemically or enzymatically linked to an antibody that selectively binds to an internalizing tumor-associated antigen. This strategy allows specific delivery of the cytotoxic agent to the tumor site while minimizing the exposure to normal tissues.

PF-06647020 is an anti-PTK7 ADC intended to be for the treatment of patients with cancer. PF-06647020 is comprised of a humanized anti-PTK7 monoclonal antibody (mAb) linked to an auristatin (Aur0101) via a cleavable cysteine-reactive linker. Auristatins are fully synthetic dolastatin-based pentapeptide inhibitor of tubulin polymerization that induce G2/M cell cycle arrest and cell death at low picomolar intracellular concentrations.[13,14]

PTK7 is a phylogenetically conserved member of the pseudokinase family of receptor tyrosine kinases (RTKs) with no observable kinase activity.[4] Genetic and biochemical studies in multiple organisms have demonstrated a key function for PTK7 in planar cell polarity via the Wnt-pathway signaling, and PTK7-deficient embryos have developmental defects.[3,7,11] In addition, PTK7 promotes cell survival in colorectal cancer and acute myeloid leukemia (AML), and PTK7 may promote resistance to chemotherapy in AML.[9,12] Bioinformatics and literature analysis have revealed that PTK7 mRNA expression levels in many types of tumors are higher than corresponding normal tissues including bladder, brain, breast, colorectal, gastric, kidney, liver, lung, pancreatic and skin cancer. In addition, PTK7 was found to be enriched in cancer stem cells (CSCs), also known as tumor-initiating cells, harvested from patient-derived xenografted tumor models of triple negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC) in preclinical studies.[19] It was also reported that higher expression of PTK7 is linked to poor prognosis in patients with NSCLC and TNBC who received chemotherapy, particularly in a subgroup patient population who received anthracycline treatment.[2,19] In preclinical studies, PF-06647020 induced sustained tumor regressions in models of ovarian cancer (OVCA), NSCLC and TNBC.[19]

TNBC accounts for 15% to 20% of breast cancers and is diagnosed based on lack of estrogen receptor (ER) and progesterone receptor (PgR) expression by immunohistochemistry (IHC) and lack of HER2 over expression or gene amplification by IHC or in situ hybridization, respectively. TNBC is a heterogeneous disease, not only on the molecular level, but also on the pathologic and clinical levels. The majority of patients with TNBC respond with high sensitivity to chemotherapies including anthracyclines and taxanes in the neoadjuvant or adjuvant settings. However, TNBC is associated with a significantly higher probability of relapse and poor overall survival (OS) in the first few years after diagnosis compared with other breast cancer subtypes. Positive expression of PTK7 in TNBC was observed in ~84% of archived samples surveyed using a research grade IHC assay (Pfizer internal data).

NSCLC accounts for approximately 85% cases of lung cancer, the leading cause of cancer-related mortality in the United States (US) and worldwide. Most patients with NSCLC have locally advanced and distant metastatic disease (stage III/IV) at the time of presentation, which is associated with a poor prognosis with 5-year OS rate less than 10%. Although targeted therapies (eg, Erlotinib and Crizotinib) for patients with NSCLC whose tumors carry epidermal growth factor receptor (EGFR) mutation or are anaplastic lymphoma kinase (ALK)-positive have provided encouraging clinical outcome and promising immunotherapies are being developed, the unsatisfactory treatment outcomes in advanced NSCLC highlights the need of novel alternative therapies. In addition, PTK7 expression in NSCLC was observed to cover a dynamic range (Pfizer internal data), suggesting that patient selection by PTK7 expression levels may identify patients that may be more likely to benefit.

OVCA is the 6$^{th}$ most common malignancy in developed countries with approximately 100,000 new cases resulting in nearly 65,000 deaths per year.[15] Patients are typically treated with surgery followed by chemotherapy. Initial therapy consists of combinations with platinum-containing agents which results in responses in 70-80% of patients. However, the disease relapses in almost all patients requiring further therapy. The timing of the relapse from the end of the platinum-containing regimen has been shown to be prognostic with platinum-resistant tumors (defined as progression while receiving initial therapy or relapse <6 months from end of initial regimen), as having the worst outcomes.[16] Pegylated doxorubicin and topotecan are both indicated as single agents in patients with refractory OVCA. In patients with platinum-resistant disease, both of these compounds result in response rate (RR) of 10-15%, progression free survival (PFS) of 14 weeks, and OS 35-40 weeks highlighting the need for alternative therapies.[16]

Avelumab (MSB0010718C), a fully human antibody of the immunoglobulin G1 (IgG1) isotype, specifically targets and blocks programmed death-ligand 1 (PD-L1), the ligand for programmed death 1 (PD-1) receptor. This interaction inhibits the suppressive effects of PD-L1 on cluster of differentiation 8 (CD8) positive T cells, and thus restores the cytotoxic T cell response against the tumor. In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity.[20] Broad expression of PD-L1 was observed in ovarian cancer samples, and higher expression of PD-L1 was associated with significantly worse prognosis.[32] Preliminary data from the ongoing OVCA Study EMR 100070-001, which is being conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004) showed an overall response rate (ORR) of 10.7% (8/75) and stable disease (SD) in an additional 44% (33/75) of patients with advanced OVCA.

Available adverse event (AE) and laboratory abnormality data from patients with advanced solid tumors treated with single-agent avelumab suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and immune related Adverse Events (irAEs)/autoimmune disorders have been identified as important risks for avelumab.

Several lines of evidence suggest that combining the PTK7-targeted ADC with avelumab would improve clinical outcomes. In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity.[20] A recent preclinical study demonstrated that immunotherapy can be enhanced by localized chemotherapy but not systemic chemotherapy;[21] indeed the PTK7-targeted ADC delivers a potent chemotherapy preferentially to the tumor cells and thus is distinguished from standard chemotherapies. In addition, the PTK7-targeted ADC could stimulate anti-tumor immunity (and thus stimulate the response to avelumab) by multiple mechanisms: (1) auristatins can activate dendritic cells (Pfizer, unpublished data), and the expression of PTK7 on dendritic cells could increase the delivery of auristatin to those cells; (2) anti-angiogenic activity can promote immune cell infiltration into tumors, and the PTK7-targeted ADC specifically inhibits angiogenesis; (3) immunogenic cell death can stimulate anti-tumor immunity, and auristatins induce this phenotype in cancer cell lines.[19]

This is a first in human Phase 1, safety, pharmacokinetic (PK), and efficacy study of PF-06647020 in adult patients with advanced solid tumors, initially containing two parts: dose escalation (Part 1) in patients with advanced solid tumors, followed by dose expansion (Part 2) in OVCA, TNBC, and NSCLC patients on a dosing schedule of every 3 weeks (Q3W). The study has been expanded (Amendment 7) for safety, PK, and efficacy evaluation on a dosing schedule of every 2 weeks (Q2W) as a single agent treatment of PF-06647020 in OVCA and NSCLC, as well as combination treatment of PF-06647020 with avelumab in OVCA patients.

The design and procedure details of the Q2W regimen expansion unique from the main study can be found in Appendix 8.

**Study Objectives and Endpoints (Original Protocol through Amendment 6)**

**Dose Escalation (Part 1) Objectives**

**Primary Objectives**

- To assess safety and tolerability at increasing dose levels of PF-06647020 administered intravenously on an every 21-day dosing schedule to patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available.

- To determine the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

**Secondary Objectives**

- To evaluate the overall safety profile.

- To characterize the single and multiple dose PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101).

- To evaluate the immunogenicity as measured by presence of anti-drug antibodies (ADA) in patients treated with PF-06647020.

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

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**Dose Expansion (Part 2) Objectives**

**Primary Objective**

- To further evaluate safety and tolerability of PF-06647020 at the MTD and to establish RP2D in patients with NSCLC, TNBC and OVCA.

**Secondary Objectives**

- To evaluate the overall safety profile at the RP2D.

- To evaluate preliminary anti-tumor activity of PF-06647020 at the RP2D in patients with NSCLC, TNBC and OVCA.

- To characterize the single and multiple dose PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101).

- To evaluate the immunogenicity as measured by presence of ADA in patients treated with PF-06647020.

- To evaluate the effect of the co-administration of fluconazole on the PK of unconjugated payload (PF-06380101), ADC (PF-00647020) and total antibody (hu6M024 mAb) following administration of ADC (PF-06647020).

- To assess the effects of fluconazole on the safety and tolerability of a single dose of PF-06647020.

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**Primary Endpoints**

**Primary Endpoints (Part 1)**

- First cycle Dose Limiting Toxicities (DLTs) in order to determine the MTD and RP2D of PF-06647020 administered by intravenous (IV) infusion in a 21-day dosing cycle.

**Secondary Endpoints (Part 1)**

- Adverse events as characterized by type, frequency, severity [as graded by National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE v.4.03)], timing, seriousness and relationship to study treatment.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.
- Single and multi-dose PK parameters of multiple analytes [ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101)].
- Incidence of anti-PF-066407020 antibodies.
- Preliminary evidence of anti-tumor activity based on RR, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.

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**Primary Endpoints (Part 2)**

- Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study treatment.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

**Secondary Endpoints (Part 2)**

- Objective response (OR), Duration of Response (DoR), Disease Control (DCR), Time to Progression (TTP), and PFS, as determined by Investigator [as assessed by RECIST version 1.1].
- Single and multi-dose PK parameters of multiple analytes (ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101).

- Incidence of anti-PF-066407020 antibodies.

- The PK parameters of multiple analytes [ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101)] following ADC (PF-06647020) administration alone and when co-administered with fluconazole.

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**Objectives and Endpoints for Q2W Regimen Expansion**

**Primary Objectives**

- Part 1: To assess safety and tolerability at increasing dose levels of PF-06647020 administered intravenously as a single agent on a Q2W dosing schedule.

- Part 1: To determine the MTD and select the RP2D of PF-06647020 as a single agent treatment on a Q2W dosing schedule.

- Part 2: To evaluate the overall safety profile of PF-06647020 as a single agent and in combination with avelumab at Q2W dosing schedule in OVCA and NSCLC patients at the RP2D.

**Secondary Objectives**

- To characterize the single and multiple dose PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101) when PF-06647020 administered alone or on combination with avelumab, and PK of avelumab.

- To evaluate the immunogenicity as measured by presence of ADA in patients treated with PF-06647020 or PF-06647020 in combination with avelumab.

- To evaluate anti-tumor activity of PF-06647020 as a single agent and when given in combination with avelumab in patients with OVCA and NSCLC.

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**Primary Endpoints**

- Part 1: First Cycle DLTs for the dose escalation portion. A cycle is 28 days in duration.
- Part 2: AEs (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate); or electrocardiograms (ECGs).

**Secondary Endpoints**

- Pharmacokinetics: PK parameters of PF-06647020, total antibody (hu6M024 mAb), unconjugated payload (PF-06380101), and avelumab.
- Immunogenicity: Incidence of ADA and neutralizing antibodies (Nab) against PF-06647020 and avelumab.
- Efficacy: OR, DoR, DCR, TTP, and PFS, as determined by Investigator [As assessed by RECIST version 1.1]. (Appendix 2).

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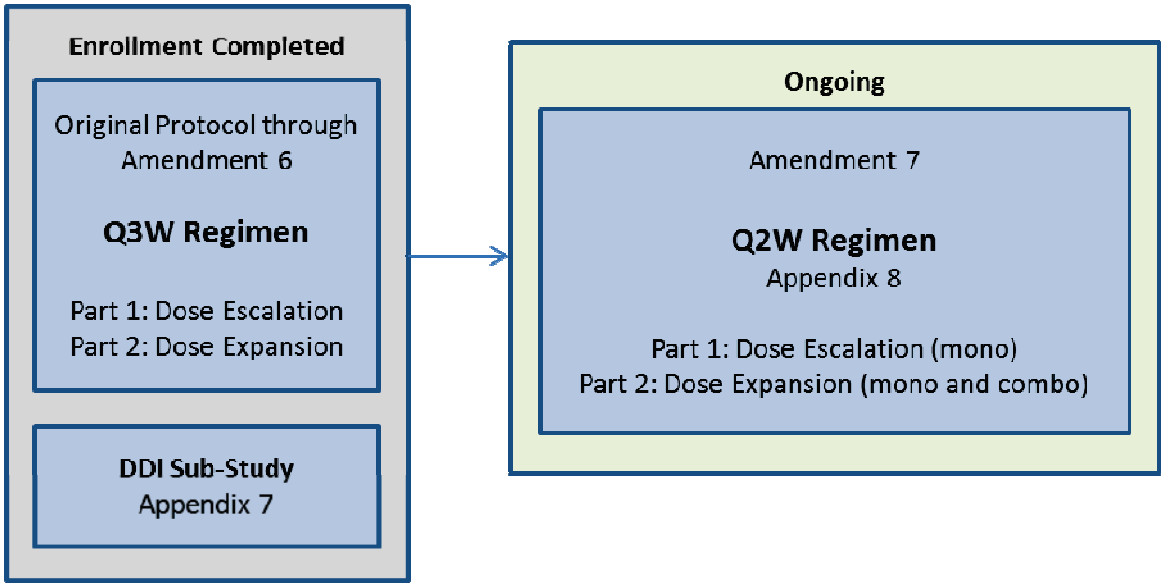
**Study Design:**

This is a Phase 1, open label, multi-center, non-randomized, multiple dose, safety, PK and pharmacodynamic study, initially designed to evaluate single agent PF-06647020 in sequential cohorts of adult patients with advanced solid tumors for whom no standard therapy is available. Successive cohorts of patients received doses of PF-06647020 intravenously Q3W starting at a dose of 0.2 mg/kg. This study has been expanded for safety, PK, and efficacy evaluation of PF-06647020 following a Q2W dosing schedule as a single agent treatment in OVCA and NSCLC patients, as well as combined treatment of PF-06647020 with avelumab in OVCA patients.




Initial Design: Q3W Regimen (Original Protocol through Amendment 6)

This clinical study will include two parts. Part 1 will estimate the MTD/RP2D in dose escalation cohorts in patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available. Part 2 will include approximately 87 patients enrolled at a RP2D selected by the Sponsor and Investigators from Part 1, to explore benefit from treatment and to better define the safety profile, as well as the RP2D. This expansion cohort will include approximately 22 patients with metastatic or recurrent TNBC, 45 patients with advanced epithelial ovarian cancer, primary peritoneal or fallopian tube cancer (OVCA) and 20 patients with advanced NSCLC. CCI

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A drug-drug interaction (DDI) sub-study for evaluating the effect of multiple-dose fluconazole on the PK of unconjugated payload (PF-06380101) is currently ongoing. The DDI sub-study is an open-label, 2-period, fixed sequence design in up to 10 patients to determine the effect of multiple-dose fluconazole, a model moderate CYP3A4 inhibitor, on the PK of PF-06380101 (payload), when fluconazole is co-administered with PF-06647020. This sub-study will be set up as a separate cohort from above mentioned studies in TNBC, NSCLC and OVCA, and the sub-study design and procedure details can be found in Appendix 7.

Current Q2W Regimen Expansion (Amendment 7)

The Q2W regimen expansion is designed to evaluate safety, PK and anti-tumor efficacy of a Q2W dosing schedule as a single agent treatment of PF-06647020 in patients with OVCA and NSCLC, and combined treatment of PF-06647020 with avelumab in OVCA patients. If supported by safety and anti-tumor efficacy, additional combination study of PF-06647020 with avelumab may also be investigated (eg, in approximately 24 patients with NSCLC). The study contains two parts, a Part 1 dose escalation to evaluate safety, PK and preliminary anti-tumor efficacy of PF-06647020 as a single agent treatment, and a Part 2 dose expansion to evaluate safety, PK and efficacy of PF-06647020 as single agent treatment and in combination with avelumab.

Part 1 contains a dose escalation scheme to estimate the MTD/RP2D of PF-06647020 as single agent treatment in patients with platinum-refractory or resistant OVCA and patients with recurrent NSCLC (in approximately 20 patients) using modified toxicity probability interval (mTPI) method. Successive cohorts of patients will receive doses of PF-06647020 starting at a dose of 2.1 mg/kg, Q2W. Once a RP2D is determined and preliminary efficacy is observed, dose expansion (Part 2) will be started to further investigate safety, PK and efficacy of Q2W PF-06647020 in three cohorts of patients:

- Cohort 1: PF-06647020 as a single agent treatment in patients with platinum resistant or refractory OVCA.
- Cohort 2: PF-06647020 as a single agent treatment in patients with recurrent advanced NSCLC.
- Cohort 3: PF-06647020 in combination with avelumab in platinum resistant or refractory OVCA.

Approximately 24 patients will be enrolled for each cohort. Patients that were enrolled in the Part 1 single agent dose escalation will be counted as part of the 24 patients in their respective Part 2 single agent cohorts. Additional cohorts (eg, approximately 24 patients with recurrent advanced NSCLC) receiving combination of PF-06647020 with avelumab may also be considered for inclusion at a later time, if supported by safety and anti-tumor activity observed in Cohort 2.

In the combination expansion cohort(s), the RP2D of PF-06647020 as determined by Part 1 will be used as the dose to combine with avelumab at 800 mg (both administered IV, Q2W). The PF-06647020 dose may be reduced (but not further escalated) for safety reasons. After at least 6 patients in the combination cohort have completed a minimum observation period of 4 weeks, safety will be reviewed by the investigators and Pfizer (using the same DLT definition described in Section A4.2). If there are no safety concerns precluding continuation of the study, enrollment of the remaining patients for this cohort will proceed. If DLT is observed in 2 out of 6 patients, at least 6 additional patients will be enrolled at a reduced dose of PF-06647020 (the reduced dose of PF-06647020 could be one dose level below the defined RP2D from Part 1 assuming the RP2D is above the starting dose of Part 1 (ie, 2.1 mg/kg), or 1.8 mg/kg of PF-06647020 in a circumstance that the RP2D from Part 1 is 2.1 mg/kg).

CCI [redacted]

Approximately 190 patients are expected to be enrolled in the study at approximately 15-20 sites (including approximately 72 patients in the Q2W Regimen Sub-Study). The actual number of patients enrolled will depend upon the tolerability of PF-06647020 and the number of dose levels required to identify the MTD/RP2D.

Patients will participate in the study for approximately 6 months or until disease progression (PD) as per RECIST 1.1 [or immune-related response evaluation criteria in solid tumors (irRECIST) in Cohort 3 of the Q2W regimen expansion], patient withdrawal of consent, unacceptable toxicity occurs, patient loss to follow up, or the study is terminated by the Sponsor, whichever comes first. This includes a 4 week screening period, a 4 month treatment period and a 4 week post dose follow-up period. A follow-up visit within 4 weeks after the last dose of study drug for AE and serious adverse event (SAE) collection will be conducted. The time on study can vary depending on the observed toxicity and potential benefit an individual patient derives. The study is expected to be completed in approximately 36 months.

## SCHEDULE OF ACTIVITIES (ORIGINAL Q3W REGIMEN)

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Assessments section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

| **Visit Identifier** | **Screen/ Baseline**[1] (≤28 days) | **Treatment Period** | | | | | | | **Post Treatment** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Cycle 1 Only** (Days 1 to 21) | | | | **Cycle 2 and Subsequent Cycles** (Days 1 to 21) | | | | |
| | | **Day 1** | **Day 4** (±1) | **Day 8** (±1) | **Day 15** (±2) | **Day 1** (±2) | **Day 8** (±2) | **Day 15** (±2) | **End of Treatment**[29] (+7) | **Follow Up**[30] (+7) |
| Informed Consent[2] | X | | | | | | | | | |
| Tumor History[3] | X | | | | | | | | | |
| Medical History[4] | X | | | | | | | | | |
| Full Physical Examination[5] | X | X | | | | | | | X | |
| Abbreviated Physical Examination | | | X | X | X | X | X | X | | |
| Ophthalmic Examination[6] | X | | | | | | | | | |
| Baseline Signs and Symptoms[7] | | X | | | | | | | | |
| Height | X | | | | | | | | | |
| Weight[8] | X | X | | | | | | | X | |
| Vital signs (BP/PR/Temp)[9] | X | X | X | X | X | X | X | X | X | X |
| ECOG Performance Status[10] | X | X | | | | X | | | X | X |
| (12 lead) ECG[11] | X | X | | X | | X | X | | X | |
| Laboratory | | | | | | | | | | |
| Hematology[12] | X | X | X | X | X | X | X | X | X | |
| Blood Chemistry[13] | X | X | X | X | X | X | X | X | X | |
| Coagulation Panel[14] | X | | | | | X | | | X | |
| Urinalysis[15] | X | | | | X | X | | | X | |
| Pregnancy test[16] | X | X | | | | X | | | X | |
| Registration and Treatment | | | | | | | | | | |
| Registration[17] | | X | | | | | | | | |
| Study Treatment[18] | | X | | | | X | | | | |
| Tumor assessments | | | | | | | | | | |
| CT or MRI scan or equivalent[19] | X | | | | | X (every 6 weeks) | | | X | |

| Visit Identifier | Screen/ Baseline[1] (≤28 days) | Treatment Period | | | | | | | Post Treatment | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 Only (Days 1 to 21) | | | | Cycle 2 and Subsequent Cycles (Days 1 to 21) | | | | |
| | | Day 1 | Day 4 (±1) | Day 8 (±1) | Day 15 (±2) | Day 1 (±2) | Day 8 (±2) | Day 15 (±2) | End of Treatment[29] (+7) | Follow Up[30] (+7) |
| Other samplings | | | | | | | | | | |
| CCI [redacted] | [redacted] | | | | | | | | | |
| [redacted] | [redacted] | | | | | | | [redacted] | | |
| CA-125 Serum Biomarker (OVCA only)[22] | X | | | | | X (every 6 weeks) | | | X | |
| CCI [redacted] | [redacted] | | | | | | | | | |
| Blood Samples for PK[24] | | See Pharmacokinetic, Immunogenicity and Biomarker Sampling Schedule Table below | | | | | | | | |
| Blood Sample for Immunogenicity Test (Anti-PF-06647020 Antibody)[25] | | See Pharmacokinetic, Immunogenicity And Biomarker Sampling Schedule Table below | | | | | | | | |
| [redacted] CCI | | See Pharmacokinetic, Immunogenicity and Biomarker Sampling Schedule Table below | | | | | | | | |
| Other clinical assessments | | | | | | | | | | |
| Serious and non-serious adverse Event monitoring[27] | X | X | X | X | X | X | X | X | X | X |
| Concomitant treatments and non-drug supportive interventions[28] | X | X | X | X | X | X | X | X | X | X |

Abbreviations: CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging; BP = blood pressure; PR = pulse rates; PK = pharmacokinetics; ECOG = Eastern Cooperative Oncology Group; OVCA = Ovarian cancer

Unless otherwise specified, laboratory values and assessments should be obtained prior to the PF-06647020 infusion. If the infusion is held, assessments should still be performed. For Cycle 2 and subsequent cycles, complete blood count (CBC), blood chemistry, other laboratory tests and brief physical examinations, values/assessments should be obtained within 72 hours (ideally within 24 hours) prior to the PF-06647020 infusion and key values should be received and reviewed to ensure appropriate values for dosing.

## Footnotes

1. **Screening:** To be conducted within 28 days prior to treatment start.
2. **Informed Consent:** Must be obtained prior to undergoing any study specific procedures and may be >28 days from first dose.
3. **Tumor History**: Will be collected within 28 days 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. **Full Physical Exam:** No need to repeat full physical exam on Cycle 1 Day 1 (C1D1) if baseline assessment performed within one week prior to that date.
6. **Ophthalmic Examination:** An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes Best Corrected Visual Acuity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic Exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow up.
7. **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 of starting treatment. Baseline signs and symptoms will be recorded on the Medical History Case Report Form (CRF) page.
8. **Weight:** Will not be measured at each visit, however, patients should be monitored throughout the study for significant weight change. If a patient's weight fluctuates by more than 10% in either direction, weight should be collected to recalculate the appropriate dose for the next cycle. In cases where individual institution/pharmacy require more frequent weight measurements, weight can be obtained on each day of administration, and the dose recalculated.
9. **Vital signs:** Includes blood pressure (BP), temperature (oral, tympanic or axillary) and pulse rate to be recorded in the sitting position after approximately 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. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a complete response (CR), partial response (PR) or stable disease (SD) if agreed upon by the treating physician.
10. **Performance status:** use Eastern Cooperative Oncology Group (ECOG) – see Appendix 3.
11. **12 lead ECG (singlet):** ECGs will be collected during Screening and at the End of Treatment visit. Additional ECGs will be collected prior to dosing, at end of infusion and at Day 8 of each dose of study treatment. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTc is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs should be performed as clinically indicated. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
12. **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. See Assessments section for Laboratory Tests list. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
13. **Blood Chemistry:** No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. See Assessments section for Laboratory Tests list. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
14. **Coagulation:** See Assessments section for Laboratory Tests list.
15. **Urinalysis:** Dipstick or full urinalysis is acceptable. Microscopic analyses if dipstick abnormal. If ≥2+ protein on urine dipstick, then collect spot urine sample to calculate urine protein to creatinine ratio (UPCR). See Assessments section for Laboratory Tests list.
16. **Serum/Urine Pregnancy Test:** described in the Pregnancy Testing section.

17. **Registration:** Patient number and dose level allocation will be provided by Pfizer Inc.
18. **Study Treatment:** PF-06647020 will be administered once every 21 days as an IV infusion over approximately 60 minutes.
19. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites and may include chest, abdomen and pelvis CT or MRI scans. Brain scans and bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. CT or MRI scans are to be done every 6 weeks (±5 days) from the start of study treatment until disease progression by RECIST (v1.1) or death, or at the time of withdrawal from treatment (if not done in the previous 6 weeks). The frequency may be reduced to every 12 weeks after 6 months of study treatment. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. For patients enrolled in Part 2, responses of CR or PR must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. All radiographic images will be collected for potential central review. Additional information on diagnostic imaging procedures and collection will be included in the Imaging Manual.

CCI [redacted]

22. **CA-125 Serum Biomarker:** Ovarian cancer patients only. Samples should be collected at pre-treatment, each tumor assessment (every 6 wks), and end of treatment. Additional serum samples to be collected for assessment of CA-125 as per Investigator discretion.

CCI [redacted]

24. **PK Sampling:** Specific timing for collection of serum pharmacokinetic samples can be found in the Pharmacokinetic, Immunogenicity and Biomarker Sampling Schedule table below.

25. **Immunogenicity Sample:** Specific timing for collection of anti-PF-06647020 antibody samples can be found in the Pharmacokinetic, Immunogenicity and Biomarker Sampling Schedule schedule table below.

CCI [redacted]

27. **Adverse Event (AE) Assessments:** AEs should be documented and recorded at each visit using NCI CTCAE version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.

28. **Concomitant Treatments and Non Drug Supportive Interventions:** All prior/concomitant medications within 28 days (4 weeks) prior to first dose of study treatment 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). Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.

29. **End of treatment visit:** Conducted at the visit that the patient is discontinued from the trial. Assessments should be obtained if not completed in the last week. Complete tumor assessments if not completed in the last 6 weeks.

30. **Follow up:** At least 28 days and no more than 35 days after end of treatment visit, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

## Pharmacokinetic, Immunogenicity and Biomarker Sampling Schedule (Q3W Regimen)

| Protocol Activity | Screen (≤28 days) | Treatment Period | | | | | | | | | | | | | | | | | | EOT (+7) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 Only (Days 1 to 21) | | | | | | | Cycles 2 and 3 | | Cycle 4 | | | | | | | Every Cycle Thereafter | | |
| | | Day 1 | | | Day 2 | Day 4 (±1) | Day 8 (±1) | Day 15 (±2) | Day 1 | | Day 1 | | | Day 2 | Day 4 (±1) | Day 8 (±1) | Day 15 (±2) | Day 1 | | |
| | | Pre-dose* | 1 hr* | 4 hr* | 24 hr* | | | | Pre-dose* | 1 hr* | Pre-dose* | 1 hr* | 4 hr* | 24 hr* | | | | Pre-dose* | 1 hr* | |
| Blood Samples for PF-06380101[1] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood Samples for PF-06647020 and hu6M024 mAb[2] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood Sample for Immunogenicity Test (Anti-PF-06647020 Antibody)[3] | | X | | | | | | X | X | | X | | | | | | | X | | X |
| CCI [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 samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection will always be noted on the CRF.

## Footnotes

1. **Blood sample for PF-06380101:** 4 ml of whole blood will be collected for PK analysis of unconjugated payload (PF-06380101).
2. **Blood sample for PF-06647020 and hu6M024 mAb**: 6 ml of whole blood will be collected for PK analysis of ADC (PF-06647020) and total antibody (hu6M024 mAb).
3. **Blood sample for immunogenicity test:** Blood samples (6 mL) for immunogenicity testing against PF-06647020 will be collected. Collection of serum to detect the presence of antibodies to PF-06647020 is to be obtained prior to the start of treatment. Patients having an unresolved adverse event that is possibly related to anti-PF-06647020 antibodies at their last assessment will be asked to return to the clinic for ADA and drug concentration blood sampling at up to 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

CCI [redacted]

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# 1. INTRODUCTION

## 1.1. Indication

PF-06647020 is an antibody-drug conjugate (ADC) against the PTK7 (Protein Tyrosine Kinase 7) tumor antigen. It is intended to be used for the treatment of adult patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available.

## 1.2. Background and Rationale

ADCs were developed to improve the therapeutic indices of cytotoxic anti-cancer agents. The strategy makes use of an immunoconjugate in which a cytotoxic agent is chemically or enzymatically linked to an antibody that selectively binds to an internalizing tumor-associated antigen. This strategy allows specific delivery of the cytotoxic agent to the tumor site while minimizing the exposure to normal tissues.

