A FIRST-IN-HUMAN PHASE 1, DOSE ESCALATION, SAFETY AND PHARMACOKINETIC STUDY OF PF-06647263 IN ADULT PATIENTS WITH ADVANCED SOLID TUMORS

Compound:	PF-06647263
Compound Name:	Not Applicable
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Phase:	1

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Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	01-November-2013	N/A
Amendment 1	13-December-2013	Background: Deleted incorrect name of study treatment. Rationale: Administrative Change.
Amendment 2	17-February-2014	Schedule of activities: Revision to the PK sample collection timepoints to the start of the infusion. Rationale: administrative reasons to remove the "0" hour sample nomenclature. Schedule of activities, Section 7.3: Require one 9 ml sample of whole blood per PK collection timepoint. Rationale: revision identified through assay development. Section 3.1.1.3 DLT Definitions: Revision to the definition of Dose Limiting Toxicity. Rationale: requested by the FDA. Section 4.1 Inclusion Criteria 2: Revision to the inclusion criteria for triple-negative breast cancer patients. Rationale: requested by the FDA. Section 5.2.2 Preparation and Dispensing: Inclusion of dosing details in the protocol. Rationale: requested by the FDA. Section 5.2.3 Administration: Inclusion of pretreatment medications in the case of infusion reactions and addition of: Appendix 5 Management of Infusion Related Reactions. Rationale: requested by the FDA.
Amendment 3	15 July 2015	Section: Background, Explanation/Rationale for Change Added new arm for investigation of NSCLC Section: Study Objectives and Endpoints, Explanation/Rationale for Change

		CCI [redacted] Section: Study Overview, Explanation/Rationale for Change Added additional arm (NSCLC) and clarified expansion futility and RP2D determination. Section: Schedule of Activities, Explanation/Rationale for Change Editorials changes to clarify operational logistics, Section: Pharmacokinetic, ADA and Pharmacodynamic sampling schedule (for q3w dosing regimen, Explanation/Rationale for Change Editorials changes to clarify operational logistics, Section: Pharmacokinetic, ADA, and Pharmacodynamic sampling schedule (for qw dosing regimen), Explanation/Rationale for Change Editorials changes to clarify operational logistics Section: 1.2. Background**,** Explanation/Rationale for Change Added NSCLC arm to trial Section: 1.2.1. EFNA4 expression in human cancers, Explanation/Rationale for Change Justification for adding NSCLC to trial Section: 1.3.1. Efficacy Explanation/Rationale for Change Editorial changes. CCI [redacted] Section: 1.6.2. TNBC OVCA and NSCLC in dose expansion,

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		Explanation/Rationale for Change Added additional NSCLC arm to trial CCI [redacted] CCI [redacted] Section: 2.1. Objectives, Explanation/Rationale for Change Exploratory endpoints have been further defined. Section: 2.2. Endpoints, Explanation/Rationale for Change Exploratory endpoints have been further defined. Section: 3.1. Study overview, Explanation/Rationale for Change Added additional arm (NSCLC) and clarified expansion futility and RP2D determination. Section: 3.1.1.2. Criteria for dose escalation/mtd determination, Explanation/Rationale for Change Editorial clarification for continued enrollment of patients deriving clinical benefit. Section: 3.1.1.3. DLT definitions, Explanation/Rationale for Change Clinical experience update to include hyperbilirubinemia in the DLT definition. Section: 3.1.1.5. Recommended phase 2 dose, Explanation/Rationale for Change Clarify investigator notification of dose determination for Part 2 Section: 3.1.2. Dose expansion phase

		part 2, Explanation/Rationale for Change Removal of the contingency if the ISH assay was not available at the start of part 2 of the study. Section: 4.1. Inclusion criteria, Explanation/Rationale for Change, Inclusion of the third arm for part 2 (NSCLC) and assay inclusion language. Section: 4.2. Exclusion criteria, Explanation/Rationale CCI [redacted] CCI [redacted] exclusion language added per the PF-06647263 clinical experience Section: 5.2.2. Preparation and Dispensing, Explanation/Rationale for Change Editorial change Section: 5.2.3. Administration, Explanation/Rationale for Change Editorial clarification for continued enrollment of patients deriving clinical benefit. Section: 5.2.5. Dose interruptions/delay, Explanation/Rationale for Change Editorial clarification for continued enrollment of patients deriving clinical benefit. Section: 5.2.6. Dose reductions, Explanation/Rationale for Change Dose reductions clarified for part 2 and specific dose reduction for hyperbilirubinemia added from current clinical experience Section: 7.1.3. Laboratory safety assessment, Explanation/Rationale for Change Editorial change to add Hyaluronic acid from current clinical experience Section: 7.1.4. Vital signs and physical examination, Explanation/Rationale for

[redacted]

		Change Editorial change Section: 7.1.5. (12-Lead) ECG, Explanation/Rationale for Change Editorial change Section: 7.3.1. Blood for PK analysis of pf-06647263, total antibody, and unconjugated payload cl-184538, Explanation/Rationale for Change Editorial change CCI [redacted] CCI [redacted] Section: 8.1. Adverse events, Explanation/Rationale for Change Editorial change Section: 8.2. Reporting Period, Explanation/Rationale for Change CCI [redacted] Section: 8.3. Definition of an adverse event, Explanation/Rationale for Change Editorial change Section: 8.4. Medication errors, Explanation/Rationale for Change Editorial change Section: 8.6. Serious adverse events, Explanation/Rationale for Change Editorial change. Section: 8.6.2. Potential cases of drug-induced liver injury, Explanation/Rationale for Change Editorial change Section: 8.7. Hospitalization, Explanation/Rationale for Change

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		Editorial change Section: 8.10. Exposure during pregnancy, Explanation/Rationale for Change Editorial change Section: 8.11. Occupational exposure, Explanation/Rationale for Change Editorial change Section: 8.12. Withdrawal due to adverse events (see also the section on patient withdrawal), Explanation/Rationale for Change Editorial change Section: 8.14.1. Serious adverse event reporting requirement, Explanation/Rationale for Change Editorial change Section: 8.14.3. Sponsors reporting requirements to regulatory authorities, Explanation/Rationale for Change Editorial change Section: 9.3.1. Part 1, Explanation/Rationale for Change Editorial Change Section: 9.3.2. Part 2: Explanation/Rationale for Change Clarification of Part 2 futility and sample size Section: 9.5.2. Pharmacokinetic/pharmacodynamic analysis, Explanation/Rationale for Change Editorial change Section: 15.1. Communication of results by Pfizer, Explanation/Rationale for Change Editorial change Section: Appendix 1 Abbreviations, Explanation/Rationale for Change Editorial change

Amendment 4	07 December 2015	Protocol summary: Removal of NSCLC from inclusion in Part 2 of this protocol and align objectives and endpoints accordingly. CCI [redacted] CCI [redacted] CCI [redacted] Section 1.2. Background Removal of NSCLC from inclusion in Part 2 of this protocol. Section 1.2.1. EFNA4 Expression in Human Cancers Removal of NSCLC from inclusion in Part 2 of this protocol. Section 1.6.2. TNBC and OVCA in dose expansion Removal of NSCLC from inclusion in Part 2 of this protocol. CCI [redacted]

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		CCI [redacted]
		Section 1.8. Clinical Experience Updated clinical experience reported.
		Section 2.1. Objectives- Removal of NSCLC from inclusion in Part 2 of this protocol and align objectives and endpoints accordingly.
		Section 2.2. Endpoints Removal of NSCLC from inclusion in Part 2 of this protocol and align objectives and endpoints accordingly.
		Section 3.1. Study overview Removal of NSCLC from inclusion in Part 2 of this protocol include unselected TNBC in Part 2 and align statistics accordingly.
		Section 3.1.1.2. Criteria for dose escalation/MTD determination Removal of NSCLC from inclusion in Part 2 of this protocol and align statistics accordingly with additional enrollment in Part 1
		Section 3.1.2. Dose expansion phase (part 2) Removal of NSCLC from inclusion in Part 2 of this protocol and to include unselected TNBC in Part 2 and align statistics accordingly.
		Section 4.1. Inclusion criteria Removal of NSCLC from inclusion in Part 2 of this protocol include unselected TNBC in Part 2 and align inclusion criteria accordingly.
		Section 4.2. Exclusion criteria To allow for additional prior therapies to be included aligning with the current standard of care for this patient population.
		Section 5.1. Allocation to treatment