PF-06647020 is an anti-PTK7 ADC intended to be for the treatment of patients with cancer. PF-06647020 is comprised of a humanized anti-PTK7 monoclonal antibody (mAb) linked to an auristatin (Aur0101) via a cleavable cysteine-reactive linker. Auristatins are fully synthetic dolastatin-based pentapeptide inhibitor of tubulin polymerization that induce G2/M cell cycle arrest and cell death at low picomolar intracellular concentrations.[13,14]

PTK7 is a phylogenetically conserved member of the pseudokinase family of receptor tyrosine kinases (RTKs) with no observable kinase activity.[4] Genetic and biochemical studies in multiple organisms have demonstrated a key function for PTK7 in planar cell polarity via the Wnt-pathway signaling, and PTK7-deficient embryos have developmental defects.[3,7,11] In addition, PTK7 promotes cell survival in colorectal cancer and acute myeloid leukemia (AML), and PTK7 may promote resistance to chemotherapy in AML.[9,12] Bioinformatics and literature analysis have revealed that PTK7 mRNA expression levels in many types of tumors are higher than corresponding normal tissues including bladder, brain, breast, colorectal, gastric, kidney, liver, lung, pancreatic and skin cancer. In addition, PTK7 was found to be enriched in cancer stem cells (CSCs), also known as tumor-initiating cells, harvested from patient-derived xenografted tumor models of triple negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC) in preclinical studies (unpublished data). It was also reported that positive expression of PTK7 is linked to poor prognosis in patients with NSCLC (Pfizer internal data) and TNBC who received chemotherapy, particularly in a subgroup patient population who received anthracycline treatment.[2] In preclinical studies, PF-06647020 induced sustained tumor regressions in models of ovarian cancer (OVCA), NSCLC and TNBC.[19]

For complete details of the in vitro and nonclinical studies, refer to PF-06647020 Investigator's Brochure (IB).[22]

TNBC accounts for 15% to 20% of breast cancers and is diagnosed based on lack of ER and PgR expression by IHC and of HER2 over expression or gene amplification by IHC or in situ hybridization, respectively. TNBC is a heterogeneous disease, not only on the molecular level, but also on the pathologic and clinical levels. The majority of patients with TNBC

respond with high sensitivity to chemotherapies including anthracyclines and taxanes in the neoadjuvant or adjuvant settings. However, TNBC is associated with a significantly higher probability of relapse and poor OS in the first few years after diagnosis compared with other breast cancer subtypes. Positive expression of PTK7 in TNBC was observed in ~84% of archived samples surveyed using a research grade IHC assay sets tested (Pfizer internal data).

NSCLC accounts for approximately 85% cases of lung cancer, the leading cause of cancer-related mortality in the United States (US) and worldwide. Most patients with NSCLC have locally advanced and distant metastatic disease (stage III/IV) at the time of presentation, which is associated with a poor prognosis with 5-year OS rate less than 10%. Although targeted therapies (eg, Erlotinib and Crizotinib) for patients with NSCLC whose tumors carry EGFR mutation or are ALK-positive and promising immunotherapies are being developed, the unsatisfactory treatment outcomes in advanced NSCLC highlights the need of novel alternative therapies. In addition, PTK7 expression in NSCLC was observed to cover a dynamic range (Pfizer internal data), suggesting that patient selection by PTK7 expression levels may identify patients that may be more likely to benefit. This is the first in human study of PF-06647020 in patients with advanced solid tumors, unresponsive to existing therapies, or for whom no standard treatment is available.

OVCA is the 6th most common malignancy in developed countries with approximately 100,000 new cases resulting in nearly 65,000 deaths per year.[15] Patients are typically treated with surgery followed by chemotherapy. Initial therapy consists of combinations with platinum-containing agents which results in responses in 70-80% of patients. However, the disease relapses in almost all patients requiring further therapy. The timing of the relapse from the end of the platinum-containing regimen has been shown to be prognostic with platinum-resistant tumors (defined as progression while receiving initial therapy or relapse <6 months from end of initial regimen), as having the worst outcomes.[16] Pegylated doxorubicin and topotecan are both indicated as single agents in patients with refractory OVCA. In patients with platinum-resistant disease, both of these compounds result in RR of 10-15%, PFS of 14 weeks, and OS 35-40 weeks highlighting the need for alternative therapies.[16]

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[redacted]

### 1.2.2. Nonclinical Pharmacokinetics

Following a single IV or intraperitoneal (IP) dose of PF-06647020 to nod/SCID mice, systemic exposure of ADC and total Ab were similar. After repeat IV dosing of PF-06647020 to Wistar Han rats and cynomolgus monkeys, mean systemic exposure (as assessed by $C_{max}$ and area under the curve [AUC]) increased with increasing dose for ADC, total Ab, and unconjugated Aur0101 and no sex-related differences were observed. Further, mean $C_{max}$ and $AUC_{504}$ ratios on Day 22 relative to Day 1 were generally similar with ratios (Day 22/Day 1) less than 2.0 for ADC, total Ab, or unconjugated payload. In addition, the mean systemic exposure of ADC and total Ab were similar.

In Wistar Han rats, the incidence of ADA induction to PF-06647020 was highest in the 12 mg/kg/dose group (22% in toxicokinetic animals). In general, serum concentrations in most ADA-positive rats were similar to ADA-negative rats. In cynomolgus monkeys, the incidence of ADA induction to PF-06647020 ranged from 75% to 93% across all dose groups (0.5, 2, and 4 mg/kg/dose). On Study Day 1, systemic exposure in ADA-positive animals was similar to that of ADA-negative animals; whereas, on Study Day 22 systemic exposure in ADA-positive animals was lower than ADA-negative animals.

After an IV dose of Aur0101 payload at 20 μg/kg to Wistar Han rats, Aur0101 exhibited a mean systemic clearance (CL) of 70 mL/min/kg and a volume of distribution ($V_{ss}$) of 14,700 mL/kg, resulting in a terminal elimination half-life ($t_{½}$) of approximately 6 hours. Following repeat IV dosing of Aur0101 to Wistar Han rats, mean systemic exposure increased with increasing dose. Mean $C_{max}$ and $AUC_{336}$ ratios on Day 29 relative to Day 1 were generally similar with ratios (Day 29/Day 1) less than 2.0, suggesting there was no accumulation of Aur0101 observed over the dosing interval.

Aur0101 was moderately to highly bound to plasma proteins (monkey < rat and human plasma proteins). In vitro studies with non-radiolabeled compound suggest that Aur0101 preferentially distributes into human plasma relative to whole blood. In vitro studies indicate that Aur0101 is a P-glycoprotein (P-gp) substrate.

Based on preliminary in vitro and in vivo assessments, Aur0101 is the only released chemical species resulting from PF-06647020 following incubation with rat, monkey, and human liver S9 or in rat and monkey serum after IV administration of PF-06647020. A preliminary assessment of the metabolism of Aur0101 using non-radiolabeled compound was conducted using rat, monkey and human liver S9 fractions and human recombinant cytochrome P450 (rCYP) enzymes. All metabolites were oxidative in nature and β-Nicotinamide adenine dinucleotide phosphate (NADPH)-dependent with no amide hydrolysis products or glucuronide conjugates observed. There was no evidence of human specific metabolites. Initial reaction phenotyping experiments suggest that CYP3A4 is the predominant enzyme involved in the metabolism of Aur0101.

Based on the in vitro direct inhibition, metabolism-dependent inhibition, and induction data and the anticipated low systemic concentrations in humans ($C_{max}$ <0.001 μM or <0.001 μg/mL, based on the assumption that levels of released Aur0101 are the same in humans as in monkeys), Aur0101 has an anticipated low probability to perpetrate pharmacokinetic DDI with compounds for which CYP (1A2, 2B6, C8, 2C9, 2C19, 2D6, and/or 3A4/5)-mediated metabolism constitutes the primary mechanism of clearance. However, since Aur0101 is primarily metabolized by CYP3A4, there is a potential that its metabolism may be altered in the presence of a potent inhibitor or inducer of CYP3A4. In addition, coadministration with a potent CYP3A4 inducer would result in accelerating clearance and lowering systemic Aur0101 concentrations.

### 1.2.3. Nonclinical Safety

The nonclinical safety profile of PF-06647020 was characterized in a series of nonclinical in vivo studies. Repeat-dose exploratory and pivotal (Good Laboratory Practice (GLP) compliant) studies were conducted in Wistar Han rats and cynomolgus monkeys. An in vivo micronucleus assay was conducted in the rat pivotal toxicity study and safety pharmacology assessments (cardiovascular function in particular) were included in the monkey pivotal toxicity study. In addition, a GLP tissue cross-reactivity study was conducted with normal tissues of cynomolgus monkeys and humans. The major clinically significant findings in the repeat-dose toxicity studies were reversible bone marrow toxicity (all lineages) with associated hematological changes in both rats and monkeys. PF-6647020 was positive in the rat micronucleus assay and there were no adverse findings in the monkey cardiovascular function assessments.

Wistar Han rats were dosed with PF-06647020 once every 3 weeks for 3 cycles at 2, 6 or 12 mg/kg/dose in an exploratory study and the pivotal GLP study. In the pivotal rat study, administration of 12 mg/kg/dose resulted in the early euthanasia of 2/30 animals on Days 8 and 9 due to poor clinical condition (eg decreased activity and skin turgor, gasping, lame/limping, chromodacryorrhea), which was secondary to bone marrow and lymphoid depletion associated with secondary bacterial infection. Major effects in surviving animals consisted of reversible bone marrow hypocellularity (minimal to mild at 2 mg/kg/dose and moderate to severe at ≥6 mg/kg/dose) that was associated with hematological changes of transient decreases in all major blood cell types. Additional adverse changes were noted in the testes (tubular degeneration) at ≥2 mg/kg/dose, thymus at ≥6 mg/kg/dose (lymphoid depletion) and skin (intraepidermal vesicle/cleft formation) at 12 mg/kg/dose. Other non-adverse changes (based on the small magnitude of the findings) consisted of increased mitoses and/or single cell necrosis in a variety of organs at ≥2 mg/kg/dose, connective tissue inflammation around various organs at ≥6 mg/kg/dose and mammary gland atrophy in males at 12 mg/kg/dose. Lastly, adverse injection site findings were seen at all doses and considered mostly related to extravasation of the test article. All changes, with the exception of the testicular findings, were fully recovered at the end of the 6-week reversibility period. The severely toxic dose for 10% of the animals (STD10) (was considered be 6 mg/kg/dose in the pivotal rat study.

Cynomolgus monkeys were dosed with PF-06647020 once every 3 weeks for 3 cycles at 0.5, 2 or 5 mg/kg/dose in an exploratory study and at 0.5, 2 or 4 mg/kg/dose in a pivotal study. In the exploratory study, administration of 5 mg/kg/dose resulted in the early euthanasia of 1/6 animals on Day 49 (6 days after the last dosing) due to lameness and swelling of the left hind limb, which correlated with microscopic findings of necrosis and inflammation at the injection site consistent with extravasation of the test article. Similar clinical and microscopic injection site findings were observed in other animals at ≥2 mg/kg/dose. Test article-related effects were seen in the bone marrow (multifocal hematopoietic necrosis, altered myeloid to erythroid ratio) at ≥2 mg/kg/dose and lymphoid organs (lymphoid depletion) and testes (tubular degeneration) at ≥0.5 mg/kg/dose. In the pivotal monkey study, mild transient clinical signs (eg focal erythema or swelling, decreased activity, ataxia, emesis) consistent with a mild infusion reaction were observed in some animals at ≥2 mg/kg/dose and were possibly related to ADA formation. Clinical signs were noted within 5-60 min after the 2nd or 3rd dosing and were resolved by 4.5 hours post dosing. The most significant hematology changes in these monkeys consisted of minimal to marked transient decreases in neutrophil counts at ≥0.5 mg/kg/dose, which were most prominent at mid-cycle (eg, 10 days after dosing) and were considered adverse at 4 mg/kg/dose based on the magnitude of the changes. Additional non-adverse hematology changes consisted of minimal to mild decreases in RBC mass parameters ≥2 mg/kg/dose. Hematology changes were attributable to bone marrow toxicity and associated with altered myeloid to erythroid ratio. Other microscopic findings consisted of non-adverse minimally increased mitoses and/or single cell necrosis in several organs at 4 mg/kg/dose. Hematology and histology changes were recovered at the end of the 6-week reversibility period. It is noteworthy that, due to a change in dosing procedure (post-dose flushing), there were no clinical signs or microscopic findings of test article extravasation at the injection sites in the pivotal monkey study. Last, there were no test article-related effects on electrocardiograms and heart rate. The highest non-severely toxic dose (HNSTD) was considered to be 4 mg/kg/dose in the pivotal monkey study.

The tissue cross-reactivity study conducted with PF-06647020 indicated membrane expression of PTK7 in the esophagus (squamous epithelium), cervix (squamous epithelium), and skin (epidermis, hair follicle and/or sweat glands) in monkeys and humans. However, no test article related clinical and microscopic findings were observed in these organs in the Cynomolgus pivotal study.

Overall, the nonclinical safety profile of PF-06647020 has been adequately characterized and supports its use in advanced cancer patients.

### 1.2.4. Clinical Safety (PF-06647020)

As of 17 March 2017, 112 patients have been treated with PF-06647020 Q3W, including 0.2, 0.5, and 1.25 mg/kg (2 patients at each dose level), 4 patients at 2.1 mg/kg, 96 patients at 2.8 mg/kg, and 6 patients at 3.7 mg/kg. Of the 112 patients treated, 40 (36%) experienced at least 1 Grade ≥3 treatment-related Treatment Emergent Adverse Event (TEAE), and 95 patients (85%) had treatment-related TEAEs (regardless of grade).

The most frequent reported (incidence ≥10%) treatment-related TEAEs (any grade) are summarized in Table 2. The most frequently reported (in ≥2 patients) Grade ≥3 treatment-related TEAEs are presented in Table 3.

**Table 2. Most Frequently Reported (Incidence ≥10%) Treatment Related Treatment Emergent Adverse Events (TEAEs) (Any Grade)**

| MedDRA PT | n (% in total n=112 patients) |
|---|---|
| Number of patients with at least 1 TEAE | 95 (84.8) |
| Nausea | 50 (44.6) |
| Alopecia | 45 (40.2) |
| Fatigue | 40 (35.7) |
| Headache | 36 (32.1) |
| Neutropenia | 32 (28.6) |
| Vomiting | 28 (25.0) |
| Arthralgia | 18 (16.1) |
| Decreased appetite | 18 (16.1) |
| Diarrhea | 17 (15.2) |
| Peripheral sensory neuropathy | 16 (14.2) |
| Myalgia | 15 (13.4) |
| Anemia | 12 (10.7) |

Source: Table 14.3.1.3.11.4

**Table 3. Most Frequently Reported (in ≥2 Patients) Grade ≥3 Treatment Related TEAEs**

| MedDRA PT | n (% in total n=112 patients) |
|---|---|
| Number of patients with at least 1 TEAE | 50 (44.6) |
| Neutropenia | 26 (23.0) |
| Headache | 5 (4.5) |
| Vomiting | 4 (3.6) |
| Fatigue | 3 (2.7) |
| Anemia | 3 (2.7) |
| Febrile neutropenia | 3 (2.7) |
| Lymphopenia | 3 (2.7) |
| White blood cell count decreased | 3 (2.7) |
| Myalgia | 2 (1.8) |
| Stomatitis | 2 (1.8) |
| Aspartate aminotransferase increased | 2 (1.8) |
| Thrombocytopenia | 2 (1.8) |

Source: Table 14.3.1.3.11.4

Overall, 33 of the 112 patients (29.5%) treated had serious TEAEs (not considered treatment related). Seven patients (6.3%) died while on study, of which 5 patients (4.9%) primary cause of death was attributed to disease progression, 1 patient experienced respiratory arrest and 1 patient experienced urosepsis (all considered unrelated to PF-06647020 treatment).

Twelve serious TEAEs considered treatment-related by the Investigator were reported for 10 patients (8.9%) and is summarized in Table 4.

**Table 4. Serious TEAEs Considered Treatment-Related by Investigator**

| MedDRA PT | n (% in total n=112 patients) |
|---|---|
| Grade 3 Febrile neutropenia | 3 (2.7) |
| Grade 3 Abdominal pain | 1 (1) |
| Grade 2 Constipation | 1 (1) |
| Grade 3 Drug-induced liver injury | 1 (1) |
| Grade 2 Headache | 1 (1) |
| Grade 3 Neutropenia | 1 (1) |
| Grade 4 Neutropenia | 1 (1) |
| Grade 3 Stomatitis | 1 (1) |
| Grade 2 Vomiting | 1 (1) |
| Grade 3 Vomiting | 1 (1) |

Source: Table 16.2.7.1

Five (5) patients (4.9%) treated on study withdrew permanently from trial treatment due to TEAE and is summarized in Table 5.

**Table 5. Patients Withdrawn From Study Due to TEAEs and Relationship with PF-06647020**

| MedDRA PT | Relationship with PF-06647020 |
|---|---|
| Grade 2 Pruritus | Related |
| Grade 2 Fatigue | Related |
| Grade 3 Fatigue | Related |
| Grade 4 Pulmonary embolism | Unrelated |
| Grade 3 Mental status changes | Unrelated |

Source: Table 14.3.1.1.2

Starting from 08 June 2016, use of prophylaxis for diarrhea, nausea and vomiting in the first cycle of PF-06647020 was permitted (at the discretion of treating physician) and incidence and severity of these adverse events were reduced.

Two patients (1.9%) experienced Grade 2 and 3 infusion-related reactions at the 2.8 mg/kg dose level, starting post infusion in Cycle 1, and lasting 1 and 2 days respectively. The infusion-related reactions in both patients were well managed by treatment of antihistamines and steroids in following the guidance provided in the protocol, and this adverse event did not recur in subsequent cycles in either patient. Guidelines for the management of infusion-related reactions and severe hypersensitivity reaction are found in Section 5.4.

Most commonly (≥10%) reported drug related AEs in 42 OVCA patients (treated at RP2D 2.8 mg/kg) are summarized in Section 1.2.4. Severity of AEs observed in OVCA patients were mostly limited to Grade 1-2. A total of 15 patients (35.7%) experienced a Grade ≥3 treatment-related AE, of which most common AEs were neutropenia (10 patients, 23.8%), and headache, myalgia, vomiting, and hypomagnesaemia (2 patients (4.8%) each).

**Table 6. Most Frequently Reported (Incidence ≥10%) Treatment-Related TEAEs in OVCA Patients Treated at 2.8 mg/kg PF-06647020 (Any Grade)**

| MedDRA PT | n (% in total OVCA n=42 patients) |
|---|---|
| Number of patients with at least 1 TEAE | 38 (90.5) |
| Nausea | 19 (45.2) |
| Alopecia | 16 (38.1) |
| Fatigue | 16 (38.1) |
| Neutropenia | 13 (31.0) |
| Headache | 12 (28.6) |
| Arthralgia | 9 (21.4) |
| Myalgia | 9 (21.4) |
| Decreased appetite | 8 (19.0) |
| Vomiting | 8 (19.0) |
| Constipation | 6 (14.3) |
| Anemia | 5 (11.9) |
| Peripheral sensory neuropathy | 7 (16.6) |

Source: Table 14.3.1.3.11.2

An essentially similar safety profile was observed in 22 patients with NSCLC that received PF-06647020 at RP2D 2.8 mg/kg, which is summarized in Table 7.

**Table 7. Most Frequently Reported (Incidence ≥10%) Treatment-Related TEAEs in NSCLC Patients Treated at 2.8 mg/kg PF-06647020 (Any Grade)**

| MedDRA PT | n (% in total NSCLC n= 22 patients) |
|---|---|
| Number of patients with at least 1 TEAE | 18 (81.8) |
| Alopecia | 9 (40.9) |
| Fatigue | 9 (40.9) |
| Arthralgia | 8 (36.4) |
| Nausea | 8 (36.4) |
| Diarrhea | 5 (22.7) |
| Headache | 5 (22.7) |
| Vomiting | 5 (22.7) |
| Neutropenia | 5 (22.7) |
| Myalgia | 4 (18.2) |
| Decreased appetite | 3 (13.6) |

Source: Table 14.3.1.3.11.1

Additional information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.[22]

### 1.2.4.1. Pharmacokinetics (PF-06647020)

Pharmacokinetics of PF-06647020 (ADC, measured as conjugated antibody), hu6M024 mAb (total antibody), and PF-06380101 (unconjugated payload) following the first 1-hour infusion of PF-06647020 have been characterized in 59 patients treated in the dose escalation and the dose expansion phases of the ongoing First-in-Patient (FIP) study, B7661001. This preliminary analysis revealed that the systemic exposure based on area under the concentration-time curve during the dosing interval ($AUC_{\tau}$) and maximum concentration ($C_{max}$) values for ADC, total antibody, and unconjugated payload generally increased in a dose related manner across the 0.2, 0.5, 1.25, 2.1, 2.8, and 3.7 mg/kg doses. Apparent terminal half-life ($t_{1/2}$) values for ADC and total antibody tended to increase with doses with comparable half-life values among 2.1, 2.8, and 3.7 mg/kg doses, likely related to target mediated disposition at lower doses.

The Cycle 1 PK parameters were comprehensively characterized for the 2.8 mg/kg dose level, where data were available from 41 patients. Following single IV infusion of PF-06647020 at dose of 2.8 mg/kg, ADC and total antibody peak concentrations (82.6 and 86.9 μg/mL respectively) occurred at or shortly after the end of infusion, followed by a multi-phasic decline of concentrations with terminal $t_{1/2}$ values of approximately 2.7 and 3.3 days for ADC and total antibody, respectively. Unconjugated payload (PF-06380101) concentrations appeared to increase following PF-06647020 infusion and reached a mean $C_{max}$ of 8.8 ng/mL at 24 h post-dose, and the mean $t_{1/2}$ was 2.9 days. There were no appreciable drug accumulations over repeated doses following Q3W regimen.

### 1.2.4.2. Efficacy in Patients treated with PF-06647020

As of 17 March 2017, total of 112 patients with heavily pre-treated cancers have been treated with PF-06647020 on a Q3W regimen at different dose levels in the ongoing Phase I study, of which 44 were OVCA patients, 25 were NSCLC patients, and 31 were TNBC patients, 12 patients had other types of solid tumor.

Of the total 44 OVCA patients who received PF-06647020 treatment, 42 were treated at 2.8 mg/kg, 1 at 2.1 mg/kg, and 1 at 3.7 mg/kg. In 38 patients who were considered evaluable for ORR assessment, 9 patients achieved objective response (1 CR, and 8 PR) with an ORR of 24% (95% CI, 13%, 39%) and 18 patients (47%) had a best response with SD. Median PFS was 12.6 weeks (95% CI, 12, 24). Median duration of treatment with PF-06647020 was 8.1 weeks (range 0.1-45.3 weeks).

Of the total 25 NSCLC patients received PF-06647020 treatment, 22 were treated at 2.8 mg/kg, 2 at 1.25 mg/kg, 1 at 2.1 mg/kg. In 23 patients who were considered evaluable for ORR assessment, 4 patients achieved PR with an ORR of 17% (95% CI, 7%, 37%) and 9 patients (39%) had a best response with SD. Median PFS was 18.1 weeks (95% CI, 6, 30.1) and median duration of treatment with PF-06647020 was 9.0 weeks (range 0.1-46.3 weeks).

Of the total 31 TNBC patients received PF-06647020 treatment, 27 were treated at 2.8 mg/kg, 2 at 2.1 mg/kg, 2 at 3.7 mg/kg. In 27 patients who were considered evaluable for ORR assessment, 6 achieved PR with an ORR of 22% (95% CI, 11%, 41%). Eight (30%) patients had a best response of SD. Median PFS was 8.3 weeks (95% CI, 6, 23.6) and a median duration of treatment with PF-06647020 was 3.0 weeks (range 0.1-40.3 weeks).

### 1.3. Starting Dose Rationale

The selection of the starting dose of PF-06647020 for this FIP study is based on the preclinical toxicology results in accordance with the International Conference on Harmonization (ICH) S9 Guidance entitled "Nonclinical Evaluation for Anticancer Pharmaceuticals". Cynomolgus monkey was considered to be the most appropriate species for determining the proposed starting dose in patients. The HNSTD in cynomolgus monkey was determined to be 4 mg/kg. The proposed starting dose of 0.2 mg/kg given as an IV infusion Q3W represents approximately $1/6^{th}$ of monkey HNSTD (based on human equivalent dose normalized to body surface area). In addition, given the projected human PK parameters based on allometric scaling from cynomolgus monkey PK, the projected human $C_{av}$ for PF-06647020 at the proposed starting dose of 0.2 mg/kg is expected to be approximately $1/11^{th}$ of the observed monkey $C_{av}$ at HNSTD.

PK/PD parameters were estimated from mouse xenograft models where at least 3 different doses of PF-06647020 were evaluated (Figure 2, TNBC BR13, TNBC BR22). The PK/PD relationship between mouse PF-06647020 concentration and measured xenograft tumor size data was analyzed based on a cell distribution transduction pharmacodynamic model. Human dose prediction was achieved by assuming direct translation of the mouse xenograft PD parameters and predicted human PK parameters. Stasis was considered as a criterion for minimal efficacy in the clinic compensating for the difference in tumor growth rates between xenograft and clinical tumors. Based on these projections, an efficacious clinical dose of 1.5 to 1.6 mg/kg of PF-06647020 administered once every 3 weeks is expected to achieve concentrations of PF-06647020 sufficient to drive efficacy.

### 1.4. PTK7 Immunohistochemistry (IHC) Assay for PTK7 Expression

A PTK7-specific IHC assay was developed using control cancer cell lines with a range of PTK7 expression reflective of PTK7 expression in clinical samples. The PTK7 high, moderate, low and negative control cancer cells lines were characterized for PTK7 mRNA expression and protein levels using qRT-PCR, nanostring and western blot methodologies. Xenografts from the control cell lines were stained with the IHC assay and PTK7 membrane expression was assessed. PTK7 H-scores were highly correlated with PTK7 readouts from orthogonal methodologies (qRT-PCR, nanostring and western blot). Control cell line xenografts were subjected to various pre-analytical variables (eg, time to fixation and time of fixation) and stained with the PTK7 IHC assay. The IHC assay was robust to pre-analytic variables, enabling the IHC assay to be performed on routinely collected formalin-fixed paraffin embedded clinical samples.

PTK7 expression as measured by IHC staining was evaluated in 73 whole slide sections of formalin-fixed, paraffin-embedded epithelial malignancies of lung, ovary, and breast. H-scores were generated based on PTK7 membrane staining of tumor epithelial cells and ranged from 0 to 273. Stromal staining was also observed in at least one-third of the cases. PTK7 H-scores correlated with PTK7 readouts from orthogonal methodologies (qRT-PCR, nanostring and western blot).

The PTK7 H-scores were ranked lowest to highest and the resulting graph reflects the dynamic range of PTK7 expression within an indication. The ranked IHC values were then divided into lowest, middle, and highest statistical tertiles based on total patient number. The middle one-third tertile of H-scores define the moderate PTK7 expressing tumors, whereas the tertile with the highest H-score values define the high PTK7 expressing tumors.

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A digital H-score is being implemented.

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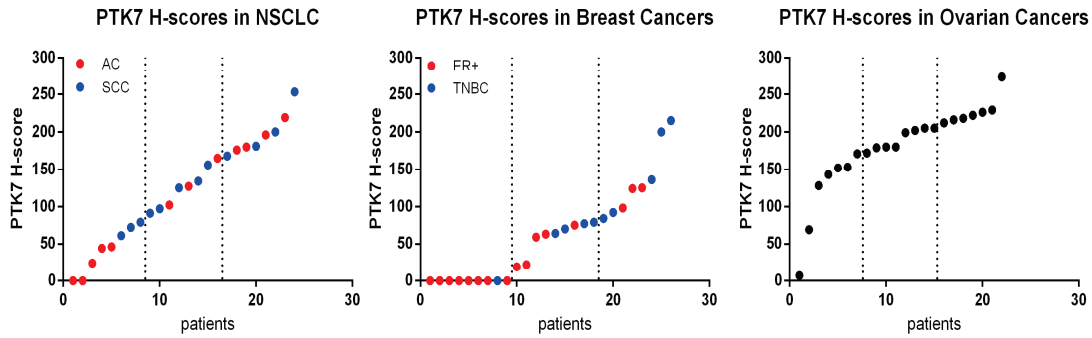
A digital H-score is being implemented. CCI

**Figure 3. PTK7 H-scores in NSCLC, Breast and Ovarian Cancers**



### 1.5. Triple Negative Breast Cancer, NSCLC and OVCA in Dose Expansion

The selection of the indications in dose expansion was based on the literature reviews, the expression of PTK7 in human TNBC, NSCLC and OVCA samples, the efficacy demonstrated in preclinical studies, and early signs of efficacy in this study.

### 1.6. Rationale for Expansion of OVCA Cohort (Protocol Amendment 5)

To further understand PF-06647020 anti-tumor activity in ovarian cancer, the protocol is amended to enroll approximately 25 additional patients with OVCA who are platinum-resistant or refractory for further evaluating the anti-tumor activity of PF-06647020. This additional enrollment is supported by the following statistical model assessment: Based on preliminary early readout of the ongoing Part 2 OVCA study, an approximately 27% of ORR is assumed for the available evaluable patients, and an inference can be made for the next 24 evaluable patients (including on-going patients) using Bayesian probability of achieving a target ORR (in the 50 evaluable patients). Assuming a uniform prior (ie, Beta(1,1)), if 9, 10, 11 and 12 responses are observed in the next 24 evaluable patients, then a posterior probability of 65%, 78%, 88% and 94%, respectively, would be predicted to achieve ORR ≥30% in all 50 evaluable OVCA patients. Analogously, a 66%, 78%, 87% and 94% predictive probability would be achieved if there are respectively 11, 12, 13 and 14 responses out of the next 24 evaluable patients when ORR ≥34% is targeted in all 50 evaluable OVCA patients. Note that ORR ≥34% in 50 evaluable patients implies that the lower bound of the 95% confidence interval (CI) of this ORR is >20% which is the null hypothesis (Ho) in the sample size calculation. The Bayesian model is specified by a prior distribution (Beta function), sampling distribution (binomial function), response predictions and probability of exceeding a critical threshold. The calculation is done using Markov Chain Monte-Carlo methods (eg, in OpenBUGS – an open source computing tool for Bayesian inference Using Gibbs Sampling).

This expansion study (Protocol Amendment 5) was discontinued and the protocol has been amended to investigate Q2W PF-06647020 as a single agent and in combination with avelumab treatment (Protocol Amendment 7) in patients with OVCA and NSCLC.