		Clarification of dosing for Part 2.
		Section 5.2.6. Dose reduction To prevent sub therapeutic dose administration, as determined by pharmacokinetics of Part 1.
		Section 5.2.7. Compliance Operational clarification
		Section 7.1.3. Laboratory safety assessment CCI [redacted]
		Section 7.1.4. Vital signs and physical examination Clarification of dosing weight window.
		CCI [redacted]
		CCI [redacted]
		Section 9.2. Statistical methods and properties Further expansion of the mTPI table to accommodate additional enrollment in Part 1 for safety data collection.
		Section 9.3.2. PART 2 Removal of NSCLC from inclusion in Part 2 of this protocol include unselected TNBC in Part 2 and align statistics accordingly.
		CCI [redacted]
		Section 9.5. Analysis of other endpoints CCI [redacted]
		Appendix 1 Abbreviations *Updated table*

[redacted]

		to align with current protocol.
		Appendix 6 Detailed Dose Escalation/De Escalation Scheme for mTPI design Further expansion of the mTPI table to accommodate additional enrollment in Part 1 for safety data collection.
Amendment 5	17 August 2016	Protocol Summary: Removal of references to ovarian cancer and clarification of objective endpoint wording.
		CCI [redacted]
		Introduction: Removal of ovarian cancer to the overview; update to section 1.7- removal of ovarian cancer for EFNA4 expression; section 1.8 – update clinical experience to July 27th 2016.
		Section 2, 3, 4: Update objective and endpoints; removal of ovarian cancer throughout the document
		CCI [redacted]
		Section 9.3: update to sample size, accounting for removal of ovarian cancer from the study
		Editorial and administrative updates throughout the document

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

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PROTOCOL SUMMARY

Background

Antibody-drug conjugates (ADCs) are compounds comprised of a cytotoxic agent which is chemically linked to an antibody that selectively binds to an internalizing tumor-associated antigen.[1] By delivering the cytotoxic agent to the tumor while minimizing the exposure to normal tissues, ADCs have the potential for improving the therapeutic index of cytotoxic anti-cancer agents.

PF-06647263 is an anti-EFNA4 ADC for the treatment of patients with cancer. EFNA4 is a novel ADC target that was identified through analysis of the gene expression profiles of aggressive tumor cell populations called cancer stem cells (CSCs) or tumor-initiating cells. EFNA4 mRNA expression levels have been found to be enriched in some nonclinical models of colorectal cancer (CRC) and pancreatic cancer[1] Pfizer's in-house bioinformatics analysis suggests that EFNA4 mRNA expression is also elevated in patients with CRC, breast cancer, including triple negative breast cancer (TNBC), ovarian cancer (OVCA), non-small cell lung cancer (NSCLC), chronic lymphocytic leukemia (CLL) and hepatocellular carcinoma (HCC) relative to the corresponding normal tissues. In non-tumor tissues, EFNA4 is believed to be involved in axonal guidance, wound healing, epidermal differentiation, transendothelial migration of leukocytes, retinal neovascularization, and craniosynostosis.[2,3,4] CCI [redacted]

TNBC is a heterogeneous disease constituting approximately 15-20% of breast cancers and is characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PgR), and the absence of human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification. It occurs more frequently in women less than 50 years old and generally behaves more aggressively than other breast cancer subtypes.[6] Although TNBC patients experience higher rates of pathological complete responses (pCR), when treated with neoadjuvant chemotherapy, they experience shorter duration-free survival (DFS) and overall survival (OS) relative to patients with non-TNBC.[8] The majority of patients receive anthracyclines and taxanes in the neoadjuvant or adjuvant settings. A variety of single agent and combination regimens are active in metastatic TNBC, although rapid progression is observed in most patients.[9] Thus, novel therapeutic options are urgently needed.

Study Objectives and Endpoints

Part 1 (Dose escalation) Primary Objective

- To assess safety and tolerability at increasing dose levels of PF-06647263 administered as an intravenous (IV) infusion every 3 weeks (Q3W) and weekly (QW) in patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available, in order to estimate 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 pharmacokinetics (PK) of PF-06647263, total antibody, and unconjugated payload;
- To evaluate the immunogenicity of PF-06647263;
- To document preliminary evidence of anti-tumor activity based on response rate (RR) correlating ORR (overall response rate) to EFNA4 expression in archival tumor samples

Part 2 (Expansion) Primary Objective

- To confirm safety and tolerability and explore preliminary evidence of anti-tumor activity of PF-06647263 based on response rate (RR) at the RP2D in previously treated metastatic TNBC patients.

Secondary Objectives

- To evaluate the overall safety profile at the RP2D;
- To characterize the single and multiple dose PK of PF-06647263, total antibody, and unconjugated payload;
- To evaluate the immunogenicity of PF-06647263;
- To document preliminary evidence of anti-tumor activity based on progression free survival (PFS) and overall survival (OS).

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Endpoints

Primary Endpoint (Part 1)

- First cycle Dose Limiting Toxicities (DLTs) in order to determine the MTD and RP2D.

Primary Endpoint (Part 2)

- Response rate (RR) as determined by the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 criteria.

Secondary Endpoints (Parts 1 and 2)

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute (NCI) CTCAE v.4.03), timing, seriousness and relationship to study therapy;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;
- Vital Sign abnormalities;
- Systemic PK exposure of PF-06647263, total antibody, and unconjugated payload
- Immunogenicity of PF-06647263; incidence of anti-PF-06647263 antibodies (ADA);
- Objective tumor response, as assessed using RECIST version 1.1 by calculating the Overall Response Rate (ORR), Clinical Benefit Response Rate (CBRR), Progression Free Survival (PFS), and Overall Survival (OS)-stratifying for EFNA4 expression Part 2 only.

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Study Overview

This is a Phase 1, two part, open label, multi-center, single arm, non-randomized, multiple dose, safety, PK and PD study of single agent PF-06647263 in adult patients with advanced solid tumors for whom no standard therapy is available.

The clinical study will include 2 parts. Part 1 will estimate the MTD in dose escalation cohorts in patients with advanced solid tumors for whom no standard therapy is available in order to establish the RP2D. The initial dosing regimen tested in Part 1 will be PF-06647263 administered once every 3 weeks (Q3W). Evaluation of a weekly (QW) regimen will be initiated when the first patient treated with the Q3W regimen experiences a DLT or Grade 2 thrombocytopenia related to study treatment. The starting dose of the QW regimen will not exceed one-third of the highest Q3W dose evaluated. Once initiated, the 2 regimens will be evaluated independently based on the same dose-escalation criteria as described below. The collective safety and efficacy data will be used to identify the regimen or regimens to be used in Part 2 of the study. Part 2 will include patients with previously treated metastatic triple negative breast cancer (TNBC).

It is anticipated that the maximum sample size of approximately 70 patients are expected to be enrolled in Part 1 of the study at approximately 3 - 4 sites. The actual number of patients enrolled will depend upon tolerability of PF-06647263, and the number of dose levels required to identify the MTD in the Q3W and QW dosing regimens.

The TNBC expansion cohort (Part 2) will enroll approximately 24 response evaluable patients. (defined as having at least one on-study tumor assessment). Enrollment of TNBC patients may be discontinued if no or minimal antitumor activity is observed (eg, no response is observed in the first 8 evaluable patients). Conversely, if a high ORR is observed in TNBC patients (See Section 9.3.2), up to 10 additional patients may be enrolled following discussion between the Sponsor and Investigators. In the event DLTs occur in more than 33% of the patients enrolled in Part 2, enrollment will stop and the MTD dose will be reevaluated. Additional safety information gathered in Part 2 may be used to modify the dose recommended for future Phase 2 trials.

Patients will participate in the study for approximately 6 months in Part 1 and up to approximately 18 months in Part 2. This assumes up to 4 weeks of screening, approximately 4 months of treatment, and a follow-up visit within 4 weeks after the last dose for adverse event (AE) and serious adverse event (SAE) collection and, in Part 2 only, long-term follow-up for survival every two months for up to 12 months after the last dose. Treatment with study drug will continue until disease progression, patient refusal, unacceptable toxicity occurs, or the study is terminated. Note: Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and Sponsor.

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SCHEDULE OF ACTIVITIES

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

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

		Treatment Period								Post Treatment	
		Cycle 1 Only (Days 1-21)					Cycle 2 and Subsequent Cycles (Days 1 to 21)				
Protocol Activity	**Screen/ Baseline[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 4 (±1)**	**Day 8 (±1)**	**Day 15 (±2)**	**Day 1 (±2)**	**Day 8 (±2)**	**Day 15 (±2)**	**End of Treatment[25] (+7)**	**Follow Up[26] (+7)**
Informed Consent[2]	X										
Tumor History[3]	X										
Medical History[4]	X										
Complete Physical Examination including skin examination[5]	X	X								X	
Abbreviated Physical Examination including skin examination			X	X	X	X	X	X	X		
Baseline Signs and Symptoms[6]		X									
Height	X										
Weight[7]	X	X					X			X	
Vital signs (BP/PR/Temp)[8]	X	X			X	X	X	X	X	X	X
ECOG Performance Status[9]	X	X					X			X	X
(12 lead) ECG[10]	X	X			X		X	X		X	
Laboratory											
Hematology[11]	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[12]	X	X			X	X	X	X	X	X	
Coagulation Panel[13]	X						X			X	
Urinalysis[14]	X					X	X			X	
Pregnancy test[15]	X	X					X			X	
Registration and Treatment											
Registration[16]		X									
Study Treatment (Q3W)[17]		X					X				
Study Treatment (QW)[17]		X			X	X	X	X	X		

		Treatment Period								Post Treatment	
		Cycle 1 Only (Days 1-21)					Cycle 2 and Subsequent Cycles (Days 1 to 21)				
Protocol Activity	**Screen/ Baseline[1] (≤28 days)**	**Day 1**	**Day 2**	**Day 4 (±1)**	**Day 8 (±1)**	**Day 15 (±2)**	**Day 1 (±2)**	**Day 8 (±2)**	**Day 15 (±2)**	**End of Treatment[25] (+7)**	**Follow Up[26] (+7)**
Tumor assessments											
CT or MRI scan or equivalent[18]	X						X (every 6 weeks, ± 7 days)			X[25]	
Other samplings											
[redacted] CCI	[redacted]								[redacted]		
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Blood Samples for PK[20]		See Pharmacokinetic, ADA, and Pharmacodynamic Sampling Schedule Table below									
Blood Sample for Anti-PF-06647263 Antibody[21]		See Pharmacokinetic, ADA, and Pharmacodynamic Sampling Schedule Table below									
[redacted] CCI	[redacted]	[redacted]									
Other clinical assessments											
Adverse Events[23]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication and non drug supportive interventions[24]	X	X	X	X	X	X	X	X	X	X	X

Unless otherwise specified, laboratory values and assessments should be obtained prior to the PF-06647263 infusion. If the infusion is held, assessments should still be performed. For subsequent infusions, 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-06647263 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. **Physical Exam**: Complete physical exam may be performed within 72 hours (ideally within 24 hours) prior to the first dose of PF-06647263.

6. **Baseline Signs & Symptoms:** On Day 1 prior to the start of study treatment, patients will be asked about any signs and symptoms experienced within the past 14 days. Baseline signs and symptoms will be recorded on the Medical History CRF page.
7. **Weight:** Weight may be collected within 7 days prior to the PF-06647263 infusion for dose preparation on Day 1 of each cycle. The weight measurement taken for Day 1 of each cycle should be used to calculate the patient's dose of study treatment for all doses in that cycle.
8. **Vital signs:** Includes blood pressure (BP), and pulse rate (PR) to be recorded in the sitting position after 5 minutes of rest. On Day 1 of each cycle, vital signs should be measured prior to infusion start (- 120 mins pre-dose) and 1 hour (+/- 15 minutes) after the start of the infusion.
9. **Performance status:** per ECOG scale **(**see Appendix 4).
10. **12 lead ECG:** ECGs will be collected during Screening (singlet) and at the End of Treatment visit (triplicate). Additional ECGs (triplicate) will be collected on Day 1 and Day 8 of each cycle both prior to the start of the study treatment infusion, and at 1 hour (within 15 minutes) before the end of the infusion . If the mean QTc is prolonged (value of ≥501 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs should be performed as clinically indicated. See Section 7 for additional considerations regarding ECG.
11. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils. No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date.
12. **Blood Chemistry:** Should include sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, AST/SGOT, ALT/SGPT, alkaline phosphatase, total bilirubin, and lactate dehydrogenase (LDH) No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date.
13. **Coagulation:** Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT).
14. **Urinalysis:** Dipstick 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).
15. **Pregnancy Test (serum or urine):** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, (within 72 hours of the first investigational product administration). Pregnancy tests will also be routinely repeated at every 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 IRB/IECs or if required by local regulations.
16. **Registration:** Patient randomization number and dose level allocation will be provided by Pfizer Inc.
17. **Study Treatment:** For patients enrolled in the Q3W regimen, PF-06647263 will be administered once every 21 days as an IV infusion over approximately 60 minutes. For patients enrolled in the QW regimen, PF-06647263 will be administered once a week as an IV infusion over approximately 60 minutes.
18. **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 (±7 days) from the start of study treatment until disease progression by RECIST (v1.1) or death, or until permanent discontinuation of study treatment. Note: Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade

0-1 or baseline, only after discussion between the investigator and Sponsor. 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. Given the exploratory nature of the study confirmation of response (CR/PR) is not required. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.

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20. **PK Sampling:** Specific timing for collection of pharmacokinetic samples can be found in the Pharmacokinetic, ADA and Pharmacodynamic Sampling schedule table below.
21. **Anti PF-06647263 Antibodies:** Specific timing for collection of anti-PF-06647263 antibody samples can be found in the Pharmacokinetic, ADA, and Pharmacodynamic Sampling schedule table below.

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23. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using NCI CTC AE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. Serious Adverse Events must be reported from the date the informed consent document is signed until 28 days after the last study drug administration or whenever (independently of the elapsed time) there is the suspicion of a causal relationship to the study drug.
24. **Concomitant Medications 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).
25. **End of treatment visit:** Conducted at the visit that the patient is discontinued from the trial and no longer than 1 week after the patient has been discontinued. Complete tumor assessments if not completed in the last 6 weeks.
26. **Follow up:** At least 28 days and no more than 35 days after the discontinuation of treatment visit (end of treatment), patients will return to undergo review of concomitant medications, vital signs, ECOG performance status, 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. Patients in Part 2 will be followed for survival by phone call/email/visit every 2 months until death or until 12 months from the End of Treatment visit, whichever is earlier. If a patient is classified as having PD at a post-baseline tumor assessment, then confirmation of PD by a second scan in the absence of rapid clinical deterioration is required. Additionally prior to having PD tumor assessments should continue until subsequent therapy or death.