### 1.7. Rationale for DDI Sub-Study

The major cytochrome P450 isoform involved in the metabolism of the unconjugated payload (PF-06380101) in humans was determined to be CYP3A4. (See Section 1.2.2 Nonclinical Pharmacokinetics). Physiologically-based PK modeling in SimCYP, utilizing nonclinical and preliminary clinical data, predicted an average 2- to 10-fold increase in unconjugated payload AUC with co-administration of ketoconazole, a potent CYP3A4 inhibitor, at a clinical dose (200 mg twice daily [BID]). Moderate CYP3A4 inhibitors, such as fluconazole, are predicted to have less impact on unconjugated payload AUC than ketoconazole, with average AUC increase estimated approximately 2-fold at clinical doses. The effect of fluconazole on unconjugated payload exposure cannot be precisely predicted at this time due to the lack of certainty surrounding the overall contribution of the CYP3A4 pathway to elimination of PF-06380101. A DDI sub-study will be performed to determine the effect of multiple-dose fluconazole on the pharmacokinetics of

unconjugated payload (PF-06380101), when fluconazole is co-administered with ADC (PF-06647020).

The primary aim of the DDI sub-study is to verify the DDI related PK alterations (eg, decreased clearance of unconjugated payload) and to enable informed decisions regarding inclusion of patients taking concomitant medications, specifically CYP3A4 inhibitors.

See Appendix 7 for details.

Complete information for fluconazole may be found in the SRSD, which for this study is the Investigator Brochure (IB).

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Objectives

#### 2.1.1. Objectives – Dose Escalation (Part 1)

**Primary Objectives**

- To assess safety and tolerability at increasing dose levels of PF-06647020 administered intravenously on an every 21-day dosing schedule to patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available.
- To determine the MTD and select the RP2D.

**Secondary Objectives**

- To evaluate the overall safety profile.
- To characterize the single and multiple dose PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101).
- To evaluate the immunogenicity as measured by presence of ADA in patients treated with PF-06647020.
- To document any preliminary evidence of anti-tumor activity.

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- [redacted]

#### 2.1.2. Objectives – Dose Expansion (Part 2)

**Primary Objective**

- To further evaluate safety and tolerability of PF-06647020 at the MTD and to establish RP2D in patients with NSCLC, TNBC and OVCA.

[redacted]

**Secondary Objectives**

- To evaluate the overall safety profile at the RP2D.
- To evaluate preliminary anti-tumor activity of PF-06647020 at the RP2D in patients with NSCLC, TNBC and OVCA.
- To characterize the single and multiple dose PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101).
- To evaluate the immunogenicity as measured by presence of ADA in patients treated with PF-06647020.
- To evaluate the effect of the co-administration of fluconazole on the PK of unconjugated payload (PF-06380101), ADC (PF-00647020) and total antibody (hu6M024 mAb) following administration of ADC (PF-06647020).
- To assess the effects of fluconazole on the safety and tolerability of a single dose of PF-06647020.

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- [redacted]
- [redacted]

## 2.2. Endpoints

### 2.2.1. Endpoints – Part 1

**Primary Endpoint (Part 1)**

- First cycle DLTs in order to determine the MTD and RP2D of PF-06647020 administered by IV infusion in a 21-day dosing cycle.

**Secondary Endpoints (Part 1)**

- Adverse events as characterized by type, frequency, severity (as graded by NCI-CTCAE v.4.03), timing, seriousness and relationship to study treatment.

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.
- Single and multi-dose PK parameters of multiple analytes [ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101)].
- Incidence of anti-PF-066407020 antibodies.
- Preliminary evidence of anti-tumor activity based on RR, as assessed using RECIST version 1.1.

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### 2.2.2. Endpoints – Part 2

**Primary Endpoints (Part 2)**

- Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study treatment.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

**Secondary Endpoints (Part 2)**

- OR, DoR, DCR, TTP, and PFS, as determined by Investigator [As assessed by RECIST version 1.1].
- Single and multi-dose PK parameters of multiple analytes [ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101)].
- Incidence of anti-PF-066407020 antibodies.
- The PK parameters of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101) following ADC (PF-06647020) administration alone and when co-administered with fluconazole.

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- [redacted]

Study OBJECTIVES AND ENDPOINTS for the Q2W regimen expansion can be found in Appendix 8.

## 3. STUDY DESIGN

### 3.1. Study Overview

This is a Phase 1, open label, multi-center, non-randomized, multiple dose, safety, pharmacokinetic and pharmacogenomic study, initially designed to evaluate single agent PF-06647020 in sequential cohorts of adult patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available. Successive cohorts of patients received doses of PF-06647020 intravenously Q3W starting at a dose of 0.2 mg/kg.

This clinical study will include two parts. Part 1 will estimate the MTD/RP2D in dose escalation cohorts in patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available. Part 2 will include approximately 87 patients enrolled at a RP2D selected by the Sponsor and Investigators from Part 1, to explore benefit from treatment and to better define the safety profile, as well as the RP2D. This expansion cohort will include approximately 22 patients with metastatic or recurrent TNBC, 45 OVCA patients and 20 patients with advanced NSCLC.

CCI [redacted]

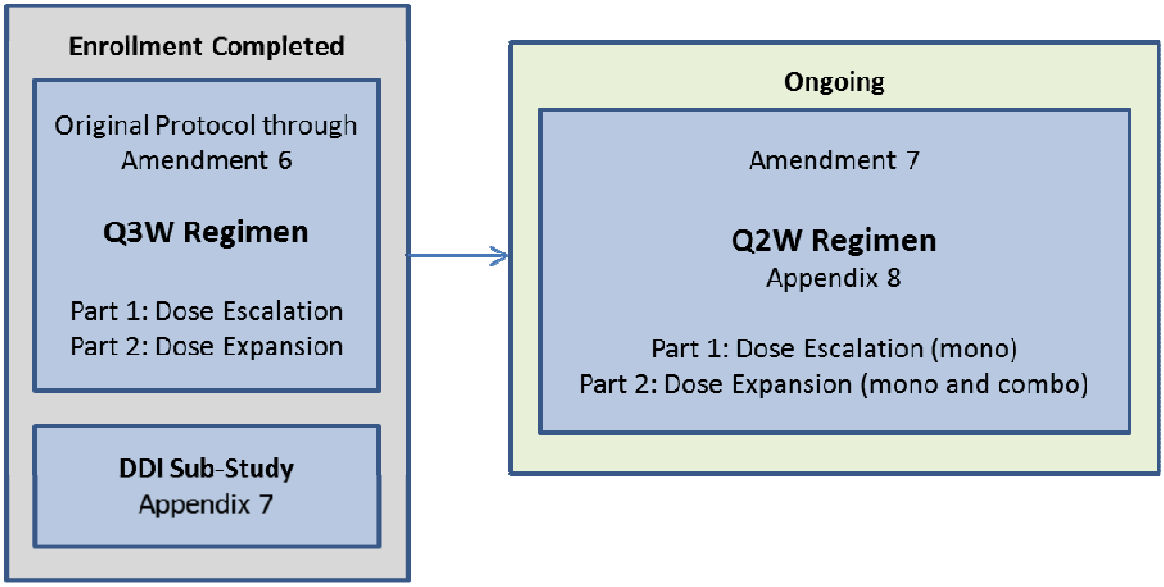
A DDI sub-study for evaluating the effect of multiple-dose fluconazole on the PK of unconjugated payload (PF-06380101) is currently ongoing.

The DDI sub-study is an open-label, 2-period, fixed sequence design in up to 10 patients to determine the effect of multiple-dose fluconazole, a model moderate CYP3A4 inhibitor, on the PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101), when fluconazole is co-administered with PF-06647020. The sub-study will be in a separate cohort from the studies for TNBC, NSCLC and OVCA, and study design and procedure details can be found in Appendix 7.

Approximately 190 patients enrolled from 15-20 sites will participate in this study (including the Q2W Regimen Expansion). The actual number of patients enrolled will depend upon tolerability of PF-06647020 and the number of dose levels required to identify the MTD/RP2D.

Patients will participate in the study for approximately 6 months or until disease progression, (PD) as per RECIST 1.1 (or irRECIST in Cohort 3 of the Q2W regimen expansion), patient withdrawal of consent or unacceptable toxicity occurs, patient loss to follow up, or the study is terminated by the Sponsor, whichever comes first. This includes a 4 week screening period, a 4 month treatment period and a 4 week post dose follow-up period. A follow-up visit within 4 weeks after the last dose of study drug for AE and SAE collection will be conducted. The time on study can vary depending on the observed toxicity and potential benefit an individual patient derives. The study is expected to be completed in approximately 36 months.

This study is being expanded, in this Amendment 7, for safety, PK and efficacy evaluation of the Q2W dosing schedule for PF-06647020 as a single agent treatment or in combination with avelumab in patients with platinum resistant or refractory OVCA and recurrent advanced NSCLC. The Q2W regimen expansion is included as a sub-study to this protocol; the design and procedure details can be found in Appendix 8.




### 3.2. Dose Escalation Phase (Part 1)

A modified toxicity probability interval (mTPI) method, targeting a DLT rate of 25% and an acceptable DLT interval (20%-30%)[8] will be utilized in Part 1 (see Table 8).

**Table 8. Dose Escalation Table**

| | Number of patients treated in current dose | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| DLT | n=2 | n=3 | n=4 | n=5 | n=6 | n=7 | n=8 | n=9 |
| 0 | E | E | E | E | E | E | E | E |
| 1 | na | S | S | S | E | E | E | E |
| 2 | U | D | D | S | S | S | S | S |
| 3 | na | U | U | D | D | S | S | S |
| 4 | na | na | U | U | U | D | D | D |
| 5 | na | na | na | U | U | U | U | U |
| 6 | na | na | na | na | U | U | U | U |
| 7 | na | na | na | na | na | U | U | U |
| 8 | na | na | na | na | na | na | U | U |
| 9 | na | na | na | na | na | na | na | U |

D: De-escalate the dose; E: Escalate the dose; S: Stay at the dose; U:Unacceptable toxicity, na: Not applicable

The target size of each cohort will be 3 patients. However, patients may be enrolled in cohorts of 2-4, starting with 0.2 mg/kg for the first cohort. In cohorts with 2 patients enrolled, an additional patient may be enrolled for dose escalation assessment if one of the two patients has a DLT. Subsequent dose levels may include a maximum 250% escalation until either the dose reaches 1.25 mg/kg, or a patient experiences a DLT. Starting from 1.25 mg/kg, dose escalation in subsequent cohorts will follow a modified Fibonacci scheme with maximum dose increases of 68%, 34%, 33%, 33%, and 33%, respectively. If a high DLT rate is observed at the starting dose, a lower dose (eg, 0.1 mg/kg) will be considered. The study may be stopped if the drug is deemed not tolerable at the lowest dose. Table 9 illustrates the potential dose levels in the dose escalation Part 1 study.

**Table 9. Table of Potential Dose Levels**

| Dose Level | Dose (mg/kg) |
|---|---|
| -1 | 0.10 |
| 1 (starting dose) | 0.20 |
| 2 | 0.50 |
| 3 | 1.25 |
| 4 | 2.10 |
| 5 | 2.80 |
| 6 | 3.70 |
| 7 | 4.90 |

*Modified Fibonacci^ scheme starts from dose level 3

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. Doses higher than 1.25 mg/kg will be escalated no greater than 68%. In the event dose de-escalation is required, an intermediate dose between the dose that requires de-escalation and the dose immediately prior will be considered. In any event, no patients should be treated at the dose level that has been de-escalated or higher for the remainder of the study.

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

1. The maximum sample size has been achieved (approximately 40 patients total).
2. At least 9 patients have been accumulated on a dose that is predicted to be the MTD.
3. All doses explored appear to be overly toxic and the MTD cannot be determined.

Although dose levels are capped at 4.90 mg/kg in the table illustrated (Table 9), the mTPI will continue to operate subject to the constraints detailed above while allowing for doses higher than specified. Doses beyond 4.90 mg/kg may be allowed in 30% increments if necessary.

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

Patients will continue with study treatment every 21 days until disease progression, patient refusal or unacceptable toxicity occurs. Patients experiencing a DLT may be managed with dose modification (after dose interruption) or discontinuation. Subsequent dose levels may not be opened until all patients entered at the current dose level have been treated and observed for at least one complete cycle and the number of DLTs among those patients in their first cycle has been determined. Intra-patient dose escalation will not be permitted in this study.

In the first cohort of the study there will be a minimum of 48 hours separation between dosing of each patient.

The Q2W regimen expansion sub-study contains a dose escalation portion (Part 1) using the mTPI method and dose expansion portion (Part 2); details of the sub-study are included in Appendix 8.

### 3.3. DLT Definition

Severity of adverse events will be graded according to CTCAE version 4.03. For the purpose of dose escalation (Part 1), any of the following adverse events occurring in the first cycle of treatment (within 21 days of first dose or until patient receives 2$^{nd}$ infusion if there are treatment delays) 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 neutropenia ≥ Grade 3 and a single body temperature >38.3°C or a sustained temperature of ≥ 38°C for more than one hour;
  - Grade ≥3 neutropenic infection;

- Grade 4 anemia;
- Grade ≥3 thrombocytopenia with clinically significant bleeding;
- Grade 4 thrombocytopenia:
  - any <10,000;
  - 10,000-25,000 for >3 days.

- Hepatic:
  - Grade ≥3 serum bilirubin, hepatic transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or alkaline phosphatase. For patients with Grade 2 hepatic transaminase or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis, a hepatic transaminase or alkaline phosphatase level >10 times the upper limit of normal (ULN) will be considered as a DLT.
  - ALT or AST ≥3.0 x ULN concurrent with elevation in bilirubin ≥2.0 x ULN.
- Non-hematologic, non-hepatic:
  - Grade ≥3 toxicities that are considered non-hematologic, non-hepatic major organ toxicity (excluding alopecia of any grade, Grade 3 diarrhea that responds to therapy, and Grade 3 nausea and vomiting in the absence of premedication that responds to therapy).
  - Delay by more than 2 weeks in receiving the next scheduled cycle due to persisting toxicities attributable to PF-06647020.

In addition, clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by Pfizer and the investigators. All DLTs need to represent a clinically significant shift from baseline.

Grade ≥3 cytokine release syndrome, infusion reaction, and allergic reaction will not be considered as DLTs (as it is unlikely to be dose related), but may be a reason for study discontinuation, protocol amendment (eg, pre-infusion treatments, infusion duration) and should be reviewed with Pfizer.

In principle, a patient needs to be on study for at least 21 days to be evaluable for DLT observation, and may be replaced if they terminate study participation earlier than 21 days. However, in circumstances of an event not related to study drug (eg, traffic accident, clear disease progression) that leads to study termination close to/before 21 days, the patient might be deemed evaluable if the investigators and sponsor agree.

The DLT definition for the Q2W regimen expansion is included in Appendix 8.

### 3.4. MTD Definition

The MTD would be any doses with true toxicity probabilities in the Equivalence Interval (EI) where the EI is defined as [20%-30%].

The MTD will be the highest dose in the EI.

### 3.5. Dose Expansion Phase (Part 2)

The expansion cohorts will include approximately 22 patients with metastatic or recurrent TNBC, 45 OVCA patients and 20 patients with advanced NSCLC. CCI

[redacted]

Additional safety information gathered in Part 2 may be used to modify the dose recommended for future Phase 2 trials.

### 3.6. Recommended Phase 2 Dose (RP2D) Definition

The 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.

## 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 SELECTION details for the Q2W regimen expansion are included in Appendix 8.

### 4.1. Inclusion Criteria

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

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

1. For the dose escalation phase (Part 1): Histological or cytological diagnosis of solid tumor that is advanced/metastatic and resistant to standard therapy or for which no standard therapy is available.

2. For the dose expansion phase (Part 2): Histological or cytological diagnosis of the following:

   a. CCI [redacted] The TNBC is characterized by:

      - ≤1% of tumor cell nuclei immunoreactive for ER or PR;

        *and*

      - IHC ≤2+ for HER2 or a fluorescence in situ hybridization ratio of <2.2 (HER2 to CEP17) or average HER2 gene copy number fewer than 6 signals per nucleus without an internal control.

   b. CCI [redacted]
   Patients with adenocarcinoma subtype NSCLC should be tested for ALK alterations and EGFR mutations and have exhausted all FDA-approved available targeted therapies.

   c. Advanced epithelial ovarian cancer, primary peritoneal or primary fallopian tube cancer (OVCA). All patients must have progressed while receiving or within 6 months after completion of at least 4 cycles of the most recently administered platinum-containing therapy regimen (single agent or combination). Patient's prior line of therapy could be up to a maximum of three chemotherapy regimens with approved agents (single or combination), as long as the following criteria are met:

      1. Requirements for first line therapy: Patients must have received first-line treatment with a taxane/platinum based combination chemotherapy. Patients must have experienced disease progression during administration of or within 6 months after completing at least 4 cycles of the first line therapy. A third therapeutic agent is permitted if it is part of the initial first line treatment. A neo-adjuvant and an adjuvant chemotherapy constituting of a platinum and a taxane (cisplatin or carboplatin and docetaxel or paclitaxel) should be considered as one line of treatment providing that the treatment free interval is less than four months (calculated from the last administration of the neo-adjuvant regimen to the first administration of the adjuvant regimen).

      2. Requirements for patients who received two prior line of therapy: The first line regimen must be as described in Section 2.1.1. The second line regimen must consist of either platinum salt, gemcitabine, docetaxel, paclitaxel, cyclophosphamide, liposomal doxorubicin, or topotecan, administered as a single agent or in combination therapy.

      3. Requirements for patients who received three prior regimens: the first and second line of prior regimens must be as described in Section 2.1.2. The third line regimen must consist of a platinum salt as a single agent or in combination with gemcitabine, docetaxel, paclitaxel, cyclophosphamide,

liposomal doxorubicin, or topotecan. Patients must have progressed within 6 months of receiving at least 4 cycles of third line therapy or should have experienced documented disease progression, or toxicity requiring cessation of treatment.

Patients who received consolidation/maintenance therapy with approved agent after completion of the platinum-based chemotherapy (ie, additional cycles of a taxane) are permitted to enroll in the study proving they experienced documented disease progression within 6 months from last administration of platinum-based chemotherapy.

CCI [redacted]

3. For the dose escalation phase (Part 1): Patients may have measurable or non-measurable disease.
4. For the dose expansion phase (Part 2): TNBC and NSCLC patients must have at least one measurable lesion as defined by RECIST version 1.1. OVCA patients must either be measurable according to RECIST version 1.1 or assessable according to the Gynecological Cancer Intergroup (GCIG, 2011)[18] CA-125 criteria and require chemotherapy treatment.
5. CCI [redacted]
6. Adults age ≥18 years.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.
8. Adequate bone marrow function, including all of the following:
   a. Absolute Neutrophil Count (ANC) ≥1,500/$mm^3$ or ≥1.5 x $10^9$/L;
   b. Platelets ≥100,000/$mm^3$ or ≥100 x $10^9$/L;
   c. Hemoglobin ≥9 g/dL.
9. Adequate renal function, including all of the following:

a. Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥60 ml/min as calculated using the method standard for the institution.

10. Adequate liver function, including all of the following:

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

    b. Aspartate and alanine transaminase (AST & ALT) ≤3.0 x ULN; ≤5.0 x ULN if there is liver metastasis;

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

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

12. Negative serum/urine pregnancy test (for females of childbearing potential) at screening and within 72 hours of starting treatment.

13. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 30 days after the last dose of assigned treatment.

    Female patients who are not of childbearing potential (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 post-menopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum Follicle Stimulating Hormone (FSH) level within the laboratory's reference range for postmenopausal females that are <60 years old.

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

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

16. Life expectancy of at least three months.

DDI Sub-Study: See Appendix 7 for additional inclusion criteria.

### 4.2. Exclusion Criteria

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

1. Patients with known symptomatic brain metastases requiring steroids. 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.

2. Major surgery, radiation therapy (other than palliative radiotherapy to lesions that will not be followed for tumor assessment on this study ie, non-target lesions) or systemic anti-cancer therapy within 3 weeks or 5 half-lives (whichever is shorter) of starting study treatment (6 weeks for mitomycin C or nitrosoureas) or hormonal, biological or investigational agents within 2 weeks [or within 5 times the half-life of the agent (whichever is shorter)] of starting study treatment. If the immediate prior regimen included only weekly chemotherapy, then a 2 week washout period is acceptable.

3. Previous high dose chemotherapy requiring stem cell rescue.

4. Presence of Grade ≥2 peripheral neuropathy.

5. OVCA patients with any of the following:

    a. Non-epithelial, including malignant mixed Müllerian tumors.

    b. Ovarian tumors with low malignant potential (ie, borderline tumors).

    c. Previous treatment with > three (3) anti-cancer regimens.

    d. Any prior radiotherapy to the pelvis or abdomen.

    e. Patients with CA-125-only disease.

    f. Previous exposure to murine CA-125 antibody (only applicable to those patients with non-measurable disease by RECIST version 1.1) (Appendix 2).

    g. Unresolved bowel obstruction, including sub-occlusive disease, related to the underlying disease and history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess.

6. Prior treatment with a compound of the same mechanism.

7. Currently receiving active treatment in another clinical study.

8. Patients currently on or anticipated to be put on either strong CYP3A inhibitors or inducers (defined in US Food and Drug Administration (FDA) guidance “Drug interaction studies - study design, data analysis, implications for dosing and labeling

recommendations" and summarized in Appendix 6). Patients may undergo a washout period of 4 to 5 times the half-life of the inducer or inhibitor prior to enrollment in the study.

9. Active and clinically significant bacterial, fungal or viral infection including known hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

10. Any of the following in the previous 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.

11. Known or suspected hypersensitivity to recombinant human or murine proteins.

12. Any ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, any grade of atrial fibrillation, or QTcF interval >470 msec, except for documented Right Bundle Branch Block, at screening.

13. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

14. 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 trial.

15. Pregnant female patients; breastfeeding female patients; male and female patients of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 30 days after last dose of investigational product.

DDI Sub-Study: See Appendix 7 for additional exclusion criteria.

### 4.3. Lifestyle Guidelines

In this study, male patients who are able to father children and female patients who are of childbearing potential receive PF-06647020, a compound for which a teratogenic risk is currently unknown. Those who, in the opinion of the investigator, are sexually active and at risk for pregnancy must agree to use two (2) methods of highly effective contraception throughout the study and continue to do so for at least 30 days after the last dose. The investigator or his/her designee, in consultation with the patient, will select two appropriate methods of contraception for the individual patient from the list of permitted contraception methods (see below) and instruct the patient in their consistent and correct use. Patients need

to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly 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 one or both selected contraception methods are 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, implanted or transdermal hormonal methods of contraception are 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 or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

   UK only: Per Medicines and Healthcare products Regulatory Agency (MHRA), a condom with or without spermicide is not considered a highly effective method of contraception in the UK. Other highly effective methods of contraception described in this section should be used.

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).

   Female patients of non-childbearing potential must 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; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

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

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 at least 28 days after the last dose.

Applicable to Appendix 8, UK only: All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using 2 highly effective methods of contraception as described in this section, beginning with the first dose of investigational product and continuing for at least 120 days after the last dose of investigational product (150 days if the male patient is participating in the combination cohort with avelumab).

### 4.4. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, 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 help desk 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 help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used 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 help desk 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

### 5.1. Allocation to Treatment

Eligible patients will be enrolled to receive PF-06647020 in an open-labeled, unblinded manner. Patients will be successively assigned to the next available treatment slot at a dose level decided on after the previous cohort's safety evaluation and ongoing observations of earlier enrolled patients.

Patient number and dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will email a complete Registration Form to the designated sponsor study team member. The sponsor will assign a patient identification number, which will be used on all

CRF pages and other study-related documentation or correspondence referencing that patient and email to the site.

No patient shall receive study drug 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

All doses of investigational product will be administered by the appropriately designated study staff at the investigational site.

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

### 5.3. Drug Supplies

PF-06647020 will be supplied for the study by Pfizer.

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

DDI Sub-Study: Commercially-available fluconazole tablets will be provided by the site. See Appendix 7 for details.

#### 5.3.1. Dosage Form and Packaging

PF-06647020 for injection, 60 mg extractable per vial, is presented as a sterile lyophilized product, white to off white cake, and packaged in a 6 mL glass vial. Each vial of PF-06647020 for injection is reconstituted with water for injection (WFI). The vial is designed for single use. The packages will be properly labeled according to local regulatory requirements.

Fluconazole Tablets United States Pharmacopeia (USP), for oral administration contains 50, 100, 150, or 200 mg of fluconazole, USP.

### 5.3.2. Preparation and Dispensing

See the Investigational Product Manual for instructions in 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 chemotherapeutic agents.

## 5.4. Administration

PF-06647020 will be administered on Day 1 of each 21-day cycle per the Investigational Product Manual as an IV infusion over approximately 60 minutes on an outpatient basis.

Details for preparation and administration of the PF-06647020 infusion are provided in the current PF-06647020 Investigational Product Manual. 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-06647020 required for dose preparation. The decision to recalculate PF-06647020 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-06647020 required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

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 21 days. Each patient may receive PF-06647020 until disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

In the event of infusion related reactions, Investigators should institute treatment measures according to best medical and nursing practice. The monitoring and treatment guidelines are provided in Appendix 5. In the case of infusion related reactions, characterized by fever and chills, and less commonly hypotension, the sponsor should be notified and pre-treatment medication should be administered prior to subsequent infusions (in the case that the patient is able to continue on treatment as per Appendix 5). The decision to incorporate pre-medication in all patients will be made following discussions between the sponsor and the investigators. Patients should be pre-treated with acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each PF-06647020 administration. The pre-treatment medications will not be supplied by Pfizer.

Suggested starting doses are 650 to 1000 mg acetaminophen and 50 mg diphenhydramine (or equivalent of other antihistamine) IV or oral. Two (2) additional doses of acetaminophen may be administered approximately every 4 hours after the initial pre-treatment or as needed.

Details of PF-06647020 Administration in the Q2W regimen expansion are included in Appendix 8.

### 5.4.1. 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 worst 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.

### 5.4.2. Dose Interruptions/Delays

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

If a treatment interruption continues beyond Day 21 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle. 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 $\geq$1,000/mm$^3$;
- Platelets count $\geq$75,000/mm$^3$;
- Non-hematologic toxicities have returned to baseline or Grade $\leq$1 severity (or, at the investigator discretion, Grade $\leq$2 if not considered a safety risk for the patient).

If these conditions are not met, treatment must be delayed by 1 week. If, after a 1-week delay, all toxicities have recovered within the limits described above treatment with PF-06647020 can be resumed. Please refer to section Dose Reductions for adverse events requiring dose reduction at the time of treatment resumption.

Initiation of the next cycle can only be delayed by a maximum of 2 weeks. Therefore, if persisting toxicity does not allow PF-06647020 treatment resumption within 35 days of Day 1 of previous cycle, this will result in discontinuation of the patient from treatment unless discussed and agreed with the Sponsor.

### 5.4.3. Dose Reductions

Following dose interruption or cycle delay due to toxicity, PF-06647020 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.

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.

Dose reduction of PF-06647020 by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Patients enrolled in the first cohort should be discontinued from the study if more than 1 dose reduction is required. Patients enrolled in subsequent cohorts should be discontinued from the study if more than 2 dose reductions are required, unless otherwise agreed between the investigator and the sponsor. 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.

For patients experiencing an adverse event related to PF-06647020 that fails to recover to CTCAE Grade 1 (or within 1 grade of starting values for pre-existing laboratory abnormalities) leading to treatment delay of >2 weeks should be discontinued unless discussed with the Sponsor.

Recommended dose reductions are illustrated in Table 10.

Patients experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved.

## Table 10. Dose Modifications for Toxicity Considered Possibly Drug-Related

| Toxicity | Action |
|---|---|
| Grade 3 or 4 nonhematologic toxicity (including persistent nausea, vomiting, diarrhea despite optimal medical therapy) | • Hold PF-06647020 infusion until recovery to Grade 0-1 or baseline and reduce by 1 dose level.<br>• Discontinue PF-06647020 if dose delay is more than 2 weeks.<br>• If toxicity reoccurs despite reduction, patient may be dose reduced again by another dose level upon recovery to grade 0-1 or baseline unless the patient is in the first dose group, then only 1 dose reduction is allowed.<br>• Prompt palliative measures are strongly encouraged (eg, anti-emetics). |
| Grade 4 nonhematologic toxicity | • Patients who experience Grade 4 non hematologic toxicities despite intervention should be discontinued from treatment. |
| Grade ≥3 hepatic toxicity (including serum bilirubin, ALT, AST, alkaline phosphatase) | • Hold PF-06647020 infusion until recovery to Grade 0-1 or baseline and reduce by 1 dose level.<br>• Discontinue PF-06647020 if dose delay is more than 2 weeks.<br>• If toxicity reoccurs despite reduction, patient may be dose reduced again by another dose level upon recovery to grade 0-1 or baseline unless the patient is in the first dose group, then only 1 dose reduction is allowed. |
| ALT or AST ≥3.0 x ULN concurrent with elevation in bilirubin ≥2.0 x ULN | • Discontinue treatment |
| Hematologic toxicities<br>• Grade 4 neutropenia, ie, ANC <500/$mm^3$ (0.5 x $10^9$/L) for more than 7 days.<br>• Febrile neutropenia, ie, fever with a single temp >38.3°C or sustained temp ≥38°C for more than 1 hour with ANC <1000/$mm^3$.<br>• Grade 4 Anemia<br>• Grade ≥3 Thrombocytopenia with bleeding.<br>• Grade 4 Thrombocytopenia, ie, PLTS <25,000 $mm^3$ (25.0 x $10^9$/L). | • Hold PF-06647020 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 platelets/$mm^3$).<br>• Reduce PF-06647020 by 1 dose level.<br>• If toxicity reoccurs despite dose reduction, patient may either be held until recovery and continuation at same dose, or undergo further dose reduction by another dose level unless the patient is in the first dose group, then only 1 dose reduction is allowed. |
| Other grade 4 hematologic toxicity | • Hold PF-06647020 until recovery to Grade 0-1 or baseline and reduce PF-06647020 dose by 1 dose level.<br>• If toxicity reoccurs despite dose reduction, patient may either be held until recovery and continuation at same dose, or undergo further dose reduction by another dose level unless the patient is in the first dose group, then only 1 dose reduction is allowed. |
| No recovery of toxicities within 2 weeks of scheduled PF-06647020 infusion | • Discontinue treatment |

## 5.5. Drug Storage

The investigator, or an approved representative (eg, pharmacist) will ensure that all investigational product is 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 Investigational Product Manual for storage conditions of the product.

Storage conditions stated in the SRSD (ie, Investigator Brochure) 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 study. Even for continuous monitoring systems, a log or site procedure which 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 labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

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

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

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

## 5.6. Drug Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

### 5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable

environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

### 5.7. Concomitant Treatment(s)

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

All concomitant treatments including supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, blood products, as well as non-drug interventions (eg, transfusions, analgesic use or paracentesis) received by patients within 28 days (4 weeks) prior to first dose of study treatment until the end of study visit will be recorded on the CRF. This will include the name of the procedure or medication, route and duration of treatment.