Pharmacokinetic, ADA, and Pharmacodynamic Sampling Schedule (for Q3W dosing regimen)

		Treatment Period																	
		Cycle 1 Only (Days 1 to 21)							Cycles 2 and 3		Cycle 4						Every Cycle Thereafter		EOT (+7)
Protocol Activity	**Screen (≤28 days)**	**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 PK[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Anti-PF-06647263 Antibodies [2]		X						X	X		X							X		X
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***Sampling times are related to the start of infusion; 1 hr samples should be collected within the 15 minutes before the infusion ends. All sample time windows, except the pre-dose and 1 hr samples, will be ±10% of nominal time. Therefore, a 4 hr sample will have a ± 24 minutes collection window. Samples collected on Day 4, 8 and 15 will have a ±1 or ±2 day window as indicated in the table.**

Footnotes

1. **Blood sample for PK:** A 9 ml sample of whole blood will be collected at each timepoint for PK analysis of PF-06647263, total antibody, and unconjugated payload CL-184538.
2. **Anti PF-06647263 Antibodies (ADA):** Collection of serum to detect the presence of antibodies to PF-06647263 is to be obtained prior to the start of treatment. Patients having an unresolved adverse event that is possibly related to anti-PF-06647263 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.

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Pharmacokinetic, ADA, and Pharmacodynamic Sampling Schedule (for QW dosing regimen)

		Treatment Period																
		Cycle 1 Only (Days 1 to 21)											Every Cycle Thereafter					EOT (+7)
Protocol Activity	**Screen (≤28 days)**	**Day 1**			**Day 2**	**Day 4**	**Day 8**		**Day 11**	**Day 15**		**Day 18**	**Day 1**		**Day 8**		**Day 15**	
		Pre-dose	1 hr*	4 hr*	24 hr*	72 hr*	Pre-dose	1 hr*	72 hr*	Pre-dose	1 hr*	72 hr*	Pre-dose	1 hr*	Pre-dose	1 hr*	Pre-dose	1 hr*	
Blood Samples for PK[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Anti-PF-06647263 Antibodies [2]		X								X			X						X
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*** Sampling times are related to the start of infusion; 1 hr samples should be collected within the 15 minutes before the infusion ends. All sample time windows, except the pre-dose and 1 hr samples, will be ±10% of nominal time. Therefore, a 4 hr sample will have a ± 24 minutes collection window..**

Footnotes

1. **Blood sample for PK**: A 9 ml sample of whole blood will be collected at each timepoint for PK analysis of PF-06647263, total antibody, and unconjugated payload CL-184538.
2. **Anti PF-06647263 Antibodies**: Collection of serum to detect the presence of antibodies to PF-06647263 is to be obtained prior to the start of treatment. Patients having an unresolved adverse event that is possibly related to anti-PF-06647263 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.

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1. INTRODUCTION

1.1. Indication

PF-06647263 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

Antibody-drug conjugates (ADCs) are compounds comprised of a cytotoxic agent which is chemically linked to an antibody that selectively binds to an internalizing tumor-associated antigen.[1] By delivering the cytotoxic agent to the tumor while minimizing the exposure to normal tissues, ADCs have the potential for improving the therapeutic index of cytotoxic anti-cancer agents.

PF-06647263 is an anti-EFNA4 ADC for the treatment of patients with cancer. EFNA4 is a novel ADC target that was identified through analysis of the gene expression profiles of aggressive tumor cell populations called cancer stem cells (CSCs) or tumor-initiating cells. EFNA4 mRNA expression levels have been found to be enriched in some nonclinical models of colorectal cancer (CRC) and pancreatic cancer (Clinical Cancer Res. 2015 May 26). Pfizer's in-house bioinformatics analysis suggests that EFNA4 mRNA expression is also elevated in patients with CRC, breast cancer, including triple negative breast cancer (TNBC), ovarian cancer (OVCA), non-small cell lung cancer (NSCLC), chronic lymphocytic leukemia (CLL) and hepatocellular carcinoma (HCC) relative to the corresponding normal tissues. In non-tumor tissues, EFNA4 is believed to be involved in axonal guidance, wound healing, epidermal differentiation, transendothelial migration of leukocytes, retinal neovascularization, and craniosynostosis.[2,3,4] CCI [redacted]

TNBC is a heterogeneous disease constituting approximately 15-20% of breast cancers and is characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PgR), and the absence of human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification. It occurs more frequently in women less than 50 years old and generally behaves more aggressively than other breast cancer subtypes.[6] Although TNBC patients experience higher rates of pathological complete responses (pCR), when treated with neoadjuvant chemotherapy, they experience shorter duration-free survival (DFS) and overall survival (OS) relative to patients with non-TNBC.[8] The majority of patients receive anthracyclines and taxanes in the neoadjuvant or adjuvant settings. A variety of single agent and combination regimens are active in metastatic TNBC, although rapid progression is observed in most patients.[9] Thus, novel therapeutic options are urgently needed.

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1.3. PF-06647263

PF-06647263 comprises the huE22 humanized IgG1 antibody and the [redacted] linker-payload. Calicheamicin generates double-strand deoxyribonucleic acid (DNA) breaks and therefore impacts both rapidly proliferating and quiescent or slowly proliferating cells.[7,10]

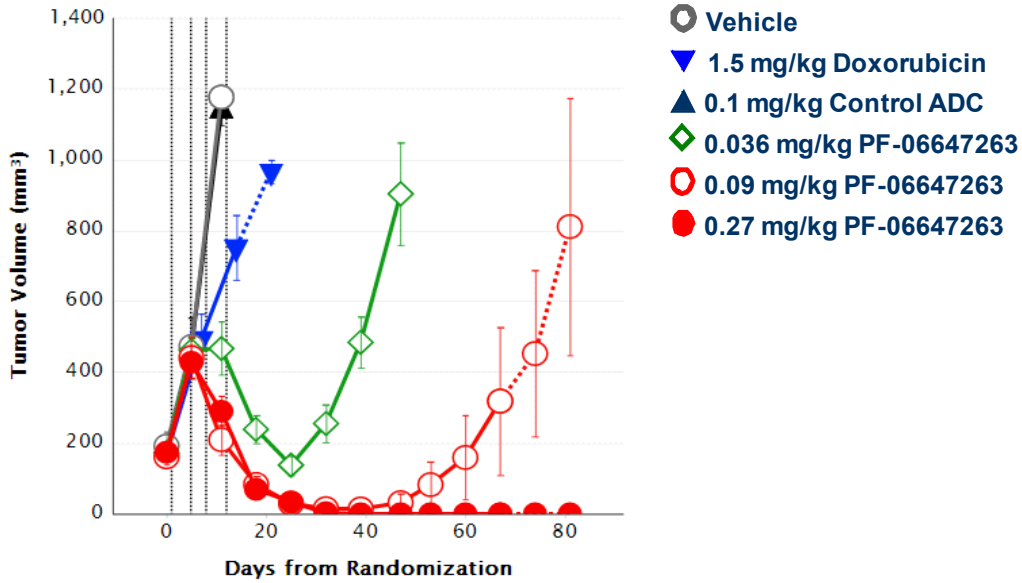
1.3.1. Efficacy

Efficacy studies were carried out in immune-compromised mice harboring subcutaneous human tumor xenografts. The panel of tumor models represented a broad range of tumor types and included both PDX and cell line xenografts (CLX). Target expression was retrospectively assessed in tumor extracts by qPCR, immunoblot and/or MesoScale Discovery (MSD) immunoassay or in formalin-fixed tumors by mRNA ISH.

PF-06647263 treatment resulted in sustained tumor regressions in tumor models where the standard-of-care (SOC) agents dosed at their maximum tolerated dose, were shown to have little impact on tumor growth.