Based on the anticipated low systemic concentrations of released Aur0101, PF-06647020 is considered to be of low risk to impact the PK of compounds primarily metabolized by CYP enzymes. As Aur0101 is a P-gp substrate and is primarily metabolized by CYP3A4, there may be a potential change in Aur0101 PK exposure when PF-06647020 is co-administered with potent CYP3A/P-gp inhibitors and/or inducers. Therefore, co-administration of PF-06647020 and potent CYP3A/P-gp inhibitors and/or inducers, as listed in Appendix 6, is not recommended. Selection of an alternate concomitant medication with no or minimal enzyme inhibition and/or induction potential is recommended. Any questions regarding administration of concomitant medications should be directed to the sponsor.

During the study, co-administration of potent CYP3A inducers and strong CYP3A inhibitors (see Appendix 6) with PF-06647020 is not permitted. This restriction is included to minimize the potential influence of a pharmacokinetic drug interaction on the determination of the maximum tolerated dose. Patients may undergo a washout period of 4 to 5 times the half-life of the inducer or inhibitor prior to screening and enrollment in the study.

DDI Sub-Study: See Appendix 7 for further details on concomitant medications.

Guidance for concomitant treatment in the Q2W regimen expansion is included in Appendix 8.

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

No additional anti-tumor treatment including chemotherapy, hormonal therapy, radiotherapy, or experimental anticancer medications will be permitted while patients are receiving study therapy. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression.

### 5.7.2. Supportive Care

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

### 5.7.3. Hematopoietic Growth Factors

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

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

### 5.7.4. Anti Diarrhea, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is permitted in the first and subsequent cycles at the investigator's discretion. Investigators should follow National Comprehensive Cancer Network (NCCN) Guidelines and/or institutional standard operating procedures for selection of the prophylactic drug, assuming the drug is not included in the Concomitant Treatment(s) section.

### 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 ≥12.5 mg/day or dexamethasone ≥2 mg/day) for palliative or supportive purpose is not permitted. Acute emergency administration, topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed.

### 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-06647020 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06647020 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF--06647020 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

# 6. STUDY PROCEDURES

## 6.1. Screening

All patients being considered for the study and eligible for screening must provide evidence of informed consent for the study before completing any study-specific procedures and may be >28 days from first dose. 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 Assessments section on Patient Information and Informed Consent.

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.

For screening procedures see the Schedule Of Activities and Assessments section. Following completion of the screening assessments and confirmation of eligibility, patients may be enrolled.

## 6.2. Treatment Period

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

## 6.3. Follow-up Visit

For follow-up procedures see Schedule Of Activities and Assessments section. Patients will return to the clinic at least 28 days and no more than 35 days after the end of treatment visit to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

## 6.4. Patient Withdrawal

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

Lost to Follow-Up: All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a

minimum of three documented phone calls, faxes, or emails as well as lack of response by patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.

Withdrawal due to disease progression: According to published and internally generated data, an ADC may trigger immune responses in NSCLC adenocarcinoma resulting in a "delayed" response phenomenon in which the mechanism of the delayed response is to be explored. It is possible that a patient with NSCLC adenocarcinoma treated with PF-06647020 could demonstrate disease progression at an early time point of response measurement and later demonstrate a clinical improvement which could be a result of a delayed response. In scenarios where clinical improvement is seen at the Follow Up Visit and the patient has not received any additional anti-cancer therapy since the last dose of study drug, the Investigator may discuss with the Sponsor about the possibility of keeping the patient on study and resume treatment with the study drug.

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 study drug for adverse events.

An End of Treatment visit will be conducted at the visit that the patient is discontinued from the trial. Assessments should be obtained if not completed in the last week. Tumor assessments should be performed if not completed in the last 6 weeks.

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 investigator site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression according to RECIST 1.1;
- 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.

Reasons for withdrawal from study follow-up may include:

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

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

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

## 7. ASSESSMENTS

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

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

DDI Sub-Study: See Schedule of Activities (Table A1and Table A2) in Appendix 7 for details.

Q2W Regimen Expansion: See Schedule of Activities (Tables A3, A4 and A5) in Appendix 8 for details.

### 7.1. Safety Assessment

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

#### 7.1.1. Pregnancy Testing

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 on Day 1 of Cycle 1 before investigational product administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will be repeated at every treatment cycle during the active treatment period, at the end of study treatment and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards/Ethics Committees (IRB/EC) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication but may remain in the study.

#### 7.1.2. Adverse Events

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

#### 7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule Of Activities and analysed at local laboratories. On Day 1 of Cycle 1, the hematology, coagulation, blood chemistry and urinalysis samples do not need to be repeated if the laboratory screening assessments are performed within 72 hours prior to dosing. Hematology and blood chemistry will be collected on Days 1, 4, 8 and 15 of the first cycle. For subsequent cycles, hematology and blood chemistry will be collected on Days 1, 8, and 15 of each cycle. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.

Investigators may have additional blood tests performed for the purpose of planning treatment administration, dose modification, or following AEs.

| Hematology | Chemistry | Coagulation | Urinalysis | Pregnancy Test |
|---|---|---|---|---|
| Hemoglobin | ALT/SGPT | PT or INR | Urine dipstick or full urinalysis is acceptable | For female patients of childbearing potential, serum or urine |
| Platelets | AST/SGOT | PTT | For urine protein: If | |
| WBC | Alk Phos | | ≥2+ protein on urine | |
| Absolute Neutrophils | Sodium | | dipstick, then collect | |
| Lymphocytes (absolute or %) | Potassium | | spot urine sample to | |
| Monocytes (absolute or %) | Magnesium | | calculate urine | |
| Eosinophils (absolute or %) | Chloride | | protein to creatinine | |
| Basophils (absolute or %) | Calcium | | ratio (UPCR) | |
| | Total Bilirubin*** | | | |
| | Total protein | | Microscopic analysis | |
| | BUN or Urea | | if dipstick abnormal | |
| | Creatinine | | | |
| | Uric Acid | | | |
| | Glucose (non-fasted) | | | |
| | Albumin | | | |
| | Phosphorous | | | |
| | Bicarbonate or carbon dioxide | | | |
| | LDH | | | |

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

### 7.1.4. Vital Signs and Physical Examination

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

A full physical examination (PE) will be performed at Screening, Day 1 of Cycle 1, and at the End of Treatment visit for each patient and will include an assessment of all body systems (including neurological examination, genitourinary examination is optional), the measurement of body weight, height (measured at screening only) vital signs and assessment of ECOG performance status. The full PE on Day 1 of Cycle 1 is not required if the screening full PE is performed within 1 week of dosing. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an adverse event in the CRF.

Abbreviated PEs should be performed as appropriate at each visit where full physical exams are not required, and on an as needed basis for assessment of adverse events. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.

An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes Best Corrected Visual Acuity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic Exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, the peripheral retina.

Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow up.

Weight and body surface area (BSA) do not need to be performed at each visit; however patients should be monitored throughout the study for significant weight change. If a patient's weight fluctuates by more than 10% in either direction, weight should be collected to recalculate the appropriate dose for the next cycle. In cases where individual institution/pharmacy require more frequent weight measurements, weight can be obtained on each day of administration, and the dose recalculated.

Vital signs will include measurements of blood pressure, pulse rate and temperature (oral, tympanic or axillary). 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. Sitting blood pressure (BP) will be measured after 5 minutes of rest with the patient's arm supported at the level of the heart and recorded to the nearest mmHg sufficient. The same arm (preferably the dominant arm) should preferably be used throughout the trial. The blood pressure cuff, which has been properly sized and calibrated, should be used to measure blood pressure. The use of automated devices for measuring BP and pulse rate is acceptable. When the timing of the measurements coincides with a blood collection, blood pressure and pulse rate should be obtained around to the nominal time of the blood collection.

Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.

### 7.1.5. (12-Lead) ECG

12-lead ECG will be collected as per the Schedule Of Activities and should be performed after the patient has rested quietly for a sufficient amount of time. ECGs will be compared to the patient's screening ECG and any clinically significant changes will be recorded as adverse events and evaluated further, as clinically warranted. If the mean QTc is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs should be performed if clinically indicated.

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 or after 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).

The following measurements from ECGs will be recorded: QT interval, Heart Rate, RR Interval, PR Interval, and QRS Complex.

Beginning at Cycle 8, Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.

### 7.2. Pharmacokinetics Assessments

Blood samples will be collected from patients for PK analysis as noted in the Schedule Of Activities. All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing and according to windows provided in the Schedule Of Activities. Samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection will always be noted on the Case Report Form (CRF). If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and sponsor. PK samples will be assayed 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 Laboratory Manual.

#### 7.2.1. Serum Sample Collection for PK analysis of ADC (PF-06647020), Total Antibody (hu6M024 mAb) and Unconjugated Payload (PF-06380101)

Blood samples (4 mL whole blood) to provide approximately 2 mL of serum for measurement of serum PF-06380101 concentrations and blood samples (6 mL whole blood) to provide approximately 3 mL of serum for determination of ADC (PF-06647020) and total antibody (hu6M024 mAb) concentrations will be collected from patients in dose escalation and randomized Arms A and C, in appropriately labeled tubes at times specified in the SOA.

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 should be documented in the CRF.

As part of understanding the PK disposition of the study drug, samples may be used for possible metabolite identification experiments and/or evaluation of the bioanalytical methods. These data will be used for internal exploratory purpose 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 consumed during the course of these experiments, will be discarded.

CCI [redacted] The studies may help in the future development of this drug as a single agent, or in combination with other compounds.

CCI [redacted]

CCI [redacted] Samples will be assayed using a validated analytical method 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.

### 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. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out central nervous system (CNS) metastases.

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

CT or MRI scans are to be done every 6 weeks (±5 days) from the start of study treatment until disease progression or death, or at the time of withdrawal from treatment (if not done in the previous 6 weeks). The frequency may be reduced to every 12 weeks after 6 months of study treatment. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. For patients enrolled in Part 2, responses of complete response (CR) or partial response (PR) must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.

Assessment of response will be made using RECIST version 1.1 (Appendix 2). Changes in tumor size will be categorized as CR, PR, SD, or PD, the latter incorporating the appearance of new lesions. For patients in Part 2, responses of CR or PR must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met.

All radiographic images will be collected for potential central review. Additional information on diagnostic imaging procedures and collection will be included in the Imaging Manual.

OVCA patients should have serum samples collected for CA-125 at pre-treatment, each tumor assessment (every 6 wks), and end of treatment. Additional serum samples to be collected for assessment of CA-125 as per Investigator discretion.

CCI [redacted]

One of the key elements of this study is the possibility to evaluate potential molecular targets that could be modified in vivo by PF-06647020. CCI [redacted] The studies may help in the future development of this drug as a single agent, or in combination with other compounds.

[redacted]

Table 11 summarizes representative assays to be used and the source of the samples. Refer to the Schedule Of Activities for details pertaining to specific days of sample collection and to the Study Manual for details of sample preparation.

**Table 11. Pharmacodynamic Summary**

| *Assay* | *Source* |
|---|---|
| CCI | |
| | |
| mRNA profiling | CCI |

CCI

Additionally, evaluation of T-cell receptor (TCR) usage, clonality, and frequency via TCR sequencing may be performed.

Instructions for sample collection, processing, storage and shipment will be provided in the Study Manual. Samples may be retained in accordance with local regulations and if not used within this timeframe, will be destroyed.

### 7.5.2. Immunophenotyping

CCI

Instructions for sample collection, processing, storage and shipment will be provided in the Study Manual.

Samples may be used for flow cytometry assay development. Samples used for this purpose will be retained in accordance with local regulations and if not used within this timeframe, will be destroyed.

CCI

[redacted]

[redacted]

### 7.7. Immunogenicity Assessment

Blood samples (6 mL) to provide approximately 3 mL of serum to detect ADA and neutralizing antibody (Nab) against PF-06647020 will be collected into appropriately labeled tubes at times specified in the Schedule Of Activities. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Study Manual.

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

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

CCI [redacted]

[redacted] Comparing the deoxyribonucleic acid (DNA), ribonucleic (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. CCI [redacted]

[redacted] Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. CCI [redacted] Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical study.

CCI [redacted]

[redacted] Detailed collection, processing, storage, and shipment instructions are provided in the laboratory manual.

CCI [redacted]
Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

CCI [redacted]

[redacted]

[redacted]

### 7.9. Other Assessments

#### 7.9.1. Tumor and Medical History

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

#### 7.9.2. Baseline Signs and Symptoms

On Day 1 prior to the start of treatment, patients will be asked about any signs and symptoms experienced within the past 14 days. Baseline signs and symptoms will be recorded on the Medical History CRF.

# 8. ADVERSE EVENT REPORTING

## 8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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

### 8.1.1. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

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

If a patient begins a new anticancer therapy, the AE reporting period for nonserious 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.

### 8.1.2. 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.

### 8.2. 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 adverse event(s) are captured on an adverse event AE CRF page.

### 8.2.1. Abnormal Test Findings

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

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

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

### 8.2.2. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

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

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

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

### 8.2.3. 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 on Serious Adverse Event Reporting Requirements).

### 8.2.4. Potential Cases of Drug-Induced Liver Injury

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

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

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 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, PT/ INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for 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.

### 8.2.5. 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.

### 8.3. Severity Assessment

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

#### 8.3.1. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); 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 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.

#### 8.3.1.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a 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 Serious Adverse Event (SAE) Report Form and 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 preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

Additional information regarding the exposure during pregnancy 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

#### 8.3.1.2. 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 adverse event.

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.

### 8.4. Withdrawal Due to Adverse Events (See also the Section on Patient Withdrawal)

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

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

#### 8.4.1. 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.

## 8.5. 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.

### 8.5.1. 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 exposure during pregnancy, 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.

### 8.5.2. 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.

### 8.5.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

# 9. DATA ANALYSIS/STATISTICAL METHODS

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

Additional details of the analyses will be provided in the clinical study report (CSR). This information may include details of missing and, if applicable, unused and spurious data. Deviations from the statistical plan will be reported in the clinical study report.

## 9.1. Analysis sets

Data analyses will be performed on the following analysis population.

1. Safety analysis set.
    - The safety analysis set includes all enrolled patients who receive at least one dose of study medication.
2. Full analysis set.
    - The full analysis set includes all enrolled patients.
3. Per protocol analysis set (evaluable for MTD).
    - The per protocol analysis set includes all enrolled patients who receive at least one dose of study medication and who do not have major treatment deviations during first cycle. Patients with major treatment deviations in the 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 33% of the planned dose of PF-06647020 (provided that the reduction is not due to toxicity attributable to PF-06647020;
        - Administration of more than 33% of the planned dose of PF-06647020 failure to satisfy major entry criteria (eg, confirmation of the target disease, signed informed consent);
        - Use of other anticancer treatments during the active treatment and disease follow up phases other than as defined/allowed in this protocol;
        - A baseline disease assessment and at least one post-baseline disease assessment.

4. PK analysis sets.

   - The PK parameter analysis population is defined as patients who receive at least 1 dose of study treatment and have sufficient information to estimate at least 1 of the PK parameters of interest.

5. Immunogenicity analysis set.

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

6. CCI [redacted]

7. CCI [redacted]

### 9.2. Statistical Methods and Properties

This study is designed to establish the MTD defined as the dose that yields approximately 25% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) 20% to 30%. The 25% target was chosen based on safety considerations. The prior distribution of DLT is set as a beta (0.75, 0.65), and the threshold probability for early termination and dose exclusion is set to 0.975. Doses with an incidence of DLT ≥33% cannot be selected as MTD although is allowed by the mTPI method.

#### 9.2.1. Statistical Methods for Dose Escalation/De-Escalation

The modified toxicity probability interval (mTPI) design[8] uses a Bayesian statistics framework and a beta/binomial hierarchical model 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). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to target probability (pT), the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model.

Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a two-way table as shown in Table 8. Thus, compared to other advanced model-based designs published in the literature, the mTPI design is

logistically less complicated and easier to implement. Recently, a phase I study based on the mTPI design has been published.[6]

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 underdosing interval is defined as (0; pT-$e_1$), the over-dosing interval (pT+$e_2$), 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-06647020 as a single-agent, $e_1$ is selected as 0.05, and $e_2$ is selected as 0.05. Therefore, the target interval for the DLT rate is (0.20, 0.30).

The three dosing intervals are associated with three different dose-escalation decisions. The under-dosing interval corresponds to a dose escalation (E), over-dosing corresponds to a 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[8] 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 DLT rate <30%, whichever comes first.

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

**Table 12. Escalation Probability**

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

### 9.2.2. Statistical Method for Estimating the MTD

As previously described, the estimated MTD is the highest tested dose level with DLT rate <0.30 in at least 9 DLT evaluable patients. We assume that higher doses of PF-06647020 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.

### 9.3. Sample Size Determination

Approximately 190 patients are expected to be enrolled in this study, which includes approximately 72 patients for the Q2W Regimen Expansion in Amendment 7.

The exact sample size of the mTPI design in Part 1 cannot be pre-specified in advance because it is a dynamic feature of the design. The maximum sample size after which the Part 1 will be stopped and MTD declared is 40 patients. Also, a minimum of 9 patients is required to establish the MTD. The actual sample size of Part 1 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 1, this number will be at least 9 patients. However, since not every dose listed will be studied and variable cohort size is allowed, the actual number of patients treated at each dose will vary.

The sample size in Part 2 is based on clinical consideration, rather than statistical justification. Upon identification of the MTD by the mTPI method, approximately 22 patients with TNBC, 45 patients with OVCA and 20 patients with NSCLC will be enrolled in Part 2 to further evaluate safety and preliminary efficacy parameters.

### 9.4. Efficacy Analysis

In this First in Patient study anti-tumor activity is a secondary objective.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor measurements, tumor response at each visit, and best overall response.

Objective tumor response, as assessed using the RECIST version 1.1 by calculating the Overall (OR), Duration of Response Rate (ORR) and(DoR), DCR, Time to Progression (TTP), as determined by Investigator [As assessed by RECIST version 1.1], PFS, OS and clinical benefit response rate will be summarized and presented if data permits.

#### 9.4.1. Analysis of Overall Response

For patients to be considered evaluable for efficacy they must have received at least one dose of study medication and have a baseline tumor assessment. Patients must also present with measureable disease.

The best overall response is the best response recorded from first dose until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since screening). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. All measurements (or “too small to measure”) must be provided for every target lesion to document SD or PR.

The main goal of confirmation of objective response is to avoid an incorrect estimation of the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Clinical benefit response (CBR) is defined as a CR, PR, or SD lasting for ≥6 cycles.

### 9.5. Analysis of Other Endpoints

CCI [redacted]
Data will also be displayed graphically, where appropriate. CCI [redacted] Additional details of the analyses are outlined in the SAP.

#### 9.5.1. Analysis of Pharmacokinetics

CCI [redacted] PK parameters will be determined from the respective concentration-time data using standard noncompartmental methods. Actual sample collection times will be used for the parameter calculations. For ADC (PF-06647020) and total antibody (hu6M024 mAb), PK parameters including maximum concentration ($C_{max}$), time to maximum concentration ($T_{max}$), area under the concentration-time curve over 1 dosing interval ($AUC_{\tau}$), area under the concentration-time curve from time 0 to the last measurable concentration ($AUC_{last}$), and if data permit or if considered appropriate, area under the concentration-time curve from time 0 extrapolated to infinity time ($AUC_{inf}$), terminal elimination half-life ($t_{½}$), clearance (CL), volume of distribution at steady state ($V_{ss}$), and accumulation ratio ($R_{ac}$) will be calculated. For unconjugated payload (PF-06380101), PK parameters including $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC_{inf}$, $AUC_{\tau}$, $t_{½}$, and $R_{ac}$ will be calculated as appropriate. For avelumab, PK parameters including $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC_{inf}$, $AUC_{\tau}$, $t_{½}$, CL, $V_{ss}$ and $R_{ac}$ will be calculated as appropriate.

Drug concentrations of ADC (PF-06647020), total antibody (hu6M024 mAb), unconjugated payload (PF-06380101), and avelumab will be summarized graphically and with descriptive statistics by dose/regimen/treatment, cycle, and the nominal PK sampling time. Noncompartmental PK parameters will be summarized descriptively by dose/regimen/treatment and cycle.

#### 9.5.2. Pharmacokinetic/Pharmacodynamic Analysis

Safety (eg, DLT, platelet count) and efficacy (ORR) data from both Part 1 and Part 2 will be pooled. PK/PD analyses will be conducted to explore the exposure-response relationship using appropriate model-based methods to assist MTD estimation.

CCI [redacted] PK/PD analysis using appropriate model-based methods will be explored to better understand the exposure-response relationship and results may be reported separately.

### 9.5.3. Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of patients with positive ADA and Nab each will be summarized by dose level (Part 1) or by treatment arms (Part 2). For patients with positive ADA or neutralizing antibodies, the magnitude (titer), time of onset, and duration of ADA or neutralizing antibodies response will also be described, if data permit.

Potential impact of immunogenicity on PK and CCI [redacted] safety/tolerability and efficacy of PF-06647020 will be explored, if data is warranted.

## 9.6. Safety Analysis

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

AEs will be presented with and without regard to causality based on the investigator's judgment. The frequency of overall toxicity, categorized by toxicity Grades 1 through 5, will be described. Additional summaries will be provided for AEs that are observed with higher frequency.

Adverse events, ECGs, blood pressure, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of patients. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information collected during the course of the study will not be captured for inclusion into the study database, unless otherwise noted. However, any untoward findings identified on physical and/or neurologic examinations conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be captured for inclusion into the study database, unless otherwise noted. Demographic data collected at Screening will be included in the study database.

### 9.6.1. Analysis of Primary Endpoint

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. Adverse Events constituting DLTs will be listed per dose level. Because the intent is to find a desirable dose that meets the tolerability criteria based on DLT rate while demonstrating clinical activity based on response rate, descriptive statistics (n, frequency and percentage) will be reported. Corresponding listings of data will be generated.

### 9.6.2. Analysis of Secondary Safety Endpoints

#### 9.6.2.1. Adverse Events

AEs will be graded by the investigator according to 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, 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 CTCAE grade definitions, results will be categorized as normal, abnormal or not done.

### 9.6.3. ECG

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval and QRS interval will be summarized by treatment and time. QT intervals will be corrected for heart rate (QTc) using Fridericia's correction factors (QTcF).

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

**Table 13. Safety QTcF**

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

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

If more than one ECG is collected at a nominal time post dose (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the three individual ECG tracings has a QTcF value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the patient's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the

average from those triplicate measurements is also ≥500 msec. Changes from baseline will be defined as the change between QTcF post dose and the pre-dose value on Day 1.

### 9.7. Data Safety Monitoring Committee

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

- Surveillance for 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 investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

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

# 11. DATA HANDLING AND RECORD KEEPING

## 11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator 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 chart. In these cases, data collected on the CRFs must match the data in those charts.

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

## 11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH, 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 the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

## 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 numerical codes based on a numbering system provided by Pfizer in order to de-identify study patients. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

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

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

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

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

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

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

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

## 13. DEFINITION OF END OF TRIAL

### 13.1. End of Trial in All Participating Countries

End of Trial in all participating countries is defined as Last Patient Last Visit.

## 14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06647020 at any time.

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

# 15. PUBLICATION OF STUDY RESULTS

## 15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

## 15.2. Publications by Investigators

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

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

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

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

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

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

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

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## Appendix 1. Abbreviations

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

| Abbreviation | Term |
|---|---|
| ADA | Anti-drug Antibody |
| ADC | Antibody Drug Conjugate |
| ADCC | Antibody dependent cell mediated cytotoxicity |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALK | Anaplastic Lymphoma Kinase |
| ALT | Alanine Aminotransferase |
| AML | Acute Myeloid Leukemia |
| ANC | Absolute Neutrophil Count |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Curve |
| Aur0101 | Auristatin |
| BBS | Biospecimen Banking System |
| BCVA | Best Corrected Visual Acuity |
| BID | Twice Daily |
| BOR | Best Overall Response |
| BP | Blood Pressure |
| C1D1 | Cycle 1 Day 1 |
| CBC | Complete Blood Count |
| CBR | Clinical Benefit Response |
| CD8 | Cluster of Differentiation 8 |
| CDC | Complement Mediated Cytotoxicity |
| CK | Creatine Kinase |
| CL | Clearance |
| CLIA | Clinical Laboratory Improvement Amendments |
| CNS | Central Nervous System |
| COPD | Chronic Obstructive Pulmonary Disease |
| CR | Complete Response |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSA | Clinical Study Agreement |
| CSC | Cancer Stem Cells |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA 4 | Cytotoxic T-lymphocyte–associated Antigen 4 |
| DAR | Drug:mAb Ratio |

| Abbreviation | Term |
|---|---|
| DCR | Disease Control Rate |
| DDI | Direct Inhibition, Metabolism-Dependent Inhibition and Induction |
| DDI | Drug-Drug Interaction |
| DILI | Drug-induced Liver Injury |
| DLT | Dose Limiting Toxicities |
| DNA | Deoxyribonucleic Acid |
| DoR | Duration of Response |
| EC | Ethics Committee |
| ECG | Electrocardiograms |
| ECOG | Eastern Cooperative Oncology Group |
| EDP | Exposure During Pregnancy |
| EDTA | Ethylenediaminetetraacetic Acid |
| EGFR | Epidermal Growth Factor Receptor |
| EI | Equivalence Interval |
| EPO | Erythropoietin |
| ER | Estrogen Receptor |
| EU | European Union |
| EudraCT | European Clinical Trials database |
| FDA | Food and Drug Administration |
| FFPE | Formalin-Fixed Paraffin-Embedded |
| FIP | First In Patient |
| FSH | Follicle Stimulating Hormone |
| G-CSF | Granulocyte Colony-Stimulating Factor |
| GGT | Gamma-glutamyl Transferase |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| H&E | Hematoxylin and Eosin |
| HBV | Hepatitis B Virus |
| hCG | Human chorionic Gonadotropin |
| HCV | Hepatitis C Virus |
| HIV | Human immunodeficiency Virus |
| HNSTD | Highest Non-Severely Toxic Dose |
| IB | Investigator Brochure |
| ICD | Immunogenic Cell Death |
| ICH | International Conference on Harmonisation |
| ID | Identification |
| IEC | Institutional Ethics Committee |
| IgG1 | Immunoglobulin G1 |
| IHC | Immunohistochemistry |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IOP | Intraocular Pressure |

| Abbreviation | Term |
|---|---|
| IP | Intraperitoneal |
| IP Manual | Investigational Product Manual |
| irAE | Immune-related Adverse Events |
| irCR | Immune-related Complete Response |
| irPD | Immune-related Progressive Disease |
| irPR | Immune-related Partial Response |
| irSD | Immune-related Stable Disease |
| irRECIST | Immune-related Response Evaluation Criteria in Solid Tumors |
| IRB | Institutional Review Board |
| IUD | Intrauterine Device |
| IV | Intravenous |
| LFT | Liver Function Tests |
| LSLV | Last Subject Last Visit |
| mAb | Monoclonal Antibody |
| MCC | Merkel Cell Carcinoma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg/kg | Milligram/kilogram |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MMAE | Monomethyl Auristatin E |
| MRI | Magnetic Resonance Imaging |
| MTD | Maximum Tolerated Dose |
| mTPI | Modified Toxicity Probability Interval |
| N/A | Not Applicable |
| Nab | Neutralizing Antibodies |
| NADPH | β-Nicotinamide Adenine Dinucleotide Phosphate |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NSAID | Nonsteroidal Anti-Inflammatory Drug |
| NSCLC | Non-Small Cell Lung Cancer |
| OR | Objective Response |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| OVCA | Ovarian Cancer |
| PCD | Primary Completion Date |
| PD | Progressive Disease |
| PD | Pharmacodynamic |
| PD-1 | Programmed Death 1 |
| PD-L1 | Programmed Death-Ligand 1 |
| PDX | Patient Derived Xenograft |
| PE | Physical Exam |
| PI | Principal Investigator |
| PFS | Progression Free Survival |
| P-gp | P-glycoprotein |

| Abbreviation | Term |
|---|---|
| PgR | Progesterone Receptor |
| PK | Pharmacokinetic |
| PO | By Mouth |
| PR | Partial Response |
| PR | Pulse Rate |
| PS | Performance Scale |
| PT | Prothrombin Time |
| PTK7 | Protein Tyrosine Kinase 7 |
| Q2W | Once every 2 weeks |
| Q3W | Once every 3 weeks |
| QTcF | Fridericia QT Correction Formula |
| rCyp | Human Recombinant Cytochrome P450 |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic Acid |
| RP2D | Recommended Phase 2 Dose |
| RR | Response Rate |
| RTK | Receptor Tyrosine Kinase |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Stable Disease |
| SOA | Schedule of Activities |
| SRSD | Single Reference Safety Document |
| STD10 | Severely Toxic Dose for 10% of the animals |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| t½ | Terminal Half-Life |
| TBili | Total Bilirubin |
| TCR | T-cell receptor |
| TEAE | Treatment Emergent Adverse Event |
| TNBC | Triple Negative Breast Cancer |
| TTP | Time to Progression |
| UK | United Kingdom |
| ULN | Upper Limit of Normal |
| UPCR | Urine Protein to Creatinine Ratio |
| UPM | Unit Probability Mass |
| USP | United States Pharmacopeia |
| US | United States |
| Vss | Volume of Distribution |
| WBC | White Blood Cell |
| WFI | Water for Injection |
| WHO | World Health Organization |
| 18FDG-PET | Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography |

## Appendix 2. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

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

### CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

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

**Non-measurable disease**

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

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

**Normal sites**

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

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

**Recording Tumor Assessments**

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

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

**Target lesions**

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

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

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

**Non-target disease**

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

## OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target disease

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

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

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

- 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.

Non-target disease

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

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

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

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

New Lesions

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

Supplemental Investigations

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

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

Subjective progression

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

| **Table 1. Objective Response Status at each Evaluation** | | | |
|---|---|---|---|
| **Target Lesions** | **Non-target Disease** | **New Lesions** | **Objective status** |
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Indeterminate or Missing | No | PR |
| PR | Non-CR/Non-PD, Indeterminate, or Missing | No | PR |
| SD | Non-CR/Non-PD, Indeterminate, or Missing | No | Stable |
| Indeterminate or Missing | Non-PD | No | Indeterminate |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

| **Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only** | | |
|---|---|---|
| **Non-target Disease** | **New Lesions** | **Objective status** |
| CR | No | CR |
| Non-CR/Non-PD | No | Non-CR/Non-PD |
| Indeterminate | No | Indeterminate |
| Unequivocal progression | Yes or No | PD |
| Any | Yes | PD |

## Appendix 3. ECOG Performance Status

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

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

## Appendix 4. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

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

## Appendix 5. 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 occur, the infusion should be interrupted. Patients may be treated symptomatically and the infusion should be restarted at 50% of the original rate.

**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 Administration.

**NCI-CTCAE Grade 2 allergic reaction or cytokine release syndrome**

- Stop PF-06647020 infusion.
- Administer bronchodilators, oxygen, acetaminophen, and others as medically indicated.
- Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening including respiratory status. If the reaction recurs, stop infusion. Institute premedication for subsequent infusions as per Section Administration.

**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.

**Treatment of Grade 3 or Grade 4 allergic reaction, cytokine release syndrome or anaphylaxis**

- Stop the PF-06647020 infusion immediately and disconnect infusion tubing from the patient.
- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, and others as medically indicated.

- Monitor closely respiratory and cardiovascular status, be prepared for potential need for intubation.

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

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

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

- Once the PF-06647020 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-06647020.

- 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-06647020.

- 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, PD and ADA sampling should continue as long as the sampling does not interfere with the medical treatment of the patient.

## Appendix 6. Potent CYP3A Inhibitors and Inducers

### Potent CYP3A Inhibitors

| P-gp Inhibitor | Non-P-gp Inhibitor |
|---|---|
| elvitegravir/ritonavir (RIT)<br>indinavir or indinavir / RIT<br>lopinavir/RIT<br>nelfinavir<br>ritonavir<br>saquinavir or saquinavir / RIT<br>tipranavir/RIT<br>danoprevir/RIT<br>telaprevir<br>itraconazole<br>ketoconazole<br>clarithromycin<br>mibefradil<br>conivaptan | voriconazole<br>nefazodone<br>cobicistat<br>boceprevir<br>posaconazole<br>telithromycin<br>troleandomycin |
| List of medications from fda.gov and University of Washington Drug Interaction Database. Potent CYP3A inhibitors are defined as those drugs that increase the AUC of oral midazolam or other CYP3A substrates ≥5-fold | |

### Potent CYP3A Inducers

| |
|---|
| St. John's Wort<br>avasimibe<br>carbamazepine<br>phenytoin<br>rifampin |
| List of medications from fda.gov. Potent CYP3A inducers are defined as those drugs that decrease the AUC of CYP3A substrates ≥ 80% |

As the list of CYP and/or P-gp inducers and inhibitors is a dynamic list continually changing when new information becomes available, use the following FDA website when deciding if a concomitant medication is considered a strong CYP3A/P-gp inhibitor and/or inducer:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Selection of an alternate concomitant medication with no or minimal enzyme inhibition and/or induction potential is recommended.

## Appendix 7. Drug-Drug Interaction (DDI) Sub-Study

The objective of this DDI sub-study is to evaluate the effects of multiple-dose fluconazole, a moderate CYP3A4 inhibitor, on the pharmacokinetics of unconjugated payload (PF-06380101) following single-dose administration of ADC (PF-06647020). Information on the effect of fluconazole on the PK profile of unconjugated payload (PF-06380101) will help better understand the risk of increase in exposure to PF-06380101 due to inhibition of the CYP3A4 mediated PF-06380101 elimination that may occur when moderate CYP3A4 inhibitors are present.

The potential effects of multiple-dose fluconazole on the PK of ADC (PF-06647020) and total antibody (hu6M024 mAb) will also be assessed.

**Background:**

The major cytochrome P450 isoform involved in the metabolism of unconjugated payload (PF-06380101) in humans was determined to be CYP3A4 (See Section 1.2.2 Nonclinical Pharmacokinetics). Physiologically-based PK modeling in SimCYP, utilizing nonclinical and preliminary clinical data, predicts an average 2 to 10-fold increase in PF-06380101 (payload) AUC with co-administration of ketoconazole, a potent CYP3A4 inhibitor, at a clinical dose (200 mg BID). Moderate CYP3A4 inhibitors, such as fluconazole, are predicted to have less impact on PF-06380101 AUC than ketoconazole, with average AUC increase estimated approximately 2-fold at clinical doses. The effect of fluconazole on PF-06380101 exposure cannot be precisely predicted at this time due to the lack of certainty surrounding the overall contribution of the CYP3A4 pathway to elimination of PF-06380101.

Fluconazole is a synthetic azole antifungal medication. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. In fasted healthy volunteers, administration of a single oral 400 mg dose of fluconazole leads to a mean $C_{max}$ of 6.72 µg/mL which occurs between 1 and 2 hours, with a terminal plasma elimination half-life of approximately 30 hours after oral administration. Steady-state concentrations are reached within 5-10 days following oral doses of 50-400 mg given once daily. In general, a loading dose of twice the daily dose is recommended on the first day of therapy to result in plasma concentrations close to steady-state by the second day of therapy. The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. Therefore, only patients with sufficient renal function (serum creatinine ≤1.5 x upper limit of normal or creatinine clearance ≥60 ml/min) will be eligible for this sub-study. Data from a food effect study with fluconazole indicated that Cmax and AUC of fluconazole are not affected by food. Therefore, fluconazole may be taken without regard to meals.

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and 2C19, and a moderate inhibitor of CYP3A4. In normal volunteers, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites. Due to the majority of fluconazole being excreted unchanged in the urine, and due to the low observed concentrations (<0.05 ug/mL) of PF-06380101, PF-06380101 is not expected to impact the pharmacokinetics of fluconazole.

Fluconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. If clinical signs and symptoms of liver disease develop, fluconazole treatment should be discontinued and liver function testing should be performed. Please refer to the Fluconazole Package Insert for complete information on drug interactions, contraindications, warnings and precautions.

The first dose (C1D1) of PF-06647020 administered for the DDI sub-study will be 2.8 mg/kg. The second dose (C2D1) of PF-06647020 administered will be 1.4 mg/kg. An approximately 90% increase in unconjugated payload (PF-06380101) AUC is anticipated when co-administered with fluconazole (a loading dose of 400 mg followed by 200 mg daily doses). The exposure of unconjugated payload (PF-06380101) following a single dose administration of 1.4 mg/kg of ADC (PF-06647020) with fluconazole is expected to be lower than the unconjugated payload exposure previously observed at the 3.7 mg/kg using a Q3W schedule.

**DDI Sub-Study Design:**

This is an open-label, 2-period, fixed sequence study in patients to evaluate the effect of multiple-dose fluconazole on the PK of unconjugated payload (PF-06380101) following a single dose of ADC (PF-06647020). PF-06647020 will be administered on Day 1 in 21-day cycles. The DDI sub-study will also consist of two periods of intense PK sampling, Period A (Cycle 1) and Period B (Cycle 2). In the first period, Period A, a single-dose of PF-06647020 will be administered alone on C1D1 at 2.8 mg/kg. In Period B a single-dose of PF-06647020 will be administered on C2D1 at 1.4 mg/kg, in combination with fluconazole. Fluconazole will be administered starting one day before Period B (C2D1). A maximum of 10 patients will be enrolled to ensure at least 8 patients complete the DDI sub-study procedures. (See Schedule of Activities Table A1 and Table A2 for details).

Enrollment of patients into the DDI sub-study will initially be carried out in a staggered manner. Once the first patient receives the second dose (C2D1) of PF-06647020 and has been evaluated for one week (C2D8) with no clinically significant treatment-related side effects requiring intervention or hospitalization, then a second patient may be enrolled. Remaining patients may be enrolled once the first and second patients have completed C2D8 with no clinically significant treatment-related side effects requiring intervention or hospitalization.

Once completing Cycle 2, patients will continue to receive treatment with PF-06647020 at 2.8 mg/kg every 21 days if the patient does not meet discontinuation criteria, as outlined in Section 6.4.

All study requirements and guidelines described in the main body of the protocol must be followed, in addition to any described in this Appendix 7.

**Patient Population:**

This clinical trial 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 and current medications should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

**Inclusion Criteria**:

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

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

1. Histological or cytological diagnosis of advanced/metastatic breast cancer, OVCA and NSCLC that is resistant to standard therapy or for which no standard therapy is available.
2. CCI [redacted]
3. Age ≥18 years.
4. ECOG Performance Status (PS) of 0 or 1.
5. Life expectancy ≥12 weeks.
6. Adequate Bone Marrow Function as defined by:
    a. Absolute Neutrophil Count (ANC) ≥1,500/mm3 or ≥1.5 x $10^9$/L;
    b. Platelets ≥100,000/$mm^3$ or ≥100 x $10^9$/L;
    c. Hemoglobin ≥9 g/dL.
7. Adequate Renal Function as defined by:
    a. Serum creatinine ≤1.5 x upper limit of normal (ULN); or
    b. Estimated creatinine clearance ≥60 ml/min as calculated using the method standard for the institution.
8. Adequate Liver Function as defined by:

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

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

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

9. Recovery from all prior surgical or adjuvant treatment-related toxicities, to Baseline status, or a CTCAE Grade of 0 or 1, except for toxicities not considered a safety risk, such as alopecia. Post-surgical pain will not be considered a basis for exclusion.

10. Negative serum/urine pregnancy test (for females of childbearing potential).

11. Male and female patients of childbearing potential must agree to use two highly effective method of contraception throughout the study and for at least 30 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

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

13. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

**Exclusion Criteria**:

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

1. Patients with known symptomatic brain metastases requiring steroids 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.

2. Major surgery, radiation therapy or systemic anti-cancer therapy within 4 weeks of starting study treatment (6 weeks for mitomycin C or nitrosoureas).

3. Any condition affecting absorption of oral medications.

4. Prior treatment with a compound of the same mechanism.

5. Presence of ≥ Grade 2 peripheral neuropathy.

6. Active and clinically significant bacterial, fungal or viral infection. Known infections with hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

7. Pregnant or breastfeeding; males and females of childbearing potential who are unwilling or unable to use two highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 30 days after last dose of investigational product.

8. Currently active treatment in another clinical study.

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

10. Known or suspected hypersensitivity to recombinant human or murine proteins.

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

12. Patients who are investigational site staff members directly involved in the conduct of the trial 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 trial.

13. Use of drugs or herbal supplements that are known CYP3A4 inhibitors (with exception of fluconazole doses specified in the protocol) within 7 days prior to the first dose of PF-06647020. The topical use of these medications (if applicable) may be allowed. Use of drugs or herbal supplements that are known CYP3A4 inducers within 12 days prior to the first dose of PF-06647020.

14. Concurrent or anticipated use of drugs that are CYP3A4, CYP2C9 and/or CYP2C19 substrates with narrow therapeutic indices and/or known to prolong the QT interval, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, terfenadine*, paclitaxel, warfarin, phenytoin, S-mephenytoin, erythromycin, and quinidine (*withdrawn from U.S. market).

15. Concurrent or anticipated use of hydrochlorothiazide or cimetidine. These medications may alter fluconazole exposure.

16. Patients with a history of hypersensitivity to fluconazole or its excipients or to other azole antifungals.

17. Patient having any contraindications to fluconazole administration according to the current package insert for fluconazole.

**Treatment Administration:**

ADC (PF-06647020):

PF-06647020 will be administered intravenously at a dose of 2.8 mg/kg on Cycle 1 Day 1 (Period A) and at a dose of 1.4 mg/kg on Cycle 2 Day 1 (Period B). Patients experiencing toxicity may be managed with dose modification or discontinuation as outlined in Section 5.4.1 Recommended Dose Modifications. Patients will be allowed one dose reduction to 2.1 mg/kg. Patients requiring further dose reduction will be discontinued from the study.

See Section 5.4 Administration for further details regarding administration of PF-06647020.

Once a patient has completed Cycle 2, treatment with PF-06647020 will continue at the 2.8 mg/kg dose if the patient does not meet discontinuation criteria, as outlined in Section 6.4.

Fluconazole:

Administration of fluconazole will start with a loading dose of 400 mg by mouth (PO) on the morning of Cycle 1 Day 21. Patients will continue to take fluconazole in the morning at 200 mg PO daily from Cycle 2 Day 1 through Cycle 2 Day 7. On Cycle 2 Day 1 when fluconazole and PF-06647020 are to be co-administered, fluconazole should be taken approximately 1 hour before PF-06647020 administration. Fluconazole can be taken without regard to meals.

On days of the scheduled site visits (Cycle 1 Day 21, Cycle 2 Days 1, 2, and 4), patients must take their daily dose of fluconazole at the clinic, under supervision of site staff.

Sites are to contact the Sponsor if there is any evidence of inappropriate administration of fluconazole, including delayed, missed, or multiple doses. Sponsor will use this information to determine if patient is evaluable for the DDI assessments.

**Concomitant Medication:**

In addition to Section 5.7 Concomitant Treatment(s) of the protocol, the following also applies for concomitant medications in this sub-study:

Patients must not: (1) take any medications, herbal supplements or food known to be CYP3A4 inhibitors 7 days prior to the first dose of PF-06647020 until the completion of Cycle 2 Day 21; (2) take any medications, herbal supplements or food known to be CYP3A4 inducers 12 days prior to the first dose of PF-06647020 until the completion of Cycle 2 Day 21; (3) take any medications contraindicated with fluconazole while taking fluconazole and for 5 days after (Cycle 1 Day 21 through Cycle 2 Day 12) including dihydroergotamine, ergotamine, pimozide, astemizole, cisapride, terfenadine, paclitaxel, warfarin, phenytoin, S-mephenytoin, erythromycin, and quinidine; (4) take any medications which alter fluconazole exposure (including but not limited to hydrochlorothiazide and cimetidine) while taking fluconazole and for 5 days after (Cycle 1 Day 21 through Cycle 2 Day 12).

Fluconazole is a potent inhibitor of cytochrome CYP2C9 and CYP2C19, and a moderate inhibitor of CYP3A4. Clinically or potentially significant drug interactions between fluconazole and the agents/classes provided in Table 14 have been observed or anticipated. In addition, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19, and CYP3A4 co-administered with fluconazole. These elevated plasma concentrations may increase or prolong therapeutic and adverse effects of these drugs. Caution should be exercised when using any of these combinations. Whenever possible, plasma concentrations of these drugs should be monitored, and when appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. The enzyme inhibiting effect of fluconazole persists 4–5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.

**Table 14. Drugs Which may Have Clinically Significant Drug Interactions When Administered With Fluconazole[1]**

| | |
|---|---|
| Alfentanil<br>Amitriptyline, nortriptyline<br>Amphotericin B<br>Astemizole[2]<br>Azithromycin<br>Calcium Channel Blockers (ie, nifedipine, isradipine, amlodipine, verapamil, and felodipine)<br>Carbamazepine<br>Celecoxib<br>Cimetidine[3]<br>Cisapride[2]<br>Coumarin-type anticoagulants (ie, warfarin)<br>Cyclophosphamide<br>Cyclosporine<br>Erythromycin[2]<br>Fentanyl<br>Halofantrine<br>HMG-CoA reductase inhibitors (ie, atorvastatin, simvastatin, fluvastatin)<br>Hydrochlorothiazide<br>Losartan<br>Methadone<br>Non-steroidal anti-inflammatory drugs (NSAIDs) (ie, ibuprofen, flurbiprofen, naproxen, lornoxicam, meloxicam, diclofenac) | Oral Contraceptives<br>Oral hypoglycemic (ie, glipizide, glyburide, tolbutamide)<br>Phenytoin<br>Pimozide[2]<br>Prednisone<br>Quinidine[2]<br>Rifabutin<br>Rifampin<br>Saquinavir<br>Short-acting benzodiazepines (ie, midazolam)<br>Sirolimus<br>Tacrolimus<br>Terfenadine[2]<br>Theophylline<br>Tofacitinib<br>Triazolam<br>Vinca Alkaloids<br>Vitamin A<br>Zidovudine |
| The enzyme inhibiting effect of fluconazole persists 4–5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.<br>1. This list is not all-inclusive. From Diflucan® (fluconazole tablets) Package Insert Nov 2014. Please refer to package insert for description of drug interaction risk.<br>2. Contraindicated with fluconazole.<br>3. Not permitted in this study, as it may decrease fluconazole exposure when given concomitantly. This is not representative of other histamine-2 receptor antagonists. | |

Please refer to the Fluconazole Package Insert for complete information on drug interactions, contraindications, warnings and precautions.

All concomitant medications for patients enrolling in this sub-study must be approved by the Sponsor.

**Pharmacokinetic Assessment for PF-06647020, hu6M024 mAb and PF-06380101:**

Blood samples for PK of unconjugated payload (PF-06380101), ADC (PF-06647020), and total antibody (hu6M024 mAb) will be collected as follows (also see Schedule of Activities Table A2 for details):

PK samples for determining concentrations of unconjugated payload (PF-06380101), ADC (PF-06647020), and total antibody (hu6M024 mAb) will be collected following PF-06647020 administration on Cycle 1 Day 1 during Period A (see Schedule of Activities Table A1 and Table A2 in Appendix 7).

PK samples for determining concentrations of unconjugated payload (PF-06380101), ADC (PF-06647020), and total antibody (hu6M024 mAb) will be collected after administration of PF-06647020 on Cycle 2 Day 1 during Period B (see Schedule of Activities Table A1 and Table A2 in Appendix 7).

Additional blood samples for PK evaluation should be collected if possible from patients experiencing unexpected or serious adverse events; with evidence of disease progression; or with other events where PK sampling is considered useful (upon agreement between investigator and sponsor).

**Pharmacokinetic Assessment for Fluconazole:**

Blood samples for fluconazole will be collected as follows:

Pre-dose PK samples for fluconazole will be taken prior to fluconazole administration as per the Schedule of Activities (Table A1 and Table A2 in Appendix 7). Blood samples collected for fluconazole concentrations will only be analyzed if fluconazole concentration data are required for interpreting the PF-06380101 PK results.

**ECGs:**

12-lead ECG will be collected as per the Schedule of Activities (Table A1 and Table A2 in Appendix 7) and should be performed after the patient has rested quietly for at least 10 minutes. ECGs will be compared to the patient's screening ECG and any clinically significant changes will be recorded as adverse events and evaluated further, as clinically warranted. If the mean QTc is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs should be performed if clinically indicated.

If patient experiences cardiac or neurologic AEs (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 be obtained before (preferable) or after 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). For Cycle 2, Day 1, pre-dose PK sampling should occur prior to administration of fluconazole at the site, while the pre-dose ECG should be performed approximately 1 hour after fluconazole dose (~$T_{max}$ for fluconazole), prior to PF-06647020 infusion.

**Sample Size:**

A maximum of 10 patients with advanced/metastatic solid tumor that is resistant to standard therapy or for which no standard therapy is available will be enrolled in this DDI sub-study to obtain 6 evaluable patients. Evaluable patients are those that complete Period A (Cycle 1) and Period B (Cycle 2) with no evidence of missed doses of fluconazole.

See Section 9.3 for additional details regarding sample size.

**Pharmacokinetic Data Analysis:**

Serum concentrations of unconjugated payload (PF-06380101), ADC (PF-06647020), and total antibody (hu6M024 mAb) will be measured using validated method(s). Log-transformed $C_{max}$ and AUC values for unconjugated payload (PF-06380101) will be evaluated using a mixed-effect ANOVA model. The ratios (Test/Reference) of geometric means and 90% confidence intervals for the ratios will be computed for AUC and Cmax to assess the interaction. ADC alone will be the Reference and ADC in the presence of fluconazole will be the Test.

A similar analysis will be conducted for ADC (PF-06647020) and total antibody (hu6M024 mAb), as supportive data.

Data from patients prematurely ending participation in the study or failing to meet evaluation criteria may be excluded from pharmacokinetic data evaluation.

## Table A1. SCHEDULE OF ACTIVITIES: DDI Sub-Study

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Assessments section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

| **Visit Identifier** | **Screen/ Baseline[1] (≤28 days)** | **Treatment Period** | | | | | | | | | **Post Treatment** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Cycle 1 Only (Days 1 to 21)** | | | | | **Cycle 2 and Subsequent Cycles (Days 1 to 21)** | | | | | |
| | | **Day 1** | **Day 4 (±1)** | **Day 8 (±1)** | **Day 15** (±2) | **Day 21** | **Day 1 (±2)** | **Day 7** | **Day 8 (±2)** | **Day 15 (±2)** | **End of Treatment[29] (+7)** | **Follow Up[30] (+7)** |
| Informed Consent[2] | X | | | | | | | | | | | |
| Tumor History[3] | X | | | | | | | | | | | |
| Medical History[4] | X | | | | | | | | | | | |
| Full Physical Examination[5] | X | X | | | | | | | | | X | |
| Abbreviated Physical Examination | | | X | X | X | | X | | X | X | | |
| Ophthalmic Examination[6] | X | | | | | | | | | | | |
| Baseline Signs and Symptoms[7] | | X | | | | | | | | | | |
| Height | X | | | | | | | | | | | |
| Weight[8] | X | X | | | | | | | | | X | |
| Vital signs (BP/PR/Temp)[9] | X | X | X | X | X | | X | | X | X | X | X |
| ECOG Performance Status[10] | X | X | | | | | X | | | | X | X |
| (12 lead) ECG[11] | X | X | | X | | | X | | X | | X | |
| Laboratory | | | | | | | | | | | | |
| Hematology[12] | X | X | X | X | X | | X | | X | X | X | |
| Blood Chemistry[13] | X | X | X | X | X | | X | | X | X | X | |
| Coagulation Panel[14] | X | | | | | | X | | | | X | |
| Urinalysis[15] | X | | | | X | | X | | | | X | |
| Pregnancy test[16] | X | X | | | | | X | | | | X | |
| Registration and Treatment | | | | | | | | | | | | |
| Registration[17] | | X | | | | | | | | | | |
| Study Treatment[18] | | X | | | | | X | | | | | |
| Fluconazole[18] | | | | | | X | X | X | | | | |

| Visit Identifier | Screen/ Baseline[1] (≤28 days) | Treatment Period | | | | | | | | | Post Treatment | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 Only (Days 1 to 21) | | | | | Cycle 2 and Subsequent Cycles (Days 1 to 21) | | | | | |
| | | Day 1 | Day 4 (±1) | Day 8 (±1) | Day 15 (±2) | Day 21 | Day 1 (±2) | Day 7 | Day 8 (±2) | Day 15 (±2) | End of Treatment[29] (+7) | Follow Up[30] (+7) |
| Tumor assessments | | | | | | | | | | | | |
| CT or MRI scan or equivalent[19] | X | | | | | | X (every 6 weeks) | | | | X | |
| Other samplings | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| CA125 Serum Biomarker (OVCA only)[23] | X | | | | | | X(every 6 weeks) | | | | X | |
| CCI | | | | | | | | | | | | |
| Blood Samples for PK[25] | | See Pharmacokinetic, and Immunogenicity Sampling Schedule Table A2 below | | | | | | | | | | |
| Blood Sample for Immunogenicity Test (Anti-PF-06647020 Antibody)[26] | | See Pharmacokinetic, and Immunogenicity Sampling Schedule Table A2 below | | | | | | | | | | |
| Other clinical assessments | | | | | | | | | | | | |
| Adverse Events[27] | X | X | X | X | X | | X | | X | X | X | X |
| Concomitant treatments and non-drug supportive interventions[28] | X | X | X | X | X | | X | | X | X | X | X |

Abbreviations: CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging; BP = blood pressure; PR = pulse rates; PK = pharmacokinetics; ECOG = Eastern Cooperative Oncology Group; OVCA = Ovarian cancer

Unless otherwise specified, laboratory values and assessments should be obtained prior to the PF-06647020 infusion. If the infusion is held, assessments should still be performed. For Cycle 2 and subsequent cycles, complete blood count (CBC), blood chemistry, other laboratory tests and brief physical examinations, values/assessments should be obtained within 72 hours (ideally within 24 hours) prior to the PF-06647020 infusion and key values should be received and reviewed to ensure appropriate values for dosing.

## Footnotes

1. **Screening:** To be conducted within 28 days prior to treatment start.
2. **Informed Consent:** Must be obtained prior to undergoing any study specific procedures and may be >28 days from first dose.
3. **Tumor History**: Will be collected within 28 days 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. **Full Physical Exam:** No need to repeat full physical exam on Cycle 1 Day 1 (C1D1) if baseline assessment performed within one week prior to that date.
6. **Ophthalmic Examination:** An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes Best Corrected Visual Acuity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic Exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow up.
7. **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 of starting treatment. Baseline signs and symptoms will be recorded on the Medical History Case Report Form (CRF) page.
8. **Weight:** Will not be measured at each visit, however, patients should be monitored throughout the study for significant weight change. If a patient's weight fluctuates by more than 10% in either direction, weight should be collected to recalculate the appropriate dose for the next cycle. In cases where individual institution/pharmacy require more frequent weight measurements, weight can be obtained on each day of administration, and the dose recalculated.
9. **Vital signs:** Includes blood pressure (BP), temperature (oral, tympanic or axillary) and pulse rate (PR) to be recorded in the sitting position after approximately 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. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
10. **Performance status:** use Eastern Cooperative Oncology Group (ECOG) – see Appendix 3.
11. **12 lead ECG (singlet):** ECGs will be collected during Screening and at the End of Treatment visit. Additional ECGs will be collected prior to dosing, at end of infusion and at Day 8 of each dose of study treatment. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTc is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs should be performed as clinically indicated. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
12. **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. See Assessments section for Laboratory Tests list. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
13. **Blood Chemistry:** No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. See Assessments section for Laboratory Tests list. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
14. **Coagulation:** See Assessments section for Laboratory Tests list.
15. **Urinalysis:** Dipstick or full urinalysis is acceptable. Microscopic analyses if dipstick abnormal. If ≥2+ protein on urine dipstick, then collect spot urine sample to calculate urine protein to creatinine ratio (UPCR). See Assessments section for Laboratory Tests list.

16. **Serum/Urine Pregnancy Test:** described in the Pregnancy Testing section.
17. **Registration:** Patient number and dose level allocation will be provided by Pfizer Inc.
18. **Study Treatment:** PF-06647020 will be administered once every 21 days as an IV infusion over approximately 60 minutes.
19. **Fluconazole Administration**: 400 mg of fluconazole will be administered while the patient is in the clinic on Cycle 1 Day 21. The remaining doses of fluconazole (200 mg) will be administered at the clinic on Cycle 2 Day 1 (1 hour before administration of PF-06647020) and on days when the patient returns for PK sampling (Cycle 2 Days 2 and 4). Fluconazole will be administered at the patient's home on Cycle 2 Days 3, and 5 - 7.
20. **Tumor Assessments: Tumor assessments will include all known or suspected disease sites and may include chest, abdomen and pelvis CT or MRI scans.** Brain scans and bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. CT or MRI scans are to be done every 6 weeks (±5 days) from the start of study treatment until disease progression by RECIST (v1.1) or death, or at the time of withdrawal from treatment (if not done in the previous 6 weeks). The frequency may be reduced to every 12 weeks after 6 months of study treatment. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. For patients enrolled in Part 2, responses of complete response (CR) or partial response (PR) must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. Copies of all scans will be collected for potential central review. Additional information on diagnostic imaging procedures and collection will be included in the Imaging Manual.

CCI [redacted]

23. **CA125 Serum Biomarker**: Ovarian cancer patients only. Samples should be collected at pre-treatment, each tumor assessment (every 6 wks), and end of treatment. Additional serum samples to be collected as per Investigator discretion.

CCI [redacted]

25. **PK Sampling:** Specific timing for collection of serum pharmacokinetic samples can be found in the Pharmacokinetic, and Immunogenicity sampling schedule table below.
26. **Immunogenicity Sample:** Specific timing for collection of anti-PF-06647020 antibody samples can be found in the Pharmacokinetic, and Immunogenicity sampling schedule table below.

27. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment. Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
28. **Concomitant Treatments and Non Drug Supportive Interventions:** All prior/concomitant medications within 28 days (4 weeks) prior to first dose of study treatment 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). Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
29. **End of treatment visit:** Conducted at the visit that the patient is discontinued from the trial. Assessments should be obtained if not completed in the last week. Complete tumor assessments if not completed in the last 6 weeks.
30. **Follow up:** At least 28 days and no more than 35 days after end of treatment visit, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

## Table A2. PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING SCHEDULE – DDI Sub-Study

| Protocol Activity | Screen (≤28 days) | Treatment Period | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 (Period A) and Cycle 4 | | | | | | | | Cycle 2 (Period B) | | | | | | | | Cycles 3, 5 and Every Cycle Thereafter | | EOT |
| | | Day 1 | | | Day 2 | Day 4 | Day 8 | Day 15 | Day 21 | Day 1 | | | | Day 2 | Day 4 | Day 8 | Day 15 | Day 1 | | |
| | | Pre-dose* | 1 hr* | 4 hr* | 24 hr* | | | | | Pre-dose* | 0 hr | 1 hr* | 4 hr* | 24 hr* | | | | Pre-dose* | 1 hr* | |
| Blood Samples for PF-06380101[1] | | X | X | X | X | X | X | X | | X | | X | X | X | X | X | X | X | X | X |
| Blood Samples for PF-06647020 and hu6M024 mAb[2] | | X | X | X | X | X | X | X | | X | | X | X | X | X | X | X | X | X | X |
| Blood Sample for Fluconazole[3] | | | | | | | | | X | X | | | | X | X | X | | | | |
| Blood Sample for Immunogenicity Test (Anti-PF-06647020 Antibody)[4] | | X | | | | | | X | | X | | | | | | | | X | | X |

* Sampling times are in relation to the start of the most recent infusion; 1 hr samples should be collected immediately before the infusion ends. All samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection will always be noted on the CRF.

1. **Blood PK sample for PF-06380101:** 4 mL of whole blood will be collected for PK analysis of unconjugated payload (PF-06380101).
2. **Blood PK sample for PF-06647020 and hu6M024 mAb:** 6 mL of whole blood will be collected for PK analysis of ADC (PF-06647020) and total antibody (hu6M024 mAb).
3. **Blood PK sample for fluconazole:** Cycles 1 and 2 only. Pre-dose samples (within 3 hr of the next scheduled dose of fluconazole) will be collected and actual sample collection times will be recorded. The fluconazole PK samples will not be analyzed unless required for interpreting the PF-06380101 PK results.
4. **Blood sample for immunogenicity test:** Blood samples (6 mL) for immunogenicity testing against PF-06647020 will be collected. Collection of serum to detect the presence of antibodies to PF-06647020 is to be obtained prior to the start of treatment. Patients having an unresolved adverse event that is possibly related to anti-PF-06647020 antibodies at their last assessment will be asked to return to the clinic 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.