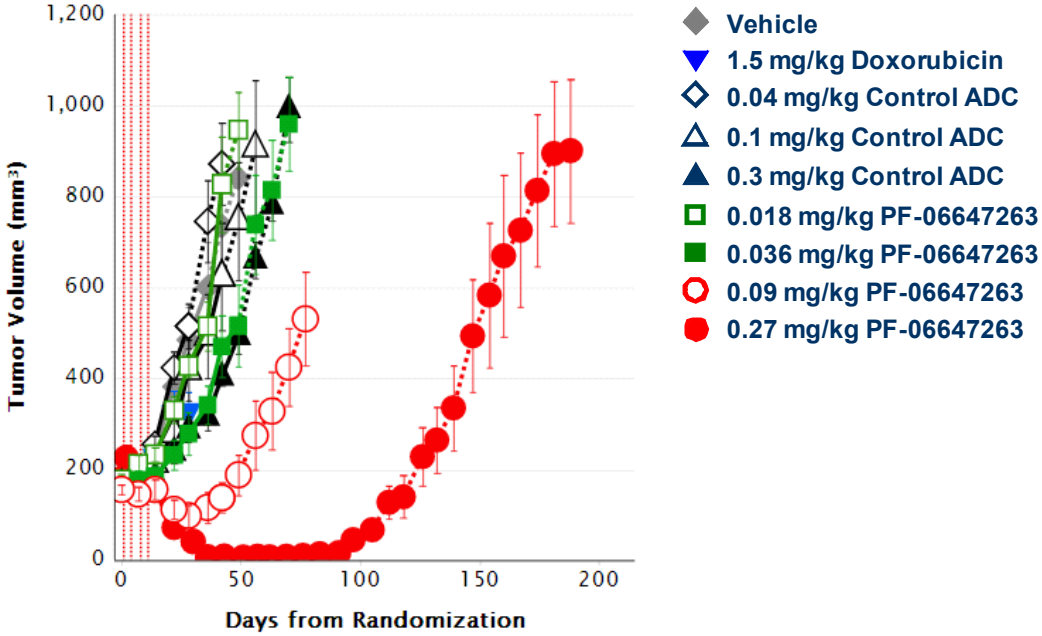
BR5 is a PDX of human TNBC. In this model, PF-06647263 treatment resulted in sustained regressions for more than 80 days in contrast, to doxorubicin or control ADC which had little impact on tumor growth (Figure 1).

Figure 1. Tumor Growth Curves in BR5 TNBC PDX.



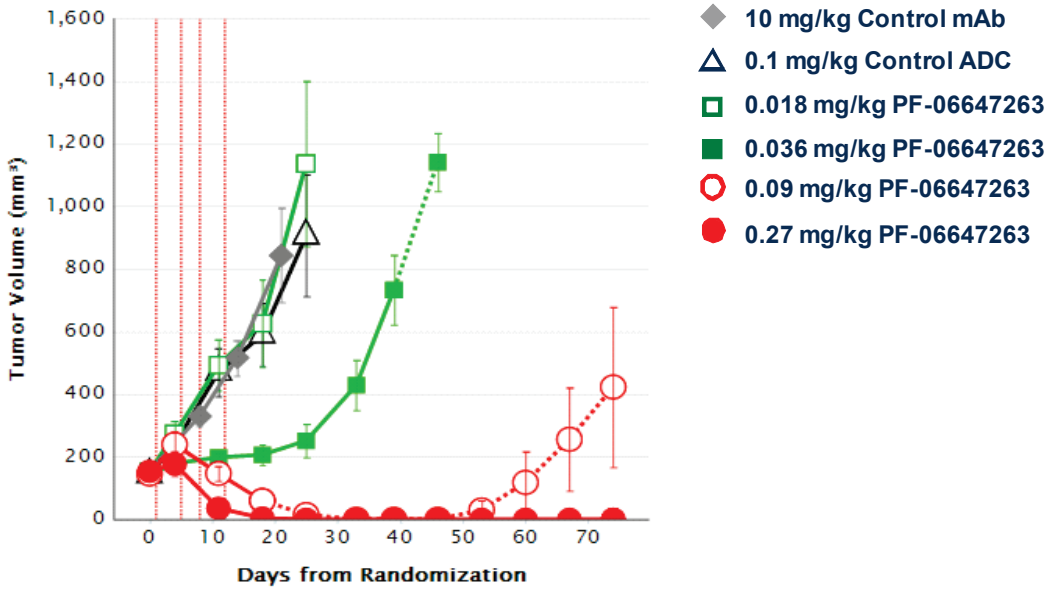
The BR22 PDX represented a less sensitive tumor model of TNBC. In this model PF-0667263 delayed tumor growth for ~40 days but did not produce any complete regressions. Dose levels below 0.27 mg/kg had minimal effect. There was no impact of doxorubicin treatment on tumor growth (Figure 2).

Figure 2. Tumor Growth Curves in BR22 TNBC PDX.



Similar to the observations in TNBC models, PF-06647263 was also active in OVCA PDX models. In the OV45 ovarian cancer PDX, PF-06647263 resulted in sustained regressions for more than 75 days in contrast to the control ADC which did not impact tumor growth (Figure 3).

Figure 3. Tumor Growth Curves in OV45 Ovarian Cancer PDX.



Several additional efficacy studies were performed in a variety of human tumor models CRC, small cell lung cancer (SCLC), NSCLC, mantle cell lymphoma (MCL), and CLL. In general, PF-06647263 strongly inhibited tumor growth in models of TNBC (non-Claudin low), OVCA, and SCLC and outperformed standard-of-care chemotherapy in all cases tested (TNBC and SCLC). In contrast PF-06647263 did not show activity in Claudin low TNBC, Her2+ breast cancer, CLL or MCL in the limited number of models tested. The Claudin low subtype of TNBC comprises ~30% of TNBC patients and is understood to be a generally refractory tumor type.

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1.6. Rationale

1.6.1. Justification for Phase 1 Clinical Starting Dose

The selection of the starting dose for the human Phase 1 trial was based on the preclinical safety study results following International Conference on Harmonisation (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. CCI [redacted] The proposed starting dose of 0.015 mg/kg given as an intravenous infusion Q3W represents approximately 1/6 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 average concentration (Cavg) for PF-06647263 at the proposed starting dose of 0.015 mg/kg is expected to be approximately 1/20th of the observed monkey Cavg at HNSTD.

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Body weight-based dosing approach (mg/kg) will be applied for the first-in-patient study of PF-06647263 with the goal to reduce interindividual variations in PK exposure. ADCs in the clinic have been administered using body-size based approaches (body weight-based, ie, mg/kg or BSA-based, ie, mg/m^2), and these approaches were consistent with the population PK of Adcetris, Kadcyla and Inotuzumab Ozogamicin, in which body weight or BSA was identified as significant covariates impacting PK exposure. CCI [redacted]

1.6.2. TNBC in Dose Expansion

The selection of the indication in dose expansion was based on the expression of EFNA4 in human TNBC samples. Furthermore, in human tumor xenograft models, PF-06647263 treatment resulted in sustained regressions and was significantly better than the standard-of-care tested in these indications. Collectively, these findings suggest that PF-06647263 should be evaluated in patients with these tumors who have few therapeutic options and constitute an urgent unmet medical need.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Part 1 (Dose escalation)

Primary Objective

- To assess safety and tolerability at increasing dose levels of PF-06647263 administered as an intravenous (IV) infusion every 3 weeks (Q3W) and weekly (QW) in patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available, in order to estimate 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 pharmacokinetics (PK) of PF-06647263, total antibody, and unconjugated payload;
- To evaluate the immunogenicity of PF-06647263;
- To document preliminary evidence of anti-tumor activity based on the response rate (RR) correlating ORR to EFNA4 expression in archival tumor samples.

Part 2 (Expansion)

Primary Objective

- To confirm safety and tolerability and explore preliminary evidence of anti-tumor activity of PF-06647263 based on response rate (RR) at the RP2D in previously treated metastatic TNBC patients.

Secondary Objectives

- To evaluate the overall safety profile at the RP2D;
- To characterize the single and multiple dose PK of PF-06647263, total antibody, and unconjugated payload;
- To evaluate the immunogenicity of PF-06647263;
- To document preliminary evidence of anti-tumor activity based on progression free survival (PFS) and overall survival (OS).

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2.2. Endpoints

Primary Endpoint (Part 1)

- First cycle Dose Limiting Toxicities (DLTs) in order to determine the MTD and RP2D.

Primary Endpoint (Part 2)

- Response rate (RR) as determined by the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 criteria.