## Appendix 8. Q2W Regimen Expansion Sub-Study (Single Agent PF-06647020 and Combination of PF-06647020 with Avelumab in patients with OVCA and NSCLC)

### A1. Background and Rationale

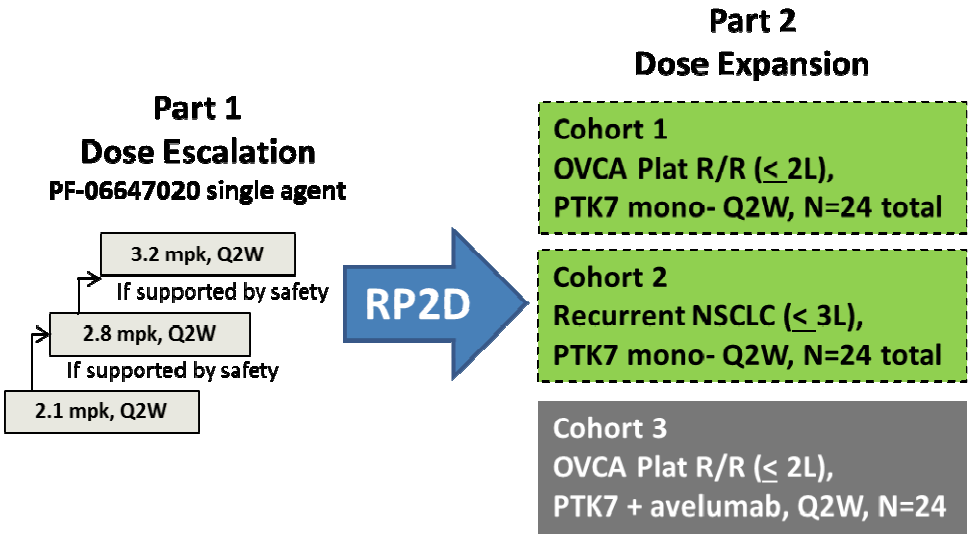
This sub-study will evaluate the safety, PK, and anti-tumor activity of single agent PF-06647020 and combination of PF-0664720 with avelumab when administered Q2W in patients with platinum-refractory or resistant OVCA and patients with recurrent advanced NSCLC.

This sub-study contains a dose escalation (Part 1) and a dose expansion (Part 2). The Part 1 will be conducted in patients with platinum resistant or refractory OVCA and patients with recurrent advanced NSCLC; and PF-06647020 will be administered Q2W as a single agent treatment. After a favorable safety profile and preliminary anti-tumor activity as a single treatment of PF-06647020 in Part 1 is observed, the Part 2 dose expansion will be started to further investigate safety, PK and efficacy of Q2W PF-06647020 in at least three cohorts of patients:

- Cohort 1 PF-06647020 as a single agent treatment in patients with platinum resistant or refractory OVCA.
- Cohort 2 PF-06647020 as a single agent treatment in patients with recurrent advanced NSCLC.
- Cohort 3 PF-06647020 in combination with avelumab in platinum resistant or refractory OVCA.

If supported by safety and anti-tumor activity, additional cohort with approximately 24 patients with recurrent advanced NSCLC may be considered in Part 2 to receive combination of PF-06647020 with avelumab.

The study scheme for the Q2W regimen expansion is described in the diagram below:




### A1.1. PF-06647020

PF-06647020, a novel ADC targeting PTK7, has been investigated in 112 patients (as of 17 March 2017) with advanced cancers including platinum and/or paclitaxel heavily pre-treated OVCA. In the ongoing Phase I study, as of 17 March 2017, total of 112 patients with heavily pre-treated cancers have been treated with PF-06647020 on a Q3W regimen at different dose levels in the ongoing Phase I study, of which 44 were OVCA patients, 25 were NSCLC patients, and 31 were TNBC patients, 12 patients had other types of solid tumor.

Of the total 44 OVCA patients who received PF-06647020 treatment, 42 were treated at 2.8 mg/kg, 1 at 2.1 mg/kg, and 1 at 3.7 mg/kg. In 38 patients who were considered evaluable for ORR assessment, 9 patients achieved objective response (1 CR, and 8 PR) with an ORR of 24% (95% CI, 13%, 39%) and 18 patients (47%) had a best response with SD. Median PFS was 12.6 weeks (95% CI, 12, 24). Median duration of treatment with PF-06647020 was 8.1 weeks (range 0.1-45.3 weeks).

Of the total 25 NSCLC patients received PF-06647020 treatment, 22 were treated at 2.8 mg/kg, 2 at 1.25 mg/kg, 1 at 2.1 mg/kg. In 23 patients who were considered evaluable for ORR assessment, 4 patients achieved PR with an ORR of 17% (95% CI, 7%, 37%) and 9 patients (39%) had a best response with SD. Median PFS was 18.1 weeks (95% CI, 6, 30.1) and median duration of treatment with PF-06647020 was 9.0 weeks (range-0.1-46.3-weeks).

Of the total 31 TNBC patients received PF-06647020 treatment, 27 were treated at 2.8 mg/kg, 2 at 2.1 mg/kg, 2 at 3.7 mg/kg. In 27 patients who were considered evaluable for ORR assessment, 6 achieved PR with an ORR of 22% (95% CI, 11%, 41%). Eight (30%) patients had a best response of SD. Median PFS was 8.3 weeks (95% CI, 6, 23.6) and a median duration of treatment with PF-06647020 was 3.0 weeks (range 0.1-40.3 weeks).

The most frequently observed PF-06647020 treatment related AEs were nausea, alopecia, fatigue, headache, vomiting, and arthralgia, most were Grade 1 or 2. A total of 15 patients (35.7%) experienced a Grade ≥3 treatment-related AE, most common was neutropenia (10 patients, 23.8%), headache, myalgia, vomiting, and hypomagnesaemia (2 patients (4.8%) each).

When administered Q3W, PF-06647020 at RP2D 2.8 mg/kg demonstrated encouraging anti-tumor activity with a generally well acceptable safety profile. Preliminary PK analyses and simulation suggest that Q2W dosing is expected to be better aligned with PK characteristics of PF-06647020, with lower peak-to-trough PK fluctuation compared to the Q3W regimen. Therefore the Q2W regimen of PF-06647020 would result in an increased exposure while maintaining a tolerable safety profile.

Several lines of evidence suggest that combining the PTK7-targeted ADC with avelumab would improve clinical outcomes. In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity.[20] A recent preclinical study demonstrated that immunotherapy can be enhanced by localized chemotherapy but not systemic chemotherapy;[21] indeed the PTK7-targeted ADC delivers a potent chemotherapy preferentially to the tumor cells and thus is distinguished from standard chemotherapies. In addition, the PTK7-targeted ADC could stimulate anti-tumor immunity (and thus stimulate the response to avelumab) by multiple mechanisms: (1) auristatins can activate dendritic cells (Pfizer, unpublished data), and the expression of PTK7 on dendritic cells could increase the delivery of auristatin to those cells; (2) anti-angiogenic activity can promote immune cell infiltration into tumors, and the PTK7-targeted ADC specifically inhibits angiogenesis; (3) immunogenic cell death can stimulate anti-tumor immunity, and auristatins induce this phenotype in cancer cell lines.[19]

### A1.2. Avelumab (MSB0010718C)

Avelumab (MSB0010718C), a fully human antibody of the IgG1 isotype, specifically targets and blocks PD-L1, the ligand for PD-1 receptor. This interaction inhibits the suppressive effects of PD-L1 on CD8 positive T cells, and thus restores the cytotoxic T cell response against the tumor. In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity.[20] Broad expression of PD-L1 was observed in ovarian cancer samples, and higher expression of PD-L1 was associated with significantly worse prognosis.[32] Preliminary data from the ongoing OVCA Study EMR 100070-001, which is being conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004) showed an overall response rate (ORR) of 10.7% (8/75) and stable disease (SD) in an additional 44% (33/75) of patients with advanced OVCA.

For complete details of the in vitro and nonclinical studies, refer to avelumab Investigator's Brochure (IB).[20]

### A1.2.1. Avelumab Safety (MSB0010718C)

As of 15 February 2015, 1300 patients had been treated in pooled expansion cohorts of patients with advanced cancers. Of the 1300 patients treated, 621 (47.8%) experienced at least 1 Grade ≥3 TEAE, and 813 (62.5%) had treatment-related TEAEs, of whom 124 (9.5%) had Grade ≥3 treatment-related TEAEs.

The most frequently reported (incidence ≥10% in the pooled expansion cohort) TEAEs (any grade) in the pooled expansion cohort are summarized in Table 15. The most frequently reported (occurring in at least 5 patients in the pooled extension cohort) Grade ≥3 treatment-related TEAEs in the pooled expansion cohort are presented in Table 16.

**Table 15. Most Frequently Reported (Incidence ≥10% in the Pooled Expansion Cohort) Treatment-Emergent Adverse Events (TEAEs) in the Pooled Expansion Cohort (Any Grade)**

| MedDRA PT | Pooled Expansion Cohort Patients (n=1300) n (%) |
|---|---|
| Number of patients with at least 1 TEAE | 1200 (92.3) |
| Fatigue | 356 (27.4) |
| Nausea | 276 (21.2) |
| Infusion-related reaction | 211 (16.2) |
| Diarrhea | 205 (15.8) |
| Constipation | 204 (15.7) |
| Decreased appetite | 194 (14.9) |
| Vomiting | 188 (14.5) |
| Weight decreased | 159 (12.2) |
| Abdominal pain | 156 (12.0) |
| Anemia | 155 (11.9) |
| Cough | 152 (11.7) |
| Dyspnea | 148 (11.4) |
| Pyrexia | 148 (11.4) |
| Chills | 137 (10.5) |

Source: Avelumab Investigator's Brochure Version 5 Table 15

**Table 16. Most Frequently Reported (in ≥5 Patients in the Pooled Expansion Cohort) Grade ≥3 Treatment-Related TEAEs in the Pooled Expansion Cohort**

| MedDRA PT | Pooled Expansion Cohort Patients (n=1300) n (%) |
|---|---|
| Number of patients with at least 1 TEAE | 124 (9.5) |
| Gamma-glutamyl transferase increased | 9 (0.7) |
| Infusion-related reaction | 9 (0.7) |
| Fatigue | 8 (0.6) |
| Lipase increased | 8 (0.6) |
| Anemia | 7 (0.5) |
| Dyspnea | 6 (0.5) |
| Aspartate aminotransferase increased | 5 (0.4) |

Source: Avelumab Investigator's Brochure Version 5 Table 17

As of 05 November 2015, 509 of 1300 patients (39.2%) in the pooled expansion cohort had at least 1 serious TEAE. Treatment-related serious TEAEs were reported in 71 of the 1300 patients (5.5%) in the pooled expansion cohort. These included infusion-related reaction (11 patients; 0.8%), pneumonitis (8 patients; 0.6%), pyrexia and dyspnea (each in 5 patients; 0.4%), autoimmune hepatitis (3 patients; 0.2%), and asthenia, blood creatine phosphokinase increased, abdominal pain, colitis, diarrhea, vomiting, hyponatremia, adrenal insufficiency, and non-cardiac chest pain (each in 2 patients; 0.2%). All other treatment-related TEAEs were reported in a single subject (0.1%) only.

As of 05 November 2015, 466 deaths (35.8%) occurred in the dose expansion cohorts. The majority of deaths in the dose expansion cohorts were due to progressive disease (360 patients; 27.7%). Overall, a total of 5 deaths (0.4%) due to TEAEs related to trial treatment were considered as primary reason of the death by the investigator. Two additional cases of death were reported and assessed as treatment-related, but the treatment related TEAEs were not considered as the primary reason of death. A total of 142 deaths (10.9%) occurred within 30 days patients of last treatment in the dose expansion cohorts. Overall there were (14%) patients who experienced treatment related AEs with fatal outcome; in 4 patients the treatment-related AE was reported as the primary cause of death as noted above. These 7 cases with AEs related to study treatment included: pneumonitis radiation induced and dyspnea; acute liver failure associated with autoimmune hepatitis (no biopsy/autopsy performed); disease progression; fatal anoxic brain injury after cardiac arrest; autoimmune hepatitis with hepatic failure and fatigue (no biopsy/autopsy performed); respiratory distress and sepsis; and acute respiratory failure, acute exacerbation chronic obstructive pulmonary disease (COPD), and leukocytosis (occurred after the end of the on-treatment period).

As of 05 November 2015, a total of 175 patients (13.5%) treated in the dose expansion cohorts withdrew permanently from trial treatment due to one or more TEAE. Of these patients with treatment discontinuations, 79 patients (6.1%) in the dose expansion cohorts had treatment discontinuations that were due to treatment-related TEAEs. These TEAEs were infusion-related reaction (25 withdrawals; 1.9%), Gamma glutamyl transferase (GGT) increased and rash (5 withdrawals each, 0.4%), and aspartate aminotransferase increased, blood creatine phosphokinase increased, and lipase increased (3 patients each, 0.2%), and ALT increase, autoimmune hepatitis, and dyspnea (2 patients each, 0.2%). All other treatment-related TEAEs leading to treatment discontinuation were observed in a single patient (0.1%) only.

CCI [redacted]

CCI [redacted]

Infusion-Related Reactions: Two unexpected serious adverse reactions (SUSARs); anaphylactic reaction and infusion-related reaction) involving 2 patients were reported in December 2013 and triggered a cumulative review of serious and non-serious cases of infusion-related reactions/hypersensitivity across the avelumab program. Following evaluation of safety signals, infusion-related reactions/hypersensitivity have been classified as a newly identified risk (previously classified as a potential risk) and a mandatory premedication regimen of a histamine H1 receptor (H1) blocker plus acetaminophen was implemented for all trial patients starting 29 January 2014.

Starting from 29 January 2014, a mandatory premedication with H1 blockers plus acetaminophen was implemented for all patients who are to receive avelumab. One hundred and ninety-four of 1259 patients (15.4%) in the pooled treatment expansion cohort experienced infusion-related reaction in the presence of premedication with 50 patients (4.0%) having Grade 1, 138 patients (11.0%) having Grade 2, 4 patients (0.3%) having Grade 3, and 2 patients (0.2%) having Grade 4 events. Two patients (5.3%) in the dose escalation cohort reported infusion-related reactions (both Grade 2) in the presence of premedication. In addition to the aforementioned patients, one case of Grade 4 cardiac arrest occurred 1.5 hours after the third infusion of avelumab (10 mg/kg). The patient died due to an anoxic brain injury 7 days later; no autopsy was performed.

Guidelines for the management of infusion-related reactions and severe hypersensitivity reaction are found in Section A7.3.3.2. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) and can be found at https://www.resus.org.uk/pages/reaction.pdfhttps://www.resus.org.uk/pages/reaction.pdfhttps://www.resus.org.uk/pages/reaction.pdf.

Additional information for this compound may be found in the SRSD, which for this study is the Investigator Brochure.[20]

### A1.2.2. Avelumab Pharmacokinetics (MSB0010718C)

PK following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 77 mainly Caucasian patients treated in the dose escalation and expansion cohorts of the Phase 1 Study EMR 100070-001 by standard non-compartmental analysis. This analysis revealed that the exposure parameters of $C_{max}$ and AUC after the first dose generally increased in an approximately dose-proportional manner in the dose range between 3 to 20 mg/kg. Apparent half-life tended to increase with dose, likely due to target mediated disposition at lower doses, but terminal half-life at 10 and 20 mg/kg doses were similar (102-120 hours). This likely indicates that target mediated elimination does not increase at these two doses and target occupancy is very high.

### A1.2.3. Efficacy and Safety in OVCA Patients treated with Avelumab (MSB0010718C)

Single-agent avelumab activity at 10 mg/kg Q2W was evaluated in heavily pre-treated epithelial ovarian cancer patients in an ovarian-specific expansion cohort in Study EMR100070-001. Patients with OVCA whose disease progressed on standard therapy were eligible. 124 patients were treated as of 23 October 2015. Median age was 62 years (range 27-84 years); ECOG performance status was 0 (48%) or 1 (52%); median number of prior therapies for locally advanced or metastatic disease (excluding adjuvant treatment) was 3 (range, 1-10). Median duration of treatment with avelumab was 12 weeks (range 2-54 weeks), and 17 patients remained on treatment. Twelve patients (9.7%, 95% CI, 5.1%, 16.3%) achieved an unconfirmed best objective response (BOR) of partial response (PR). Six out of 12 responses were ongoing at the time of data cutoff. Fifty-five (44.4%) patients had stable disease. Two additional patients had partial response by immune-related response criteria. Median progression-free survival was 11.3 weeks.

Avelumab was well-tolerated in the OVCA expansion cohort. Table 17 demonstrates treatment-related AEs observed in ≥5% of patients as of 13 February 2015 (n=75). The following Grade 3 avelumab-related AEs were observed in a total of 6 patients (8.0%): one event each of peripheral edema, localized edema, increased lipase, increased blood creatine phosphokinase, arthritis, myositis, hyperglycemia, anemia, tumor pain. There were no Grade 4 or 5 AEs related to avelumab reported in this cohort. Related serious TEAEs were observed in 3 patients (4.0%): Dyspnea (1), pyrexia (1), non-cardiac chest pain (1), flushing (1), localized edema (1), and peripheral edema (1). Immune-related TEAEs were seen in 8 patients (10.7%) and included hypothyroidism (5; 6.7%), arthritis (2; 2.7%), and myositis (1; 1.3%). No drug-related intestinal obstruction or perforations occurred. Discontinuation related to treatment with avelumab was reported in 9 patients (12.0%) [Pfizer/Merck KGaA data on file, cutoff 13 February 2015].[20]

**Table 17. Avelumab Treatment Related Adverse Events (Incidence ≥5%) in the OVCA Cohort**

| Events (n=75) | Treatment-Related AEs, all grades*, n (%) |
|---|---|
| Any event | 52 (69.3) |
| Fatigue | 12 (16.0) |
| Chills | 9 (12.0) |
| Nausea | 8 (10.7) |
| Diarrhea | 8 (10.7) |
| Infusion-related reaction | 6 (8.0) |
| Rash | 6 (8.0) |
| Vomiting | 4 (5.3) |
| Constipation | 4 (5.3) |
| Hypothyroidism | 4 (5.3) |

Source: Table 15.3.1.5C.

Complete information for avelumab may be found in the SRSD, which for this study is the avelumab Investigator's Brochure.[20]

## A1.3. Summary of Benefit/Risk Assessment

An evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

PF-06647020 as a single agent treatment with Q3W regimen in the Phase I study has demonstrated encouraging anti-tumor activity in heavily pre-treated patients with advanced solid tumors including OVCA, NSCLC and TNBC with ORR ranging from 17-24%. The median PFS (8-18 weeks) observed is within the expected range and continues to evolving due to the nature of the ongoing study.

AE and laboratory test data for PF-06647020, as of 17 March 2017, suggested PF-06647020, administered at Q3W, is generally well tolerated and has an acceptable and manageable safety profile. The AEs observed were in line with those expected in patients with advanced solid tumors treated by an ADC. Febrile neutropenia and neutropenia observed in the study are considered manageable toxicities with appropriate prophylaxis and/or clinical management but remain classified as potential safety concerns. Grade 3 headache and fatigue were identified as DLTs in the dose escalation study and were well managed with dose reduction and/or treatment following institutional guidance. Preliminary exposure-response analysis revealed an apparent correlation between PF-06647020 PK exposure and ORR in OVCA patients; sustained PF-06647020 PK exposure appeared to be associated with higher ORR. A Q2W dosing regimen is predicted to be better aligned with PK characteristics of PF-06647020, with lower peak-to-trough PK fluctuation compared to the Q3W regimen. Therefore the Q2W regimen of PF-06647020 would result in an increased PK exposure while maintaining a tolerable safety profile. A mitigation plan including prophylaxis of anti-emetics and supplement of growth factors as needed, and guideline for dose reduction or treatment discontinuation have been implemented in the ongoing Phase I dose expansion portion of the study and will be utilized in this Q2W regimen expansion study.

Available AE and laboratory abnormality data from patients with advanced solid tumors treated with single-agent avelumab suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and irAEs/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These mitigation measures include a treatment algorithm and guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with a histamine H1 receptor (H1) blocker and acetaminophen. Avelumab demonstrated clinical activity in heavily pretreated OVCA patients in an expansion cohort of an ongoing Phase 1 study and is being evaluated in ongoing Phase 3 trials as a single agent or in combination with standard of care treatment in multiple types of advanced cancers including OVCA and NSCLC.

Thus, the projected benefit/risk of PF-06647020 given as a single agent treatment or in combination with avelumab at a Q2W regimen is anticipated to be favorable for investigation inan advanced cancer patient population.

## A2. STARTING DOSE RATIONALE FOR Q2W REGIMEN

### A2.1. PF-06647020

The recommended starting PF-06647020 dose for the Q2W regimen study will be 2.1 mg/kg, administered as 1-hour IV infusions.

In the ongoing trial, single agent PF-06647020 at doses ranging from 0.2 mg/kg to 3.7 mg/kg Q3W were evaluated in 112 patients with advanced solid tumors including 44 patients with heavily pre-treated OVCA. PF-06647020 was found to be generally well tolerated with an acceptable safety profile. The RP2D of PF-06647020 was identified as 2.8 mg/kg Q3W, which was used in the ongoing dose expansion studies including TNBC, OVCA and NSCLC and has been demonstrated with encouraging anti-tumor clinical activity.

Preliminary exposure-response analysis revealed an apparent correlation between PF-06647020 exposure and ORR in OVCA patients; sustained PF-06647020 PK exposure appeared to be associated with higher ORR. Preliminary PK analysis suggested that Q2W schedule would be better aligned with the PK characteristics of PF-06647020, resulting in lower peak-to-trough PK fluctuation, compared to Q3W, likely yielding a higher exposure while maintaining a tolerable safety profile. The recommended starting dose of 2.1 mg/kg for Q2W dosing represents 75% of the MTD of 2.8 mg/kg determined for PF-06647020 Q3W. PK simulations suggests that the cumulative exposure of 6 weeks of the 2.1 mg/kg Q2W is expected to be generally comparable to that of the 2.8 mg/kg Q3W, with a slightly lower $C_{max}$, and expected to be tolerable.

### A2.2. Avelumab

To date, avelumab has been administered at the clinically active, safe and tolerable dose of 10 mg/kg Q2W to more than 1700 patients across multiple indications. Furthermore, this 10 mg/kg Q2W avelumab dosing regimen has been approved by the US Food and Drug Administration (FDA) as the first treatment for Merkel Cell Carcinoma (MCC). It has also recently been approved at this dose and regimen as a second line treatment of Urothelial Carcinoma. Avelumab was originally dosed on a mg/kg basis in order to reduce inter-subject variability in drug exposure. However, emerging data for monoclonal antibodies, including marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, reveal that body weight-based dosing regimens do not result in less variability in measures of exposure over fixed (ie, body-weight independent) dosing regimens).[29,30,31] Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times, and greater ease of administration.

Population PK analysis was conducted based on the acquired PK data across three single-agent avelumab studies in patients with 14 different types of cancer. PK simulations suggest that exposures to avelumab across the available range of body weights are similar

with 800 mg Q2W compared to 10 mg/kg Q2W. Low-weight subjects tended towards marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when fixed dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful. Furthermore, the 800 mg Q2W dosing regimen is expected to result in $C_{trough}$ >1 μg/mL required to maintain avelumab serum concentrations at >90% Target Occupancy (TO) throughout the entire dosing interval in all weight categories.

Therefore, in this clinical trial, a fixed dosing regimen of 800 mg administered as a 1-hour IV infusion Q2W will be utilized for avelumab.

## A3. OBJECTIVES AND ENDPOINTS FOR Q2W REGIMEN

### A3.1. Objectives

#### Primary Objectives

- Part 1: To assess safety and tolerability at increasing dose levels of PF-06647020 administered intravenously as a single agent on a Q2W dosing schedule.
- Part 1: To determine the MTD and select the RP2D of PF-06647020 as a single agent treatment on a Q2W dosing schedule.
- Part 2: To evaluate the overall safety profile of PF-06647020 as a single agent and in combination with avelumab at Q2W dosing schedule in OVCA and NSCLC patients at the RP2D.

#### Secondary Objectives

- To characterize the single and multiple dose PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101) when PF-06647020 administered alone or on combination with avelumab, and PK of avelumab.
- To evaluate the immunogenicity as measured by presence of ADA in patients treated with PF-06647020 or PF-06647020 in combination of avelumab.
- To evaluate anti-tumor activity of PF-06647020 as a single agent and when given in combination with avelumab in patients with OVCA and NSCLC.

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## A3.2. Study Endpoints

### Primary Endpoints

- Part 1: First Cycle DLTs for the dose escalation portion. A cycle is 28 days in duration.
- Part 2: AEs (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate); or ECGs.

### Secondary Endpoints

- Pharmacokinetics: PK parameters of PF-06647020, total antibody (hu6M024 mAb), unconjugated payload (PF-06380101), and avelumab.
- Immunogenicity: Incidence of ADA and Nab against PF-06647020 and avelumab.
- Efficacy: OR, DoR, DCR, TTP, and PFS, as determined by Investigator [As assessed by RECIST version 1.1] (Appendix 2).

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[redacted]

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[redacted]

[redacted]

[redacted]

## A4. STUDY DESIGN FOR THE Q2W REGIMEN EXPANSION

The expansion is designed to evaluate safety, PK and anti-tumor efficacy of a Q2W dosing schedule as a single agent treatment in patients with OVCA and NSCLC, and combined treatment of PF-06647020 with avelumab in OVCA patients. If supported by safety and anti-tumor efficacy, additional combination study of PF-06647020 with avelumab may also be investigated in approximately 24 patients with NSCLC.

The study contains two parts, a Part 1 dose escalation and Part 2 dose expansion. Part 1 contains a dose escalation scheme to estimate the MTD/RP2D of PF-06647020 as single agent treatment in patients with platinum-refractory or resistant OVCA and recurrent NSCLC (in approximately 20 patients) using mTPI method. Successive cohorts of patients will receive doses of PF-06647020 starting at a dose of 2.1 mg/kg, Q2W. Once the RP2D is determined and preliminary efficacy is observed, dose expansions (Part 2) will be started to further investigate safety, PK and efficacy of Q2W PF-06647020 in three cohorts of patients:

- Cohort 1: PF-06647020 as a single agent treatment in patients with platinum resistant or refractory OVCA.
- Cohort 2: PF-06647020 as a single agent treatment in patients with recurrent advanced NSCLC.
- Cohort 3: PF-06647020 in combination with avelumab in platinum resistant or refractory OVCA.

Approximately 24 patients will be enrolled for each cohort. Patients that were enrolled in the Part 1 single agent dose escalation will be counted as part of the 24 patients in their respective Part 2 single agent cohorts. An additional cohort in approximately 24 patients with recurrent advanced NSCLC receiving combination of PF-06647020 with avelumab may also be considered for inclusion at a later time, if supported by safety and anti-tumor activity observed in the single agent treatment cohort.

In the combination expansion Cohort 3, the RP2D of PF-06647020 as determined by Part 1 will be used as the dose to combine with avelumab at 800 mg (both administered IV, Q2W). The PF-06647020 dose may be reduced (but not further escalated) for safety reasons. After at least 6 patients in the combination cohort have completed a minimum observation period of 4 weeks, safety will be reviewed by the investigators and Pfizer (using the same DLT definition described in Section A4.2). If there are no safety concerns precluding continuation of the study, enrollment of the remaining patients for this cohort will proceed. If DLT is observed in 2 out of 6 patients, at least 6 additional patients will be enrolled at a reduced dose of PF-06647020 (the reduced dose of PF-06647020 could be one dose level below the defined RP2D from Part 1 assuming the RP2D is above the starting dose of Part 1 (ie, 2.1 mg/kg), or 1.8 mg/kg of PF-06647020 in a circumstance that the RP2D from Part 1 is 2.1 mg/kg).

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A total of approximately 72 patients will be enrolled in the Q2W regimen expansion. Patients will participate in the study for approximately 9 months or until disease progression, patient withdrawal of consent or unacceptable toxicity occurs, patient loss to follow up, or the study is terminated by the Sponsor, whichever comes first. This includes a 4 week screening period, a 7 month treatment period and a 4 week post dose follow-up period. A follow-up visit within 4 weeks after the last dose of study drug for adverse event AE and SAE collection will be conducted. The time on study can vary depending on the observed toxicity and potential benefit an individual patient derives. The study is expected to be completed in approximately 36 months.

All study requirements and guidelines described in the main body of the protocol must be followed, in addition to any described in this Appendix 8.

### A4.1. Dose Escalation

The Q2W regimen expansion contains a PF-06647020 dose escalation portion (Part 1) using the mTPI method and details are included in Section 3.2 and Table 8.

Patients may be enrolled in cohorts of 2-4, starting with 2.1 mg/kg Q2W for the first cohort. In cohorts with 2 patients enrolled, an additional patient may be enrolled for dose escalation assessment if one of the two patients has a DLT. If a high DLT rate (>33%) is observed at the starting dose, a lower dose may be considered. The study may be stopped if the drug is deemed not tolerable at the lowest dose. Table 18 illustrates the potential dose levels in Part 1 dose escalation.

**Table 18. Table of Potential Dose Levels***

| Dose Level | Dose (mg/kg) |
|---|---|
| -1 | TBD |
| 1 (starting dose) | 2.1 |
| 2 | 2.8 |
| 3 | 3.2 |

*additional intermediate doses may be investigated.

### A4.2. DLT Definition for the Q2W Regimen

Severity of adverse events will be graded according to CTCAE version 4.03. For the purpose of DLT assessment, any of the following adverse events occurring in the first cycle of treatment (within 28 days of first dose or until patient receives 2nd infusion if there are treatment delays) in the single agent dose escalation (Part 1) and combination of PF-06647020 with avelumab will be classified as DLTs, unless there is a clear alternative explanation (eg, related to underlying disease/progression). DLTs in combination cohort(s)

(PF-06647020 with avelumab) will continue to be monitored for approximately 84 days for any late immune-related toxicities.