Secondary Endpoints (Parts 1 and 2)

- Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;
- Vital Sign abnormalities;
- Systemic PK exposure of PF-06647263, total antibody, and unconjugated payload;
- Immunogenicity of PF-06647263; incidence of anti-PF-06647263 antibodies (ADA);
- Objective tumor response, as assessed using RECIST version 1.1 by calculating the Overall Response Rate (ORR), Clinical Benefit Response Rate (CBRR), Progression Free Survival (PFS), and Overall Survival (OS)-stratifying for EFNA4 expression Part 2 only.

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3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, two part, open label, multi-center, single arm, non-randomized, multiple dose, safety, PK and PD study of single agent PF-06647263 in adult patients with advanced solid tumors for whom no standard therapy is available.

The clinical study will include 2 parts. Part 1 will estimate the MTD in dose escalation cohorts in patients with advanced solid tumors for whom no standard therapy is available in order to establish the RP2D. The initial dosing regimen tested in Part 1 will be PF-06647263 administered once every 3 weeks (Q3W) consistent with the pre-clinical toxicity study. Evaluation of a weekly (QW) regimen will be initiated when the first patient treated with the Q3W regimen experiences a DLT or Grade 2 thrombocytopenia related to study treatment. The starting dose of the QW regimen will not exceed one-third of the highest Q3W dose evaluated. Once initiated, the 2 regimens will be evaluated in parallel and independently based on the same dose-escalation criteria as described below. The collective safety and efficacy data will be used to identify the regimen or regimens to be used in Part 2 of the study. Part 2 will include patients with previously treated metastatic triple negative breast cancer (TNBC).

It is anticipated that the maximum sample size of approximately 70 patients are expected to be enrolled in Part 1 of the study at approximately 3 - 4 sites. The actual number of patients enrolled will depend upon tolerability of PF-06647263, and the number of dose levels required to identify the MTD in the Q3W and QW dosing regimens. The expansion cohort in Part 2 will enroll approximately 24 TNBC patients. These patients will be response evaluable (defined as having at least one on-study tumor assessment). Enrollment of patients within this specific expansion cohort may be reassessed in conjunction with the totality of clinical information including exposure, expression and others, if no or minimal antitumor activity is observed in that indication (eg, no response is observed in the first 8 evaluable patients). One option for the unselected TNBC cohort would be to pause unselected enrollment and enroll patients with moderate to high EFNA4 expressing TNBC and reassess the activity after the next 8 evaluable patients. Conversely, if a high ORR is observed in TNBC (See Section 9.3.2) the available clinical data would be used to assess the risk/benefit of the treatment and up to 10 additional patients may be enrolled following discussion between the Sponsor and Investigators.

In the event DLTs occur in more than 33% of the patients enrolled in Part 2, enrollment will stop and the MTD dose will be reevaluated. Additional safety information gathered in Part 2 may be used to modify the dose recommended for future Phase 2 trials.

Patients will participate in the study for approximately 6 months in Part 1 and up to approximately 18 months in Part 2. This assumes up to 4 weeks of screening, approximately 4 months of treatment, and a follow-up visit within 4 weeks after the last dose for adverse event (AE) and serious adverse event (SAE) collection, and in Part 2 only, long term follow-up for survival every two months for up to 12 months after the EOT visit. Treatment with study drug will continue until disease progression, patient refusal, unacceptable toxicity occurs, or the study is terminated. Note: Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and Sponsor.

The proposed doses, schedule(s) and PK timepoints may be reconsidered and amended during the study based on emerging safety and pharmacokinetic data.

3.1.1. Part 1

3.1.1.1. Starting Dose

Successive cohorts of patients will receive doses of PF-06647263 intravenously (IV) on an outpatient basis every 21 days starting at a dose level of 0.015 mg/kg.

3.1.1.2. Criteria for Dose Escalation/MTD Determination

A modified toxicity probability interval method (mTPI) targeting a DLT rate of 25% with an equivalence interval (20%-30%) will be utilized in order to estimate MTD. Patients will be enrolled in cohorts of 2 to 4, starting with 0.015 mg/kg for the first cohort. Subsequent dose levels may include a maximum 100% escalation until either the dose is ≥0.060 mg/kg, a patient experiences a DLT or Grade 2 thrombocytopenia considered related to PF-06647263 after which, dose escalation in subsequent cohorts will follow a modified Fibonacci scheme with maximum dose increases of 67%, 50%, 33%, 33%. Table 4 illustrates the possible dose levels when the Modified Fibonacci scheme is initiated at the 3rd dose level. Intermediate dose levels to further evaluate the safety and/or PK may be evaluated following discussion between Sponsor and Investigator.

Table 4. Possible Dose Levels for the Q3W Regimen Based on when Modified Fibonacci Scheme is Initiated at 0.06 mg/kg

	Modified Fibonacci^ scheme starts from dose level 3
Dose Level	**Dose (mg/kg Q3W)**
-1	0.01
1 (Starting dose)	0.015
2	0.030
3	0.060
4	0.100
5	0.150
6	0.200
7	0.267

^ dose increase: 67%, 50%, 33%, 33%, 33%, 33%

The evaluation of a QW regimen will be initiated when the first patient experiences a DLT or Grade 2 thrombocytopenia considered related to PF-06647263 is observed in the Q3W regimen. The starting weekly dose will be ≤33% of the highest cumulative dose that has been evaluated. The same criteria for dose escalation will be applied to the QW dose escalation scheme.

The modified toxicity probability interval (mTPI) design uses a Bayesian statistics framework and a beta/binomial hierarchical model to tailor dose-escalation and de-escalation decisions. These rules are conceptually similar to those used by the 3+3 design and all the dose-escalation decisions for a given trial and can be pre-calculated under the mTPI design and presented in a two-way table (Table 5).

The decision rules to "dose escalate" (E), "no change in dose" (S), "dose de-escalate" (D) or "dose de-escalate, unacceptable toxicity" (U) are described below:

Table 5. Dose Escalation Scheme

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

In this table, 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 0.95. Doses with an incidence of DLT >33% (eg, 4 out of 10) will not be declared the MTD but will be allowed by the mTPI method. (Appendix 6)

Cohorts of patients could receive doses already tested but a dose that is associated with the decision "dose de-escalate, unacceptable toxicity (U)" cannot be revisited and no more patients should be treated at this dose or higher doses for the remainder of the trial.

A minimum of 9 patients treated at the MTD is required to establish such dose as the RP2D. The maximum sample size is anticipated to be approximately 70 patients but the actual sample size will depend on the underlying dose toxicity profile (the variability in actual data realization).

Dose escalation will stop under any of the following conditions:

1. The maximum sample size has been achieved.

2. At least 9 patients have been accumulated at a dose that is predicted to be the MTD.

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

Dose escalation for other regimens (eg, doses administered weekly) would follow the same escalation scheme described above and in Table 5. All significant AEs and SAEs will be reviewed by the sponsor and investigators to determine if the dose allocation schedule requires modification. The cohort steering committee comprised of the Pfizer clinical team and the investigators can override the dose escalation increment specified in this protocol if a more conservative approach is mandated.

Patients will continue with study treatment until disease progression, patient refusal, or unacceptable toxicity occurs. Note: Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and Sponsor. Patients experiencing a DLT may be managed with dose modification or discontinuation. During dose escalation, patients treated in the Q3W regimen who do not complete the DLT evaluation period (21 days following the first study treatment administration) for non safety reasons will be replaced. Patients treated in the QW regimen who do not receive all 3 of the scheduled doses during the first cycle of treatment due to non safety reasons will be replaced.

Intra-patient dose escalation will not be permitted in this study.

In general, 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. However, in certain situations, such as when sufficient numbers of patients have been evaluated for 1 cycle and the outcome in the remaining patients will not change the decision criteria, subsequent dose levels may be opened following discussion with the Sponsor.

3.1.1.3. DLT Definitions

Severity of adverse events will be graded according to NCI CTCAE version 4.03. For the purpose of dose escalation, any of the following adverse events which are not considered related to disease progression occurring in the first cycle of treatment (Q3W regimen: 21 days or until the patient receives the 2nd infusion if there are treatment delays, QW regimen: 21 days or until the patient receives the 4th infusion if there are treatment delays) will be classified as DLTs:

- 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 neutropenia with infection.

- Any grade thrombocytopenia associated with clinically significant or life-threatening bleeding.
- Grade 4 thrombocytopenia ≥72 hours or platelets ≤10,000/mm^3 regardless of duration.

- Non-hematologic:
  - Bilirubin increase ≥2x upper limit of normal (ULN) and not related to disease progression or other known cause.
  - All other Grade ≥3 toxicities, except those that have not been maximally treated (eg, nausea, vomiting, diarrhea).
  - Delay by more than 2 weeks in receiving the next scheduled cycle due to persisting toxicities not attributable to disease progression. Note: Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and Sponsor.

Grade ≥3 cytokine release syndrome, infusion related reaction, allergic reaction, or anaphylaxis will not be considered as DLTs but may be a reason for study discontinuation and should be reviewed with Pfizer.

[redacted]

3.1.1.4. 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%].

In practice, the MTD will be the highest dose associated with the occurrence of DLTs ≤33% (eg, 3/9 evaluable patients experience a DLT during the first treatment cycle).

3.1.1.5. Recommended Phase 2 Dose (RP2D) Definition

The Recommended Phase 2 Dose (RP2D) is the dose chosen for further study based on Part 1 results and will be communicated to the investigators. 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.

3.1.2. Dose Expansion Phase (Part 2)

Once the MTD or RP2D has been determined, patients with TNBC regardless of EFNA4 expression (n=24 response evaluable) will be enrolled in Part 2 of the study. CCI [redacted]

If the DLT rate exceeds 33% in the patients treated at the MTD/RP2D (in Part 1 and Part 2), enrollment will be interrupted in order to determine whether the MTD/RP2D needs to be re-assessed.

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.

4.1. 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. (Part 1 only): 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. (Part 2 only): Histological or cytological diagnosis of the following:

   a. Previously treated metastatic TNBC (n=24 response evaluable). TNBC as characterized by:

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

   And

   - **HER2 test result as negative per American Society of Clinical Oncology/Clinical Association pathologists reccomendations** if a single test (or both tests) performed show:

     - IHC (Immunohistochemistry) 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells, or:

     - IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells, or:

     - ISH negative based on: Single-probe average *HER2* copy number < 4.0 signals/cell Dual-probe *HER2*/CEP17 ratio < 2.0 with an average *HER2* copy number < 4.0 signals/cell

   http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.50.9984 accessed 3 December 2015

   Note: Moderate to high EFNA4 expression* may be required after the ongoing activity assessment in the expansion cohort.

*EFNA4 expression analyzed by NanoString ® in **Clinical Laboratory Improvement Amendments** (CLIA) validated laboratory based on the archival sample or fresh biopsy sample. (if the archival sample is unavailable)

3. (Part 1 only): Patients may have measurable or non-measurable disease.
4. (Part 2 only): Patients must have at least one measurable lesion as defined by RECIST version 1.1.
5. Patients must give consent to the collection of archival formalin-fixed paraffin-embedded (FFPE) tumor tissue block, if available, for exploratory biomarker and EFNA4 expression analysis.
6. (Part 2 only): Patients must consent to a pre-treatment biopsy if a recent biopsy is not available within 6 months prior to consent and no intervening therapy was administered.
7. Adults age ≥18 years.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.
9. 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.
10. 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;
    b. Urinary dipstick <2+ protein. If ≥2+ protein on urine dipstick, then urine protein to creatinine ratio (UPCR) ratio ≤0.5 as characterized by spot urine sample.
11. Adequate liver function, including all of the following:
    a. Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome. Note: If organ function abnormalities are considered due to tumor, total serum bilirubin must be ≤2 x ULN.;
    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).
12. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment.

[redacted]

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

14. Male and female patients of childbearing potential must agree to use two (2) highly effective methods of contraception throughout the study and for at least 28 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.

Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

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

b. Have medically confirmed ovarian failure or;

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

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

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

4.2. Exclusion Criteria

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

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 4 weeks (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) 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 or bone marrow transplant.

4. Prior irradiation to >25% of the bone marrow.

5. (Part 2 only): >4 prior systemic chemotherapy-containing regimens.

6. Significant prior allergic reaction to recombinant human or murine proteins.

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

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9. History of chronic liver disease (eg, cirrhosis) or suspected alcohol abuse.

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. Current active treatment in another interventional therapeutic clinical study.

12. 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.

13. 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.

14. Pregnant females; breastfeeding females; males and females 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 28 days after last dose of investigational product Life Style Guidelines.

In this study, patients of childbearing potential will receive PF-06647263, a compound for which the teratogenic risk is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 28 days after the last dose. The investigator, in consultation with the patient, will select two appropriate methods of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in their consistent and correct use. The investigator, at each study visit, will discuss with the patient the need to use highly effective contraception consistently and correctly and document such conversation in the patient chart. In addition, the investigator will instruct the patient to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected.

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

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the patient remains 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, suppository).
4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy.

4.3. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial 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 number, 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 patients 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 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 they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Eligible patients will be enrolled to receive PF-06647263 in an open-labeled, unblinded manner. In Part 1 patients will be successively assigned to the next available treatment slot at a dose level and treatment regimen decided on after the previous cohort's safety evaluation and ongoing observations of earlier enrolled patients. In Part 2 patients will be dosed at the RP2D.

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 Investigator or site staff will complete a Patient Registration Form and send it to the designated Sponsor study team member. The Sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that patient. The procedures for enrolling a patient will be described in the Study Manual.

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. The investigator's knowledge of the treatment should not influence the decision to enroll a particular patient or affect the order in which patients are enrolled.

5.2. Drug Supplies

PF-06647263 will be supplied for the study by Pfizer.

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

5.2.1. Formulation and Packaging

PF-06647263 for injection, 10 mg extractable per vial, is presented as a sterile lyophilized product, white to off white cake, packaged in a 10 mL amber glass tubing vial with a 20 mm rubber stopper and a 20 mm aluminum overseal. CCI [redacted] The volume of the solution in the vial after reconstitution is 2.34 mL to ensure the extractable volume (2 mL) can be withdrawn by syringe. The vial is designed for single use.

The packages will be properly labeled according to local regulatory requirements.

5.2.2. Preparation and Dispensing

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. All preparations should take place under aseptic conditions.

The starting dose level will be 0.015 mg/kg. The patient's actual body weight will be used to calculate the mg/kg dose and the calculated dose will be rounded off to the first decimal point. Specific preparation and dispensing instructions are provided in the Investigational Product (IP) Manual. Anticipated variance to the instructions in the IP Manual should be discussed with the sponsor or designee.

5.2.3. Administration

PF-06647263 will be administered per the IP Manual as an IV infusion over approximately 60 minutes (± 5 minutes) on an outpatient basis. Each patient may receive PF-06647263 until disease progression, unacceptable toxicity, withdrawal of consent, or study termination. Note: Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and Sponsor.

In the case of infusion related reactions, characterized by fever and chills, and less commonly hypotension, the Sponsor should be notified and pretreatment 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 Investigators. Premedication should include acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each PF-06647263 administration. The pretreatment medications will not be supplied by Pfizer.

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

The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the investigational product, but gravity drips are allowed. Please refer to the IP Manual for infusion rate and duration.

5.2.4. 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.

5.2.5. Dose Interruptions/Delay

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.