- Hematologic:
  - Grade 4 neutropenia lasting >7 days;
  - Febrile neutropenia (ANC<1000/$mm^3$ with a single temperature of >38.3 degrees C or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour;
  - Grade ≥3 neutropenic infection;
  - Grade 4 anemia;
  - Grade ≥3 thrombocytopenia with clinically significant bleeding (ie, gastrointestinal bleeding requiring clinical intervention and all intracranial bleeding);
  - Grade 4 thrombocytopenia:
    - any <10,000;
    - 10,000-25,000 for > 3 days;
  - Treatment delay >14 days because of hematologic adverse event.
- Hepatic:
  - Grade ≥3 serum bilirubin, hepatic transaminase (ALT or AST) or alkaline phosphatase. For patients with Grade 2 hepatic transaminase or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis, a hepatic transaminase or alkaline phosphatase level > 10 x ULN will be considered as a DLT.
  - ALT or AST ≥3.0 x ULN concurrent with elevation in bilirubin ≥2.0 x ULN.
- Non-hematologic, non-hepatic:
  - Grade ≥3 toxicities that are considered non-hematologic, non-hepatic major organ toxicity (excluding alopecia of any grade, Grade 3 diarrhea and Grade 3 nausea and vomiting that responds to therapy).
  - Delay by more than 2 weeks in receiving the next scheduled cycle due to persisting toxicities attributable to PF-06647020.
  - Grade ≥3 headache lasting >48 hours in presence of supportive care.

In addition, clinically important or persistent toxicities lasting >5 days in presence of supportive care (eg, Grade ≥3 diarrhea) that are not included in the above criteria should be considered a DLT following review by Pfizer and the investigators. All DLTs need to represent a clinically significant shift from baseline.

During Cycle 1 and subsequent cycles, primary use of granulocyte-colony stimulating factors is permitted following ASCO guidance, if ANC ≤1000/$mm^3$.

Primary prophylaxis of diarrhea, nausea and vomiting is permitted in the first cycle and subsequent cycles at the investigator's discretion.

Grade ≥3 cytokine release syndrome, infusion reaction, and allergic reaction will not be considered as DLTs (as it is unlikely to be dose related), but may be a reason for study discontinuation, protocol amendment (eg, pre-infusion treatments, infusion duration) and should be reviewed with Pfizer.

In principle, a patient needs to be on study for at least 28 days to be evaluable for DLT observation, and may be replaced if they terminate study participation earlier than 28 days. However, in circumstances of an event not related to study drug (eg, traffic accident, clear disease progression) that leads to study termination close to/before 28 days, the patient might be deemed evaluable if the investigators and Pfizer agree.

In the combination cohort (Part 2), the RP2D of PF-06647020 defined from Part 1 will be used to combine with avelumab 10 mg/kg, Q2W. There will be no dose escalation for the combination cohorts. Part 1 and Part 2 patients will be pooled for the evaluation of safety, tolerability and anti-tumor activity of PF-06647020. In Part 2, OVCA patients will be randomized to receive the combination treatment (Cohort 3) or PF-06647020 single agent treatment cohort (Cohort 1) once Cohort 3 is open for enrollment.

### A4.2.1. Late Immune-Related DLTs

In the combination of PF-06647020 with avelumab Cohort 3, late immune-related DLTs are immune-related AEs that meet the same grading criteria as DLT criteria and occur from Day 29 through the Day 84 assessment period (or completion of first 3 cycles if a patient remains on treatment). If late immune related DLTs occur, enrollment in dose expansion (if it has been started at the time the late immune related DLT is observed) will be placed on temporary hold. All safety data will be reviewed by Pfizer and investigators, and a decision will be made to either:

- Continue enrollment of dose expansion.
- All 9 patients used for DLT assessment will be followed for at least 84 days to reassess safety. The totality of patients with above described DLT and late immune related DLT will be used to reassess DLT rate and inform decision whether a lower dose of PF-06647020 should be considered to be combined with avelumab (10 mg/kg) to further investigate safety and tolerability.

- Stop the combination study.

## A5. Assessments

Assessments that are captured in the Schedule of Activities but not described below may be found in the main body of the protocol and must be followed.

### A5.1. Tumor Assessment

Anti-tumor activity will be assessed by radiological tumor assessments at 8-week intervals until documented disease progression, using RECIST version 1.1 for the single agent arms, and immune-related response criteria (irRECIST) Appendix 9 for combinations arm(s). If PR or CR is observed and the response duration exceeded 6 months, tumor assessment can be assessed at a 12-week interval.

For all patients radiologic tumor assessments must include chest, abdomen, and pelvis.

Single agent Cohorts 1 and 2: All radiographic images will be collected for potential retrospective central review. Additional information on diagnostic imaging procedures and collection will be included in the Imaging Manual.

Complete responses, partial responses and progressive disease must be confirmed on repeated imaging at least 4 weeks after initial documentation. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 4 weeks). Brain CT or MRI scans are required at baseline only when there is a suspected brain metastasis. A bone scan (bone scintigraphy) or fluorine-18 fluorodeoxyglucose positron emission tomography (18FDG-PET)/CT is required at baseline only if bone metastases are suspected, then every 16 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of CR confirmation for patients who have bone metastases. MRI is acceptable for bone imaging if consistent with local practice.

CA-125 will be assessed in a local lab every 4 weeks. CA-125 measurement alone will not be used as criteria for disease progression or response determination.

In the Part 2 PF-06647020 combination with avelumab cohort (Cohort 3), any patient observed with disease progression (based on irRECIST) will require an additional tumor assessment in >4 weeks in order to confirm disease progression. Patients can stay in the study at the discretion of investigator and sponsor until progressive disease is confirmed by the investigator. Details of tumor assessment for the combination cohort can be found in the section of Treatment after Initial Evidence of Radiologic Disease Progression (Part 2 combination cohort).

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## A5.4. Pharmacokinetics/Immunogenicity Assessments

### A5.4.1. PK Assessments

Blood samples (4 mL whole blood) to provide approximately 2 mL of serum for measurement of serum PF-06380101 concentrations and blood samples (6 mL whole blood) to provide approximately 3 mL of serum for determination of ADC (PF-06647020) and total antibody (hu6M024 mAb) concentrations will be collected from all patients, in appropriately labeled tubes at times specified in the Schedule Of Activities.

For determination of serum avelumab concentrations, blood samples (4 mL) to provide approximately 2 mL of serum will be collected from patients in combination cohort in appropriately labeled tubes at times specified in the Schedule Of Activities.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing and according to windows provided in the Schedule Of Activities. Samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection will always be noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re scheduled with agreement of clinical investigators, patient and sponsor. PK samples will be assayed 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 Laboratory Manual.

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 should be documented in the CRF.

### A5.4.2. Immunogenicity Assessment

Blood samples (6 mL) to provide approximately 3 mL of serum to detect ADA and Nab against PF-06647020 will be collected from all patients, into appropriately labeled tubes at times specified in the Schedule Of Activities.

Blood samples (3.5 mL) to provide approximately 1.5 mL of serum to detect ADA and Nab against avelumab will be collected from patients in combination cohort, into appropriately labeled tubes at times specified in the Schedule Of Activities.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Laboratory Manual. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. The ADA sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Samples tested positive for ADA may also be characterized for Nab.

### A5.5. Translational and CCI

[redacted] ADC with avelumab may improve clinical outcomes. Dendritic cells, known to express PTK7, maybe activated by the auristatin payload resulting in activation and maturation of antigen specific T-cells. Dendritic cell activation will be assessed in a peripheral blood flow cytometry assay. Additionally, internalization of PF-06647020 and delivery of the payload may result in immunogenic cell death (ICD). The potential PF-06647020 induced ICD may result in stimulation of anti-tumor immunity and improved responses to avelumab. CD8+ lymphocyte infiltration in pre- and on-treatment biopsies will be utilized as a surrogate marker of ICD. As expression signature of ICD may also be investigated in pre- and on-treatment biopsies and peripheral blood.

#### A5.5.1. Archived Tumor Biospecimens and De Novo Tumor Biopsies

Archived tumor tissue samples and de novo biopsies of primary and/or metastatic lesions (see Section 7.3.1) will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs.

Markers that may be analyzed include, but may not necessarily be limited to, the presence/absence of tumor-infiltrating CD8+ T lymphocytes and/or expression of PTK7 and PD-L1 within the tumor microenvironment by immunohistochemistry or other methodology.

CCI [redacted] Additional information on tissue collection procedures can be found in the Study Manual.

CCI [redacted] Details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Laboratory Manual.

**A5.6. Electrocardiogram Measurements**

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs.

All patients participating in the combination regimen (Cohort 3) require a triplicate ECG measurement at screening. On-treatment ECGs will be performed on Day 1 of Cycles 1, 2, and 3 pre-infusion and Day 15 of Cycle 1. At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as AEs.

To ensure safety, if there is a finding of QTc >500 msec (ie, CTCAE Grade >2), then ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia correction formula is applied. If manual reading verifies a rate corrected QTc of >500 msec, repeat ECG should be immediately performed at least two times approximately 2 to 4 minutes apart.

An electronic reading of prolonged QTc must be confirmed by manual reading. Prior to conclusion that an episode of prolongation of the QTc interval is due to study treatment, 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 QTc interval reverts to less than 500 msec, and in the judgment of investigator and sponsor is determined to be due to a cause other than study treatment, treatment may be continued with regular ECG monitoring.

## A6. PATIENT ELIGIBILITY CRITERIA

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

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

### A6.1. Inclusion Criteria

Patients (in both Part 1 and Part 2) must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Histological diagnosis of the following:
    a. CCI [redacted] Patients with adenocarcinoma subtype NSCLC should be tested for ALK alterations and EGFR mutations and have exhausted all FDA-approved available targeted therapies.
    b. Platinum-resistant or refractory advanced epithelial ovarian, fallopian tube, or peritoneal cancer.
        i. Patients must have received ≤2 prior lines of systemic anticancer therapy.¥
        ii. Histologically confirmed and documented disease. The following histological types are eligible:
            - adenocarcinoma not otherwise specified (NOS);
            - clear cell adenocarcinoma;
            - endometriod adenocarcinoma;
            - malignant Brenner's tumour;
            - mixed epithelial carcinoma;

- mucinous adenocarcinoma;
- serous adenocarcinoma;
- transitional cell carcinoma;
- undifferentiated carcinoma.

Platinum-resistant/refractory disease is defined as disease progression within 180 days from the completion of a minimum of 4 platinum based therapy cycles (resistant), or lack of response or disease progression while receiving the most recent platinum-based therapy (refractory), respectively.

[¥] One line of therapy is counted as an entire regimen taken until PD was observed.
* CCI [redacted]

2. Measurable disease by investigator assessment with at least 1 unidimensional measurable lesion by RECIST v.1.1 that has not previously been irradiated.
3. At least 18 years of age.
4. ECOG performance status 0 to 2.
5. Estimated life expectancy of at least 3 months.
6. CCI [redacted]
7. Adequate bone marrow function, including:
   a. Absolute neutrophil count (ANC) ≥1.5 x $10^9$/L;
   b. Platelet count ≥100 x $10^9$/L;
   c. Hemoglobin ≥9 g/dL (may have been blood transfused).
8. Adequate liver function, including:
   - Total bilirubin level ≤1.5 × ULN;
   - AST and ALT ≤2.5 x ULN.

9. Adequate renal function as evidenced by:

    a. Creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault equation.

10. Serum/urine pregnancy test (for females of childbearing potential) negative at screening.

11. Female patients, of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and after the last dose of assigned treatment for the following lengths of time.

    a. Patients who receive PF-06647020 alone: for at least 30 days after the last PF-06647020 dose.

    b. Patients who receive PF-06647020 in combination with avelumab: for at least 60 days after the last PF-06647020/avelumab dose.

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

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

**A6.2. Exclusion Criteria**

Patients (in both Part 1 and Part 2) with any of the following characteristics/conditions will not be included in the study:

1. OVCA patients: Non-epithelial tumor including malignant mixed Mullerian tumors or ovarian tumors with low malignant potential (ie, borderline tumors).

2. Prior therapy with an anti-PTK7 for the single agent treatment cohorts, and anti-PTK7, anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA 4) antibody (including ipilimumab, tremelimumab or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) for combination Cohort 3 in OVCA.

3. Known symptomatic brain metastases requiring steroids. 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 study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks prior to study entry and are neurologically stable.

4. Concurrent anticancer treatment within 28 days prior to study entry, eg, cytoreductive therapy, radiotherapy [with the exception of palliative radiotherapy], immunotherapy, or cytokine therapy (except for erythropoietin); major surgery within 28 days prior to study entry (excluding diagnostic biopsy); use of hormonal agents within 7 days prior to study entry; or use of any investigational drug within 28 days prior to study entry. Note: patients receiving bisphosphonate or denosumab are eligible provided treatment was initiated at least 14 days prior to study entry.

5. Diagnosis of any other malignancy within 5 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix.

6. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation, bradycardia defined as <50 bpm), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.

7. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥3, atrial fibrillation of any grade, or QTcF interval >470 msec at screening (average of triplicate ECG).

8. Prior organ transplantation including allogeneic stem-cell transplantation.

9. Prior treatment with a compound of the same mechanism.

10. Currently receiving active treatment in another clinical study.

11. Known history of a positive test for HIV or AIDS related illness.

12. Active infection requiring systemic therapy.

13. HBV or HCV infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).

14. Administration of a live vaccine within 30 days prior to study entry.

15. Current or prior use of immunosuppressive medication within 7 days prior to randomization. The following are exceptions to this exclusion criterion:

    a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection).

16. Systemic corticosteroids at physiologic doses exceed 10 mg/day of prednisone or equivalent.

17. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

18. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

19. Known severe hypersensitivity reactions to monoclonal antibodies or liposomal preparations. Known hypersensitivity to any component of the Investigational Products.

20. Persisting Grade ≥2 toxicity related to prior therapy; however, Grade 2 sensory neuropathy or alopecia is acceptable.

21. Severe gastrointestinal conditions such as clinical or radiological evidence of bowel obstruction within 4 weeks prior to study entry, uncontrolled diarrhea in the last 4 weeks prior to enrollment, or history of inflammatory bowel disease.

22. Known current alcohol or drug abuse at the time of screening.

23. 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.

24. Current use or anticipated need for treatment with drugs or foods that are known strong CYP3A4 inhibitors, (eg, grapefruit juice or grapefruit/grapefruit-related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan) or inducers (eg, rifampin, St. John's Wort, phenobarbital, and phenytoin) including their administration within 10 days prior to patient registration. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed (see Appendix 6).

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

26. UK Only: Male patients with female partners of childbearing potential who are unwilling to use a highly effective method of contraception as described in this protocol.

27. UK Only: Male patients who are unwilling or unable to use 2 highly effective methods of contraception as described in this protocol for the duration of the study and for 120 days after the last dose of investigational product (150 days if the male patient is participating in the combination cohort with avelumab).

28. Pregnant female patients; breastfeeding female patients; and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for 30 days after the last dose of investigational product (60 days if the female patient is participating in the combination cohort with avelumab).

Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum FSH level confirming the postmenopausal state;

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

- Have medically confirmed ovarian failure.

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

## A7. STUDY TREATMENTS

### A7.1. Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20 mg/mL solution and is supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Avelumab (MSB0010718C) will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. Avelumab will be packed in boxes each containing one vial. The information on the study treatment will be in accordance with approved submission documents.

Avelumab will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature monitoring devices.

## A7.2. Preparation, Dispensing and Administration

See the Investigational Product Manual (IP 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, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

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

### A7.2.1. PF-06647020 Administration

PF-06647020 will be administered on Day 1 and 15 of each 4-week cycle as an IV infusion over approximately 60 minutes on an outpatient basis. A cycle is defined as the time from Day 1 dose to the next Day 1 dose.

Details for preparation and administration of the PF-06647020 infusion are provided in the IP Manual. 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-06647020 required for dose preparation. The decision to recalculate PF-06647020 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-06647020 required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

Sites should make every effort to target PF-06647020 infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of -10/+20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs.

### A7.2.2. Avelumab Administration

Avelumab will be administered as a 1-hour IV infusion once every 14 days. Details for preparation and administration of the avelumab infusion are provided in the IP Manual. Avelumab will be administered at 800 mg on Day 1 and Day 15 of each 4-week cycle after all procedures/assessments have been completed as described in the SOA table. Avelumab may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons.

For the combination arm, where both PF-06647020 and avelumab are infused (Q2W) avelumab will be infused after PF-06647020. If premedication was administered prior to PF-06647020, the decision whether to repeat pre-medication prior to avelumab is at the discretion of the investigator depending on the elapsed time and the half-life of

corresponding premedication agent. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

Sites should make every effort to target avelumab infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion-related reactions are described in the Guidelines for Toxicity Management (below).

#### A7.2.2.1. Mandatory Premedication for Avelumab Administration

In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate. The pre-treatment medications will not be supplied by Pfizer.

#### A7.2.2.2. Treatment after Initial Evidence of Radiologic Disease Progression (Part 2 Combination Cohort 3)

In the combination of PF-06647020 and avelumab Cohort 3 in Part 2, immunotherapeutic agents such as avelumab may produce anti-tumor 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 PF-06647020, and may manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

All patients receiving the combination that demonstrate progression at initial scan (based on RECIST 1.1 and/or irRECIST), an additional tumor assessment should be repeated ≥4 weeks later and assessed in order to confirm progression. Single agent avelumab may be continued at the Investigator's discretion while awaiting radiologic confirmation (ie, expedited central review) of disease progression. If repeat imaging no longer shows PD but rather CR, PR, or SD compared to the baseline scan, treatment may be continued/resumed. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (refer to the Study Manual).

Before continuation of treatment, the patient must provide consent and be informed that in order to continue receiving the investigational products on study, the patient may be foregoing approved therapy with possible clinical benefit(s). Patients may receive avelumab while waiting for confirmation of 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 demonstrates confirmed evidence of PD, patients should be discontinued from all study treatment. 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 single agent avelumab if above criteria are met. The Investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, AEs, and laboratory data.

### A7.2.3. Food Requirements

All study drugs may be administered without regard to food.

## A7.3. Guidelines for Toxicity Management

### A7.3.1. PF-06647020: Dose Interruptions/Delays

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

If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle. 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 $\geq$1,000/mm$^3$.

- Platelets count $\geq$75,000/mm$^3$.

- Non-hematologic toxicities have returned to baseline or Grade $\leq$1 severity (or, at the investigator discretion, Grade $\leq$2 if not considered a safety risk for the patient).

If these conditions are not met, treatment must be delayed by 1 week. If, after a 1-week delay, all toxicities have recovered within the limits described above treatment with PF-06647020 can be resumed.

Initiation of the next cycle can only be delayed by a maximum of 2 weeks. Therefore, if persisting toxicity does not allow PF-06647020 treatment resumption within 28 days of previous dose administration, this will result in discontinuation of the patient from treatment unless discussed and agreed with the Sponsor.

#### A7.3.1.1. PF-06647020: Dose Reductions

Following dose interruption or cycle delay due to toxicity, PF-06647020 may need to be reduced when treatment is resumed. Patients may have PF-06647020 reduced to 1.8 mg/kg, but no further reductions are allowed. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level. Dose re-escalation is not allowed.

Refer to Section 5.4.3 for additional guidance on dose reductions.

### A7.3.2. PF-06647020 in Combination with Avelumab

For patients receiving PF-06647020 and avelumab combination, PF-06647020 dose modifications as well as infusion omissions/delays for PF-06647020 and/or avelumab may occur independently for the two drugs according to the guidance provided (see Table 10 and Table 22) and according to investigator's medical judgment. Modifications will be reported in the CRF. Patients may have PF-06647020 reduced to 1.8 mg/kg (assuming 2.1 mg/kg is the RP2D for the Q2W dosing schedule) or one dose level below the RP2D determined in the single agent treatment lead-in study (Part 1), no further reductions are allowed. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level.

Dose re-escalation is not allowed.

If PF-06647020 is delayed by 1 week, avelumab should also be delayed by 1 week so that PF-06647020 and avelumab are administered together.

For patients experiencing an AE related to PF-06647020 that fails to recover to CTCAE Grade 1 (or within 1 grade of starting values for pre-existing laboratory abnormalities) leading to treatment delay of >2 weeks should be discontinued unless discussed with the Sponsor. Recommended dose modifications are illustrated in Table 10.

For avelumab, no dose modifications are permitted in this study, but doses may be omitted based on persisting toxicity.

### A7.3.3. Guidelines for Avelumab Toxicity Management

#### A7.3.3.1. Avelumab: Adverse Drug Reactions Requiring Discontinuation or Delays

The following adverse drug reactions (ADRs), if considered to be related with avelumab treatment, require permanent treatment discontinuation of avelumab:

Any Grade 4 ADRs require permanent treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any Grade 3 ADRs require permanent treatment discontinuation of avelumab except for any of the following:

- Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management.
- Transient (≤24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolve to Grade ≤1.
- Transient Grade 3 diarrhea (≤24 hours) that resolves to Grade 1 or less without administration of steroids.
- Single laboratory values out of normal range (excluding Grade ≥3 liver function test increase) that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management.
- Tumor flare phenomena defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Change in ECOG PS to ≥3 that resolves to ≤2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥3 on the day of trial drug administration).

For any Grade 2 ADR, avelumab dosing should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤1 prior to the next scheduled dose, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤1 prior to the next scheduled dose, infusions should be withheld. If by the following scheduled infusion the event has not resolved to Grade 1, the patient should permanently discontinue treatment (except for hematological toxicities and hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy or hematologic toxicities) in the same patient, treatment with avelumab has to be permanently discontinued.

Avelumab infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), tumor lysis syndrome, and irAEs should be handled according to guidelines provided below.

### A7.3.3.2. Avelumab: Infusion-related Reactions and Hypersensitivity Reactions

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. Following the first 4 avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions. If no infusion reaction occurs in relation to the first 4 infusions, the post-infusion observation period may be discontinued. During this 2-hour observation period the patient should remain in a location where they can be observed by site staff. Vital sign measurements or other procedures are not required unless clinically indicated. If an allergic reaction occurs, the patient must be treated according to the best available medical practice. The emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator immediately.

**Table 19. Avelumab: Treatment Modifications for Symptoms of Infusion-related Reactions**

| NCI-CTCAE Grade | Treatment Modification for Avelumab |
|---|---|
| Grade 1 – mild<br>Mild transient reaction; infusion interruption not indicated; intervention not indicated. | Decrease Avelumab infusion rate by 50% and monitor closely for any worsening. |
| Grade 2 – moderate<br>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours. | Stop Avelumab infusion.<br><br>Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening. |
| Grade 3 or Grade 4 – severe or life-threatening<br>Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.<br><br>Grade 4: Life-threatening consequences; urgent intervention indicated. | Stop the Avelumab infusion immediately and disconnect infusion tubing from the patient.<br><br>Patients have to be withdrawn immediately from Avelumab treatment and must not receive any further Avelumab treatment. |

IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

Once the Avelumab infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain decreased for all subsequent infusions.

#### A7.3.3.3. Avelumab: Additional Modifications for Patients with Grade 2 Infusion-related Reactions

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 19 (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next cycle, the investigator may consider the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), in addition to the mandatory premedication. However, prophylactic steroids are NOT permitted. If the patient has a second infusion-related reaction ≥ Grade 2 on the slower infusion rate, with or without the addition of further medication to the mandatory premedication, the infusion should be stopped and the patient removed from avelumab treatment.

#### A7.3.3.4. Avelumab: Severe Hypersensitivity Reactions and Flu-like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms include impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Patients should be placed on monitor immediately, and the intensive care unit should be alerted for possible transfer if required.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (eg, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (eg, paracetamol) may be given to patients at the discretion of the investigator.

#### A7.3.3.5. Avelumab: Immune-related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grades 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring.
- Grades 1 to 2 (persistent): manage similar to high grade AE (Grades 3 to 4).
- Grades 3 to 4: treat with high dose corticosteroids.

For patients receiving PF-06647020 and avelumab combination, any event suspected to be immune-related should be managed according to the guidance for management of immune-related AEs in Table 20.

**Table 20. Avelumab: Management of Immune-related Adverse Events**

| **Gastrointestinal irAEs** | | |
|---|---|---|
| **Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)** | **Management** | **Follow-up** |
| **Grade 1**<br>Diarrhea: <4 stools/day over Baseline<br>Colitis: asymptomatic | Continue avelumab therapy<br>Symptomatic treatment (eg, loperamide) | Close monitoring for worsening symptoms<br>Educate patient to report worsening immediately<br>If worsens:<br>Treat as Grade 2 or 3/4 |
| **Grade 2**<br>Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL<br>Colitis: abdominal pain; blood in stool | Delay avelumab therapy<br>Symptomatic treatment | If improves to Grade 1:<br>Resume avelumab therapy<br>If persists >5 to 7 days or recur:<br>0.5 to 1.0 mg/kg/day methylprednisolone or equivalent<br>When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol.<br>If worsens or persists >3 to 5 days with oral steroids:<br>Treat as Grade 3 to 4 |
| **Grade 3 to 4**<br>Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL<br>Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs<br>Grade 4: life-threatening, perforation | Discontinue avelumab therapy per protocol<br>1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider lower endoscopy | If improves:<br>Continue steroids until Grade 1, then taper over at least 1 month<br>If persists >3 to 5 days, or recurs after improvement:<br>Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis |
| **Dermatological irAEs** | | |
| **Grade of Rash (NCI-CTCAE v4.03)** | **Management** | **Follow-up** |
| **Grades 1 to 2**<br>Covering ≤30% body surface area | Symptomatic therapy (for example, antihistamines, topical steroids)<br>Continue avelumab therapy | If persists >1 to 2 weeks or recurs:<br>Consider skin biopsy<br>Delay avelumab therapy<br>Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent.<br>Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy<br><br>If worsens:<br>Treat as Grades 3 to 4 |

| | | |
|---|---|---|
| **Grades 3 to 4**<br>Covering >30% body surface area; life threatening consequences | Delay or discontinue avelumab therapy<br>Consider skin biopsy<br>Dermatology consult<br>1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent | If improves to Grade 1:<br>Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections<br>Resume avelumab therapy |
| **Pulmonary irAEs** | | |
| **Grade of Pneumonitis (NCI-CTCAE v4.03)** | **Management** | **Follow-up** |
| **Grade 1**<br>Radiographic changes only | Consider delay of avelumab therapy<br>Monitor for symptoms every 2 to 3 days<br>Consider Pulmonary and Infectious Disease consults | Re-image at least every 3 weeks<br>If worsens:<br>Treat as Grade 2 or Grade 3 to 4 |
| **Grade 2**<br>Mild to moderate new symptoms | Delay avelumab therapy<br>Pulmonary and Infectious Disease consults<br>Monitor symptoms daily, consider hospitalization<br>1.0 mg/kg/day methyl-prednisolone IV or oral equivalent<br>Consider bronchoscopy, lung biopsy | Re-image every 1 to 3 days<br>If improves:<br>When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics<br>If not improving after 2 weeks or worsening:<br>Treat as Grade 3 to 4 |
| **Grade of Pneumonitis (NCI-CTCAE v4.03)** | **Management** | **Follow-up** |
| **Grades 3 to 4**<br>Severe new symptoms; New / worsening hypoxia; life-threatening | Discontinue avelumab therapy<br>Hospitalize<br>Pulmonary and Infectious Disease consults<br>2 to 4 mg/kg/day methylprednisolone IV or IV equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider bronchoscopy, lung biopsy | If improves to Baseline:<br>Taper steroids over at least 6 weeks<br>If not improving after 48 hours or worsening:<br>Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil). |
| **Hepatic irAEs** | | |
| **Grade of Liver Test Elevation (NCI-CTCAE v4.03)** | **Management** | **Follow-up** |
| **Grade 1**<br>Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN | Continue avelumab therapy | Continue liver function monitoring<br>If worsens:<br>Treat as Grades 2 or 3 to 4 |
| **Grade 2**<br>AST or ALT >3.0 to ≤5 x ULN and / or total bilirubin >1.5 to ≤3 x ULN | Delay avelumab therapy<br>Increase frequency of monitoring to every 3 days | If returns to Baseline:<br>Resume routine monitoring, resume avelumab therapy<br>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 avelumab therapy |
| **Grades 3 to 4**<br>AST or ALT >5 x ULN and / or total bilirubin >3 x ULN | Discontinue avelumab therapy<br>Increase frequency of monitoring to every 1 to 2 days<br>1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consult gastroenterologist<br>Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted | If returns to Grade 2:<br>Taper steroids over at least 1 month<br>If does not improve in >3 to 5 days, worsens or rebounds:<br>Add mycophenolate mofetil 1 gram (g) twice daily<br>If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines. |
| **Cardiac irAEs** | | |
| **Myocarditis** | **Management** | **Follow-up** |
| New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis. | Withhold avelumab therapy<br>Hospitalize in the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management<br>Cardiology consult to establish etiology and rule out immune-mediated myocarditis.<br>Guideline based supportive treatment as per cardiology consult.*<br>Consider myocardial biopsy if recommended per cardiology consult. | If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy.<br>If symptoms do not improve/worsen, viral myocarditis is excluded, and immune mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis. |
| Immune-mediated myocarditis | Permanently discontinue avelumab.<br>Guideline based supportive treatment as appropriate as per cardiology consult.*<br>Methylprednisolone 1 to 2 mg/kg/day | Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.<br>If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A) |
| *Local guidelines, or eg. ESC or AHA guidelines<br>ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines<br>AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001 | | |

| Endocrine irAEs | | |
|---|---|---|
| **Endocrine Disorder** | **Management** | **Follow-up** |
| Asymptomatic TSH abnormality | Continue avelumab therapy<br>If TSH <0.5 x LLN, or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult | |
| Symptomatic endocrinopathy | Evaluate endocrine function<br>Consider pituitary scan<br>Symptomatic with abnormal lab / pituitary scan:<br>Delay avelumab therapy<br>1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent<br>Initiate appropriate hormone therapy<br>No abnormal lab/pituitary MRI scan but symptoms persist:<br>Repeat labs in 1 to 3 weeks/MRI in 1 month | If improves (with or without hormone replacement):<br>Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections<br>Resume avelumab therapy<br>Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component. |
| Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness) | Delay or discontinue avelumab therapy<br>Rule out sepsis<br>Stress dose of IV steroids with mineralocorticoid activity<br>IV fluids<br>Consult endocrinologist<br>If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy | |

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography; irAE=immune-related adverse event, IV=intravenous, LFT=liver function test, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, anti-inflammatory drugs, T4=free thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

### A7.3.3.6. Guidelines PF-06647020-Avelumab Combination Toxicity Management

Dose modification (dose delays and dose reduction) for PF-06647020 due to ADRs should be made in accordance with the guidance provided below. The starting dose for PF-06647020 in combination will be the RP2D dose as determined by the single agent Q2W dose escalation (Part 1). Dose reduction levels are described in Table 21.

Some potential irAEs described with anti-PD-L1 drugs such as avelumab may overlap with PF-06647020 toxicities such as fatigue, nausea, or rash. For patients on combination treatment with avelumab and PF-06647020, any AE suspected to be immune-related should be managed according to the guidance for management of irAEs (Table 19). In case of a potential irAE, besides the management related to avelumab therapy, PF-06647020 may also be reduced or interrupted.

**Table 21. PF-06647020 Dose Modifications**

| Starting Dose Level of PF-06647020 | Dose Reduction |
|---|---|
| If RP2D is 2.8 mg/kg | 2.1 mg/kg |
| If RP2D is 2.1 mg/kg | 1.8 mg/kg |

### A7.3.3.7. PF-06647020-Avelumab Combination: Neutropenia

ANC must be ≥1.0 x $10^9$/L prior to each administration. For patients who do not achieve hematological recovery on the scheduled day of PF-06647020 administration, complete blood counts should be performed twice weekly until the above defined limits are achieved. If hematological recovery is achieved within 14 days after the scheduled day of PF-06647020 administration, resume PF-06647020 at the previous dose. If hematological recovery is not achieved 14 days or more after the scheduled day of PF-06647020 administration, the patient will discontinue treatment unless discussed and agreed with the Sponsor. Administration of G-CSF or EPO is permitted according to approved indications and scientific recommendations.

## Table 22. PF-06647020-Avelumab Combination: Treatment Modification for Neutropenia

| Neutropenia and Thrombocytopenia | PF-06647020 Single Agent | PF-06647020-Avelumab Combination* |
|---|---|---|
| Grade 1 | No PF-06647020 dose reduction/delay | No PF-06647020 dose reduction/delay<br>Continue avelumab as per schedule |
| Grade 2 | Delay PF-06647020 until toxicity resolves to ANC ≥1.0 x $10^9$/L, then resume PF-06647020 (no dose reduction).** | Delay PF-06647020 until toxicity resolves to ANC ≥1.0 x $10^9$/L, then resume PF-06647020 (no dose reduction).** Continue avelumab as per schedule. |
| Grade 3 | Delay PF-06647020 until toxicity resolves to ANC ≥1.0 x $10^9$/L, then resume PF-06647020 (no dose reduction).** | Delay PF-06647020 until toxicity resolves to ANC ≥1.0 x $10^9$/L, resume PF-06647020 (no dose reduction).**<br>Continue avelumab as per schedule.<br><br>If Grade 3 toxicity recurs, delay PF-06647020 and avelumab until toxicity resolves to ANC ≥1.0 x $10^9$/L, then resume PF-06647020 at reduced dose** and avelumab at standard dose.<br><br>If Grade 3 toxicity recurs with PF-06647020 at reduced dose, delay PF-06647020 until toxicity resolves to ANC ≥1.0 x $10^9$/L, then resume PF-06647020 the reduced dose. **<br>For avelumab:<br>• If toxicity resolves to ANC ≥1.0 x $10^9$/L, resume avelumab at the standard dose.<br>• If toxicity resolves to ANC ≥1.0 x $10^9$/L, permanently discontinue avelumab. |
| Grade 4 | Delay PF-06647020 until toxicity resolves to ANC ≥1.0 x $10^9$/L, then resume PF-06647020 at reduced dose level or continue at previous dose with prophylactic granulocyte growth factor support.** | Delay PF-06647020 and avelumab until toxicity resolves to Grade ≤1; then resume PF-06647020 at reduced dose level** and avelumab at standard dose.<br>• If toxicity resolves to ANC ≥1.0 x $10^9$/L, resume avelumab at the standard dose.<br>• If toxicity resolves to ANC ≥1.0 x $10^9$/L, in >14 days, permanently discontinue avelumab. |

** If hematological recovery is achieved within 14 days after the scheduled day of PF-06647020 treatment, resume PF-06647020 at the previous dose. If hematological recovery is not achieved 14 days or more after the scheduled day of the course, the patient will permanently discontinue treatment unless discussed and agreed with the Sponsor.

## A7.4. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, including PF-06647020 and avelumab, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

- Avelumab must be stored in the refrigerator at 2°-8°C (36°-46°F). Do not freeze. Protect from light. Do not shake vigorously.

Storage conditions stated in the SRSD (Investigator Brochure) will be superseded by storage conditions stated in the labeling.

Refer to Section 5.5 for additional guidance.

### A7.5. Surgery

No formal studies of the effect of PF-06647020 or avelumab on wound healing have been conducted; however, caution is advised on theoretical grounds for any surgical procedures during the study.

No surgical risk has been identified with immune checkpoint inhibitors. No surgical precautions are mentioned in pembrolizumab, nivolumab or atezolizumab product labels. If a major surgery or an interventional procedure (eg, endoscopy) is required, treatment with PF-06647020 or avelumab must be interrupted. Patients may resume PF-06647020 or avelumab 2-3 weeks after major surgery, assuming the wound has completely healed and there are no wound healing complications (eg, delayed healing, wound infection or fistula).

Avelumab treatment does not need to be delayed for minor surgical procedures that do not involve general anesthesia.

## A8. DATA ANALYSIS/STATISTICAL METHODS

Refer to Section 9 of the main protocol for more details.

## Table A3. SCHEDULE OF ACTIVITIES: Single Agent Q2W Regimens

| Protocol Activities[1] | Screening[2] | Treatment Period | | | | | | | | | | | | Post-Treatment Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | Cycle 2 | | | | Cycle 3 | | Cycle 4+ | | EOT[4] | Follow up[5] |
| | | 1 cycle = 4 weeks[3] | | | | | | | | | | | | | |
| | | Day 1 | Day 8 | Day 15 | Day 21 | Day 1 | Day 8 | Day 15 | Day 21 | Day 1 | Day 15 | Day 1 | Day 15 | | |
| Visit Time Window (days) | (≤28) | | (±1) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | | |
| Informed Consent[6] | X | | | | | | | | | | | | | | |
| Tumor History[7] | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| Ophthalmic Examination[8] | X | | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | | |
| Vital Signs[9] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Physical Examination[10] | X | X | | | | | | | | | | | | X | |
| Abbreviated Physical Examination[11] | | | X | X | X | X | X | X | X | X | X | X | X | | |
| ECOG Performance Status[12] | X | X | | | | X | | | | X | | X | | X | |
| Contraception Check[13] | | X | | | | X | | | | X | | X | | X | |
| Hematology[14] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Blood Chemistry[15] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Coagulation[16] | X | X | | X | | X | | X | | X | X | X | X | X | |
| CA-125[17] | X | X | | | | X | | | | X | | X | | X | |
| Urinalysis[18] | X | X | | | | | | | | | | | | | |
| Pregnancy Test[19] | X | X | | | | X | | | | X | | X | | X | |
| Single 12-lead ECG[20] | X | X | | X | | X | | | | X | | X | | X | |
| PK/ Immunogenicity/CCI Sampling | See Schedule of PK/Immunogenicity/Biomarker Assessment Table | | | | | | | | | | | | | | |
| Registration and Treatment | | | | | | | | | | | | | | | |
| Registration[21] | X | | | | | | | | | | | | | | |
| PF-06647020 Administration[22] | | X | | X | | X | | X | | X | X | X | X | | |
| Tumor Assessments | | | | | | | | | | | | | | | |
| CT or MRI Scan[23] | X | | | | | | | | X | | | | Every 8 weeks | X | |
| Other Clinical Assessments | | | | | | | | | | | | | | | |
| Adverse Events[24] | → | → | → | → | → | → | → | → | → | → | → | → | → | X | |
| Concomitant Treatments[25] | | → | → | → | → | → | → | → | → | → | → | → | → | X | |
| Other Patient Samples | | | | | | | | | | | | | | | |
| CCI [redacted] | [redacted] | | | | | | | | | | | | | | |

| Protocol Activities[1] | Screening[2] | Treatment Period | | | | | | | | | | | | Post-Treatment Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | Cycle 2 | | | | Cycle 3 | | Cycle 4+ | | EOT[4] | Follow up[5] |
| | | 1 cycle = 4 weeks[3] | | | | | | | | | | | | | |
| | | Day 1 | Day 8 | Day 15 | Day 21 | Day 1 | Day 8 | Day 15 | Day 21 | Day 1 | Day 15 | Day 1 | Day 15 | | |
| Visit Time Window (days) | (≤28) | | (±1) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | | |
| CCI [redacted] | [redacted] | | | | | [redacted] | | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | | | | | | | |

Abbreviations: CT = computed tomography; ECG = electrocardiogram; EOT = end of treatment; CCI [redacted]; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; BP = blood pressure; PR = pulse rates; PK = pharmacokinetics; ECOG = Eastern Cooperative Oncology Group; OVCA = Ovarian cancer

Unless otherwise specified, laboratory values and assessments should be obtained prior to study treatment. If the infusion is held, assessments should still be performed.

## Footnotes

1. **Protocol Activities:** All assessments should be performed prior to dosing with study medication unless otherwise specified. There is no need to repeat activity at Day 1 if it was done during the screening timeframe of 28 days unless otherwise specified.
2. **Screening**: All assessments to be performed within 28 days prior to randomization. Consent may be obtained >28 days.
3. **Study Cycle:** Cycle length is 4 weeks for each treatment arm.
4. **End of Treatment/Withdrawal**: Obtain these assessments if not completed within the prior week, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks.
5. **Follow-up:** At least 28 days and no more than 35 days after end of treatment visit, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
6. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
7. **Tumor History**: Includes collection of tumor history, prior anti-tumor regimen(s), including treatment duration and best response observed.
8. **Ophthalmic Examination:** An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes Best Corrected Visual Acuity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic Exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow up.
9. **Vital Signs:** Blood pressure (BP) and pulse rate should be taken before any other assessments (eg, PK, laboratory blood draws) with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.

10. **Physical Examination:** Includes an examination of major body systems, and weight (height included at screening only). Abnormal findings identified prior to first dose of study treatment should be documented on the Medical History CRF page.
11. **Abbreviated Physical Exam:** Should be performed as appropriate at each visit where full physical exams are not required, and on an as needed basis for assessment of AEs. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.
12. **ECOG Performance status:** Use Eastern Cooperative Oncology Group (ECOG).
13. **Contraception Check:** Patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient.
14. **Hematology:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See Assessments section in main body of protocol for Laboratory Tests list. Results should be available for review prior to infusion of treatment.
15. **Blood Chemistry:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See Assessments section in main body of protocol for Laboratory Tests list. Results should be available for review prior to infusion of treatment.
16. **Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section in main body of protocol for Laboratory Tests list.
17. **CA-125:** Will be assessed locally according to the schedule in the table.
18. **Urinalysis:** Dipstick is acceptable. Microscopic analyses must be performed if dipstick is abnormal.
19. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a urine or serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study treatment, once at the start of screening and once at the baseline visit, immediately before study treatment administration. Urine pregnancy tests will also be routinely repeated at every treatment cycle 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. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations. See Section 7.1.1 for contraception guidelines.
20. **12-Lead ECGs:** ECG measurement will be collected during screening and at the End of Treatment Visit. On-treatment ECGs will be performed on Day 1 of Cycles 1, 2, and 3 and Day 15 of Cycle 1 (all pre-infusion). In Cycle 4 and subsequent cycles, a single ECG should be taken pre-dose on Day 1. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. It is recommended that ECGs are performed prior to any blood collection or other invasive procedures. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated (see Section 7.1.5). Beginning at Cycle 8, the Day 8 assessments will be optional for patients that have achieved a CR, PR or SD if agreed upon by the treating physician.
21. **Registration:** Patient number and dose level allocation will be provided by Pfizer Inc.
22. **Study Treatment**: PF-06647020 will be given as a 1-hour intravenous infusion (IV) every 2 weeks. Weight should be collected prior to each infusion, assessed and documented in the CRF.
23. **Tumor Assessments***:* Tumor assessments will include all known or suspected disease sites. Tumor assessments must include chest, abdomen and pelvis CT or MRI scans and will be conducted every 8 weeks (window of 5 days prior to dosing is allowed) from the start of study treatment until disease progression by RECIST (v1.1) or death, or

at the time of withdrawal from treatment (if not done in previous 8 weeks). If PR or CR is observed and the response duration exceeded 6 months, tumor assessment can be assessed at a 12-week interval. Brain scans will be performed at baseline only if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. A bone scan (bone scintigraphy) or $^{18}$FDG-PET/CT is required at baseline only if disease is suspected and then every 16 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of CR confirmation for patients who have bone metastases. MRI is acceptable for bone imaging if consistent with local practice. Responses of complete response (CR) or partial response (PR) must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met. All radiographic images will be collected for potential central review. Additional information on diagnostic imaging procedures and collection will be included in the Imaging Manual.

24. **Adverse Event (AE) Assessments:** AEs should be documented and recorded in the CRF. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version (v) 4.03 will be used. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment. See Section 8.1.1.

25. **Concomitant Treatments:** All concomitant medications and Non-Drug Supportive Interventions should be recorded in the CRF.

CCI [redacted]

## Table A4. SCHEDULE OF ACTIVITIES: Pharmacokinetic, Immunogenicity, and Biomarker Sampling Schedule (Single Agent and Combination PF-06647020 with Avelumab Q2W Regimen)

| Protocol Activity | Cycle 1 | | | | | | | | Cycle 2 | | | | Cycle 3 | | | | | | | | Cycles ≥4 | EOT/ Withdrawal Visit | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 cycle = 4 weeks | | | | | | | | | | | | | | | | | | | | | | |
| | Day 1 | | | Day 2 | Day 4 | Day 8 | Day 15 | | Day 1 | | Day 15 | | Day 1 | | | Day 2 | Day 4 | Day 8 | Day 15 | | Day 1 | | |
| Visit Window (days) | | | | | (±1) | (±1) | (±2) | | | | (±2) | | | | | | (±1) | (±1) | (±2) | | | | |
| | Pre-dose* | EOI * | 4 hr* | 24 hr* | | | Pre-dose* | EOI * | Pre-dose* | EOI * | Pre-dose* | EOI * | Pre-dose* | EOI * | 4 hr* | 24 hr* | | | Pre-dose* | EOI * | Pre-dose* | | |
| PK Sampling for PF-06647020 and hu6M024 mAb[1] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK Sampling for PF-06380101[2] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK Sampling for Avelumab (avelumab combination cohort only)[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| CCI [redacted] | [redacted] | | | | | | | | | | | | | | | | | | | | | | |
| Blood Sample for Immunogenicity Test (Anti-PF-06647020)[5] | X | | | | | | X | | X | | | | X | | | | | | | | X | X | X |
| Blood Sampling for Immunogenicity Test (Anti-avelumab, avelumab combination cohort only)[6] | X | | | | | | X | | X | | | | X | | | | | | | | X | X | X |
| Immune Cell Phenotyping (all Part 1 and OVCA cohorts in Part 2[7] | X | | | | | X | | | | | X | | | | | | | | | | | X | |
| RNA Analysis[8] | X | X | | | X | X | | X | | X | | X | | | | | | | | | X (cycle 5 only) | X | |
| Cytokines/ Chemokines[9] | X | X | | | X | X | X | | | X | | | X | | | | | | | | X (cycle 5 only) | X | |
| Whole Blood for DNA Analysis[10] | X | | | | | | X | | X | | | | X | | | | | | | | X (cycle 5 only) | X | |

Abbreviations: EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetics, mAb = monoclonal antibody; OVCA = ovarian cancer; RNA = ribonucleic acid; DNA = deoxyribonucleic acid

* Sampling times are related to the start of infusion; all samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection will always be noted on the CRF.

## Footnotes

1. **PK Sampling for PF-06647020 and hu6M024 mAb:** Blood samples (6 mL) for PF-06647020 and hu6M024 mAb PK will be collected in all patients: pre-PF-06647020 dose, at the end of PF-06647020 infusion (immediately before the end of infusion), and 4 hours of Day 1, Day 2 (24 hours), Days 4, 8, and 15 (pre-PF-06647020 dose and at the end of PF-06647020 infusion) of Cycles 1 and 3; Pre-PF-06647020 dose and at the end of PF-06647020 infusion on Days 1 and 15 of Cycle 2; pre-PF-06647020 dose on Day 1 of Cycles 4 and beyond, at the End of Treatment and at Day 30 Safety Follow-up visit.
2. **PK Sampling for PF-06380101:** Blood samples (4 mL) for PF-06380101 PK will be collected in all patients: pre-PF-0067020 dose, at the end of PF-06647020 infusion (immediately before the end of infusion), and 4 hours of Day 1, Day 2 (24 hours), Days 4, 8, and 15 (pre-PF-06647020 dose and at the end of infusion) of Cycles 1 and 3; Pre-PF-06647020 dose and at the end of PF-06647020 infusion on Days 1 and 15 of Cycle 2; pre-PF-06647020 dose on Day 1 of Cycles 4 and beyond, at the End of Treatment and at Day 30 Safety Follow-up visit.
3. **PK Sampling for Avelumab:** Blood samples (4 mL) for avelumab PK will be collected in all avelumab combination cohort patients: pre-avelumab dose, at the end of avelumab infusion (immediately before the end of infusion), and 4 hours of Day 1, Day 2 (24 hours), Days 4, 8, and 15 (pre-avelumab dose and at the end of infusion) of Cycles 1 and 3; Pre-avelumab dose and at the end of avelumab infusion on Days 1 and 15 of Cycle 2; pre-avelumab dose on Day 1 of Cycles 4 and beyond, at the End of Treatment and at Day 30 Safety Follow-up visit.

[redacted]

5. **Blood Sample for PF-06647020 Immunogenicity Test:** Blood samples (6 mL) for immunogenicity testing against PF-06647020 will be collected in all patients at baseline (2 hours before the start of PF-6647020 infusion on Day 1 of Cycle 1), pre-dose (prior to PF-06647020 infusion) on Day 15 of Cycle 1, and pre-dose (prior to PF-06647020 infusion) on Day 1 of Cycles 2 and beyond and at the End of Treatment. An additional sample for immunogenicity must be collected at 30 days after the last dose of PF-06647020.
6. **Blood Sample for avelumab Immunogenicity Test:** Blood samples (3.5 mL) for immunogenicity testing against avelumab will be collected in all avelumab combination cohort patients at baseline (2 hours before the start of PF-6647020 infusion on Day 1 of Cycle 1), pre-dose (prior to PF-06647020 infusion) on Day 15 of Cycle 1, and pre-dose (prior to PF-06647020 infusion) on Day 1 of Cycles 2 and beyond and at the End of Treatment. An additional sample for immunogenicity must be collected at 30 days after the last dose of avelumab.
7. **Immune Cell Phenotyping:** A 4 mL whole blood sample will be collected in a K2EDTA tube at Cycle 1 Day 1 (pre-dose) and Day 8, and Cycle 2 Day 15 (pre-dose), and at End of Treatment from all patients in Part 1 and from patients in the following Part 2 cohorts 1) with platinum resistant or refractory OVCA treated with single agent PF-06647020; 2) platinum resistant or refractory OVCA treated with PF-06647020 in combination with avelumab. Immune cell functional markers will be measured by flow cytometry.
8. **RNA analysis:** A 2.5 mL whole blood sample will be collected into PAXgene (RNA) tubes at Cycle 1 Day 1 (pre-dose) and end of infusion (EOI) of the last investigational product (IP) administered, and on Cycle 1 Day 4, Day 8 and Day 15, and Cycle 2 Day 1 and Day 15, and Cycle 5 Day 1, and End of Treatment. RNA may be analyzed for expression profile of immune- and tumor-related transcripts.

9. **Cytokines/Chemokines:** A 4 mL blood sample will be collected into serum collection tubes at Cycle 1 Day 1 (pre-dose) and end of infusion (EOI) of the last investigational product (IP) administered, and on Cycle 1 Day 4, Day 8 and Day 15, and Cycle 2 Day 1, Cycle 3 Day 1, Cycle 5 Day 1 and End of Treatment. Samples may be analyzed for soluble factors associated with immune activation, regulation and potential pharmacodynamic activity of PF-06647020.

10. **Whole Blood for DNA Analysis:** A 4 mL whole blood sample will be collected in a tube optimized for deoxyribonucleic acid (DNA) preservation at Cycle 1 Day 1 (pre-dose), and Day 15 (pre-dose), Cycle 2 Day 1 (pre-dose), Cycle 3 Day 1 (pre-dose), Cycle 5 Day 1 (pre-dose) and End of Treatment. DNA may be submitted for TCR sequencing analysis.

## Table A5. SCHEDULE OF ACTIVITIES: Combination PF-06647020 with Avelumab Q2W Regimen

| Protocol Activities[1] | Screening[2] | Treatment Period | | | | | | | | | | | | Post-Treatment Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | Cycle 2 | | | | Cycle 3 | | Cycle 4+ | | | |
| | | 1 cycle = 4 weeks[3] | | | | | | | | | | | | EOT[4] | Follow up[5] |
| | | Day 1 | Day 8 | Day 15 | Day 21 | Day 1 | Day 8 | Day 15 | Day 21 | Day 1 | Day 15 | Day 1 | Day 15 | | |
| Visit Time Window (days) | (≤28) | | (±1) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | | |
| Informed Consent[6] | X | | | | | | | | | | | | | | |
| Tumor History[7] | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| Ophthalmic Examination[8] | X | | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | | |
| Vital Signs[9] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Physical Examination[10] | X | X | | | | | | | | | | | | X | |
| Abbreviated Physical Examination[11] | | | X | X | X | X | X | X | X | X | X | X | X | | |
| ECOG Performance Status[12] | X | X | | | | X | | | | X | | X | | X | |
| Contraception Check[13] | | X | | | | X | | | | X | | X | | X | |
| Hematology[14] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Blood Chemistry[15] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Coagulation[16] | X | X | | X | | X | | X | | X | X | X | X | X | |
| ACTH, Free T4, TSH[17] | X | X | | | | | | | | X | | | | X | |
| HBV, HCV[18] | X | | | | | | | | | | | | | | |
| ANA, ANCA, RF | X | | | | | | | | | | | | | | |
| CA-125[19] | X | X | | | | X | | | | X | | X | | X | |
| BRCA 1/2 Mutation Status[20] | X | | | | | | | | | | | | | | |
| Urinalysis[21] | X | X | | | | | | | | | | | | | |
| Pregnancy Test[22] | X | X | | | | X | | | | X | | X | | X | |
| Triplicate/Single 12-lead ECG[23] | X | X | | X | | X | | | | X | | X | | X | |
| PK/Immunogenicity/CCI Sampling | See Schedule of PK/Immunogenicity/Biomarker Assessment Table | | | | | | | | | | | | | | |
| Registration and Treatment | | | | | | | | | | | | | | | |
| Registration[24] | X | | | | | | | | | | | | | | |
| PF-06647020 + avelumab Administration[25] | | X | | X | | X | | X | | X | X | X | X | | |
| Tumor Assessments | | | | | | | | | | | | | | | |
| CT or MRI Scan[26] | X | | | | | | | | X | | | | Every 8 weeks | X | |
| Other Clinical Assessments | | | | | | | | | | | | | | | |
| Adverse Events[27] | → | → | → | → | → | → | → | → | → | → | → | → | → | X | |

| Protocol Activities[1] | Screening[2] | Treatment Period | | | | | | | | | | | | Post-Treatment Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | Cycle 2 | | | | Cycle 3 | | Cycle 4+ | | | |
| | | 1 cycle = 4 weeks[3] | | | | | | | | | | | | EOT[4] | Follow up[5] |
| | | Day 1 | Day 8 | Day 15 | Day 21 | Day 1 | Day 8 | Day 15 | Day 21 | Day 1 | Day 15 | Day 1 | Day 15 | | |
| Visit Time Window (days) | (≤28) | | (±1) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | (±2) | | |
| Concomitant Treatments[28] | | → | → | → | → | → | → | → | → | → | → | → | → | X | |
| Other Patient Samples | | | | | | | | | | | | | | | |
| CCI [redacted] | | | | | | | | | | | | | | | |

Abbreviations: CT = computed tomography; ECG = electrocardiogram; EOT = end of treatment; CCI [redacted]; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; BP = blood pressure; PR = pulse rates; PK = pharmacokinetics; ECOG = Eastern Cooperative Oncology Group; OVCA = Ovarian cancer; ACTH = adrenocorticotropic hormone; TSH = thyroid stimulating hormone; HBV = Hepatitis B virus; HCV = Hepatitis C virus; ANA = antinuclear antibody; ANCA = anti-neutrophil cytoplasmic antibodies; RF = rheumatoid factor

Unless otherwise specified, laboratory values and assessments should be obtained prior to study treatment. If the infusion is held, assessments should still be performed.

## Footnotes

1. **Protocol Activities:** All assessments should be performed prior to dosing with study medication unless otherwise specified. There is no need to repeat activity at Day 1 if it was done during the screening timeframe of 28 days unless otherwise specified.
2. **Screening**: All assessments to be performed within 28 days prior to randomization. Consent may be obtained >28 days.
3. **Study Cycle:** Cycle length is 4 weeks for each treatment arm.
4. **End of Treatment/Withdrawal**: Obtain these assessments if not completed within the prior week, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks.
5. **Follow-up:** At least 28 days and no more than 35 days after end of treatment visit, patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
6. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
7. **Tumor History**: Includes collection of tumor history, prior anti-tumor regimen(s), including treatment duration and best response observed.
8. **Ophthalmic Examination:** An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes Best Corrected Visual Acuity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic Exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow up.
9. **Vital Signs:** Blood pressure (BP) and pulse rate should be taken before any other assessments (eg, PK, laboratory blood draws) with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.

10. **Physical Examination:** Includes an examination of major body systems, and weight (height included at screening only). Abnormal findings identified prior to first dose of study treatment should be documented on the Medical History CRF page.
11. **Abbreviated Physical Exam:** Should be performed as appropriate at each visit where full physical exams are not required, and on an as needed basis for assessment of AEs. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.
12. **ECOG Performance status:** Use Eastern Cooperative Oncology Group (ECOG).
13. **Contraception Check:** Patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient.
14. **Hematology:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See Assessments section in main body of protocol for Laboratory Tests list. Results should be available for review prior to infusion of treatment.
15. **Blood Chemistry:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See Assessments section in main body of protocol for Laboratory Tests list. Results should be available for review prior to infusion of treatment.
16. **Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section in main body of protocol for Laboratory Tests list.
17. **ACTH and Thyroid Function Tests:** ACTH, Free T4 and TSH will be measured prior to trial treatment, every 8 weeks for 2 additional measurements, then every 12 weeks thereafter while on treatment, End of Treatment, and as clinically indicated.
18. **HBV serology and HCV serology**: measured prior to study enrollment and then as clinically indicated.
19. **CA-125:** Will be assessed locally according to the schedule in the table.
20. **BRCA status:** If BRCA1/2 mutation status is known or becomes known for a patient during the study, this information will be recorded in the CRF either at screening or at later visits. No BRCA1/2 testing is required for this study.
21. **Urinalysis:** Dipstick is acceptable. Microscopic analyses must be performed if dipstick is abnormal.
22. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a urine or serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study treatment, once at the start of screening and once at the baseline visit, immediately before study treatment administration. Urine pregnancy tests will also be routinely repeated at every treatment cycle 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. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
23. **12-Lead ECGs:** All patients require a triplicate ECG measurement at screening. On-treatment ECGs will be performed on Day 1 of Cycles 1, 2, and 3 and Day 15 of Cycle 1 (all at pre-infusion). At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart (within 10 minutes) to determine mean QTc (average of triplicates). In Cycle 4 and subsequent cycles, a single ECG should be taken pre-dose on Day 1. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. It is recommended that ECGs are performed prior to any blood collection or other invasive procedures. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.
24. **Registration:** Patient number and dose level allocation will be provided by Pfizer Inc.

25. **Study Treatment**: PF-06647020 will be given as a 1-hour intravenous infusion (IV) followed by avelumab given as a 1-hour intravenous infusion every 2 weeks. Weight should be collected prior to each infusion, assessed and documented in the CRF. There is a plus or minus 3 day window for PF-06647020 and avelumab administration, but there should be no less than 10 days between next PF-06647020 and avelumab doses. For additional information about premedications see Section A7.2.2.1.
26. **Tumor Assessments***:* Tumor assessments will include all known or suspected disease sites. Tumor assessments must include chest, abdomen and pelvis CT or MRI scans and will be conducted every 8 weeks (window of 5 days prior to dosing is allowed) from the start of study treatment until disease progression by RECIST (v1.1) or death, or at the time of withdrawal from treatment (if not done in previous 8 weeks). If PR or CR is observed and the response duration exceeded 6 months, tumor assessment can be assessed at a 12-week interval. Brain scans will be performed at baseline only if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. A bone scan (bone scintigraphy) or $^{18}$FDG-PET/CT is required at baseline only if disease is suspected and then every 16 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of CR confirmation for patients who have bone metastases. MRI is acceptable for bone imaging if consistent with local practice. Responses of complete response (CR) or partial response (PR) must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met. All radiographic images will be collected for potential central review. Additional information on diagnostic imaging procedures and collection will be included in the Imaging Manual.
27. **Adverse Event (AE) Assessments:** AEs should be documented and recorded in the CRF. The NCI CTCAE version 4.03 will be used. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment. See Section 8.1.1.
28. **Concomitant Treatments:** All concomitant medications and Non-Drug Supportive Interventions should be recorded in the CRF.

CCI [redacted]

## Appendix 9. Immune-related Response Criteria Derived from RECIST 1.1 (irRECIST)

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

This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD1\anti PDL1 which exert the anti-tumor 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.[24,25] 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 World Health Organization (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.[26,27]

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.[26,27]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST 1.1 criteria (irRECIST).[28]

For irRECIST, only target and new measurable lesions are taken into account. In contrast to the RECIST 1.1, the irRECIST criteria.

- require 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 criteria 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 diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.

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

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

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

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

Overall responses derived from changes in index, non-index, and new lesions are outlines in Table 23.

**Table 23. Overall Response Derived from Changes in Index, Non-index and New Lesions**

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

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