For patients treated in the Q3W regimen, 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. For patients treated in the QW regimen, the day when the patient receives the 4th dose will be counted as Day 1 of Cycle 2. Subsequent cycles will be 21 days in length regardless of treatment delays. A treatment delay or interruption of more than 14 days due to lack of recovery will result in discontinuation of the patient from treatment unless there is clinical benefit and discussed with the Sponsor. A dose of study treatment may be given only if:

- ANC $\geq$1,000/mm^3.
- Platelet 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-06647263 can be resumed. If the patient has not recovered after 1 week of delay, treatment may be delayed by 1 more week. However, initiation of the next cycle can only be delayed by a maximum of 2 weeks. Therefore, if persisting toxicity does not allow PF-06647263 treatment resumption within 35 days of Day 1 of the previous cycle (for the Q3W dosing regimen), treatment with PF-06647263 will be permanently discontinued. A patient may continue on study after discussion with the Sponsor if there is documentation of clinical benefit following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and Sponsor.

5.2.6. Dose Reductions

Following dose interruption or cycle delay due to toxicity, the PF-06647263 dose may need to be reduced when treatment is resumed.

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

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

Dose reduction of PF-06647263 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.

In part 2 of the study a similar dose reduction of PF-06647263 by 1 dose level can be made, if deemed necessary depending on the type and severity of toxicity observed (see action table below). As 0.015 mg/kg QW is selected as RP2D for dose expansion, 1 level dose reduction to 0.01 mg/kg QW will be recommended. Additional dose reduction or decrease in frequency will require discussion and agreement with the sponsor.

For patients experiencing an adverse event related to PF-06647263 that fails to recover to NCI CTCAE Grade 1 (or within 1 grade of starting values for pre-existing laboratory abnormalities) leading to a treatment delay of >2 weeks should be discontinued unless discussed with Pfizer. Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and Sponsor.

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.

The following table summarizes the actions following the toxicities observed during the study period.

Event	Action
Serum bilirubin ≥2 x ULN or other Grade 3 or 4 nonhematologic toxicity considered at least possibly related to PF-06647263 per investigator judgment (including persistent nausea, vomiting, diarrhea despite optimal medical therapy)	• Hold PF-06647263 infusion until recovery to Grade 0-1, serum bilirubin < 2 xULN or baseline and reduce by 1 dose level. • Discontinue PF-06647263 if dose delay is more than 2 weeks*. • If toxicity reoccurs despite reduction, patient may be dose reduced again by another dose level upon recovery to Grade 0-1 or baseline unless the patient is in the first dose group, then only 1 dose reduction is allowed. • Prompt palliative measures are strongly encouraged (eg, anti-emetics). • Patients who experience Grade 4 non hematologic toxicities despite optimal medical intervention should be discontinued from the study*.
Hematologic toxicity considered at least possibly related to PF-06647263 per investigator judgment • Grade 4 neutropenia, ie, ANC <500/mm3 (1.0×10^9/L) for more than 7 days. **Febrile Neutropenia** • Febrile neutropenia, ie, fever with a single temp >38.3°C or sustained temp ≥38°C for more than 1 hour with ANC <1000/mm3.	• Hold PF-06647263 until recovery of ANC to ≥1.0×10^9/L (1,000 cells/mm3) • Reduce PF-06647263 by 1 dose level. • 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.

Event	Action
Thrombocytopenia • Grade 4 thrombocytopenia, ie, PLTS <25,000 mm3 (25.0 x 10^9/L). • Or Grade 3 thrombocytopenia with clinically significant or life-threatening bleeding.	• Hold PF-06647263 until platelets ≥75,000/mm3. • For platelet counts 10,000 – 25,000/mm3, continue monitoring every 3 days until recovery to ≥25,000/mm3 (Grade 3 or less). For platelet counts ≤10,000/mm3 monitor daily until recovery to ≥25,000/mm3 (Grade 3 or less). • Reduce PF-06647263 by 1 dose level. • 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. • Discontinue for life-threatening bleeding.
Other Grade 4 hematologic toxicity despite medical therapy considered at least possibly related to PF-06647263 and clinically significant per investigator's judgment	• Hold PF-06647263 until recovery to Grade 0-1 or baseline and reduce PF-06647263 dose by 1 dose level. • 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-06647263 infusion	• Discontinue treatment*
*Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade 0-1 or baseline, only after discussion between the investigator and Sponsor.	

5.2.7. Compliance

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

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

5.3. Drug Storage and Drug Accountability

The investigator, or an approved representative (eg, pharmacist), will ensure that all PF-06647263 is stored in a secure area, under recommended storage conditions and in accordance with applicable regulatory requirements. PF-06647263 should be stored at 2-8°C (36-46°F) and protected from light until ready to use. PF-06647263 should not be frozen. Specific instructions on storage and handling are provided in the IP manual. To ensure adequate records, all PF-06647263 will be accounted for in the case report form and drug accountability inventory forms as instructed by Pfizer. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused must be returned

to Pfizer or its appointed agent (eg, a contract research organization [CRO]). If Pfizer authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

Storage conditions stated in the SRSD (Investigator Brochure [IB]) may be superseded by the label storage.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported to the sponsor.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

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

5.4. Concomitant Medication(s)

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

All concomitant medications, blood products, as well as non drug interventions (eg, paracentesis) received by patients from screening (within 28 days prior to the 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.

For patients who are thrombocytopenic, monitor use of nonsteroidal anti-inflammatory drugs (NSAIDs) and other platelet-interactive agents.

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.[11]

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

No additional anti-tumor therapy including chemotherapy, hormonal therapy, radiotherapy, or experimental anticancer medications will be permitted while patients are receiving study therapy. Additionally, the concurrent use of herbal supplements for an anti-cancer treatment 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.

Patients currently being treated with a gonadotropin-releasing hormone agonist (GnRH agonist) may continue treatment while on clinical trial B7521001 as long as the GnRH agonist treatment has been well tolerated for at least three months prior to study entry.

5.4.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the Investigator's discretion and according to any available ASCO guidelines.

5.4.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first cycle but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines.

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

5.4.4. Anti Diarrhea, Anti Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is permitted in this study at the investigator's discretion. The choice of the prophylactic drug is up to the investigator with sponsor approval and assuming the drug is not included in the Concomitant Medication(s) section, as well as the duration of treatment assuming there is no known or expected drug-drug interaction. If so, it must be approved by the sponsor.

5.4.5. 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 Medication(s) section.

5.4.6. 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.

5.4.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06647263 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06647263 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-06647263 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 sign an informed consent for the study before completing any study-specific procedures. A patient identification number will be assigned. The investigator (or appropriate delegate at the site) will obtain informed consent from each patient in accordance with the procedures described in the Schedule of Activities and 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.

The required screening assessments and laboratory tests are summarized in the Schedule of Activities and Assessments section. Following completion of the screening assessments and confirmation of eligibility, patients may be enrolled.

6.2. Study Period

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

6.3. Follow-up Visit

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

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

Patients enrolled in Part 2 will be followed for survival by phone call/email every 2 months until death or until 12 months from the End of Treatment visit

6.4. Patient Withdrawal

The reason for a patient's discontinuation from treatment will be documented in the end of study/withdrawal CRF. Patients will be followed for at least 28 days after the last dose of study drug for adverse events.

Patients may withdraw from treatment at any time at their own request, they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression according to RECIST;
- Global deterioration of health status requiring discontinuation;
- Adverse event;

- Medication error without associated adverse event;
- Significant protocol violation;
- Lost to follow-up;
- Patient no longer willing to participate in study;
- 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;
- Patient refusal for 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 all unused investigational product(s), 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, and 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 which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

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

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 at the baseline visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from study medication but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/ Independent Ethics Committee (IECs) or if required by local regulations.

7.1.2. Adverse Events

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

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the adverse events CRF page.

7.1.3. Laboratory Safety Assessment

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

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

Hematology	Chemistry		Urinalysis
Hemoglobin	ALT/SGPT	Creatinine	Urine dipstick for urine protein: If ≥2+ protein on urine dipstick, then collect spot urine sample to calculate urine protein to creatinine ratio (UPCR)
Platelets	AST/SGOT	Uric Acid	Urine dipstick for urine blood : If positive collect a microscopic (Reflex Testing)
WBC	Alk Phos	Glucose (non-fasted)	**Coagulation tests**
Absolute Neutrophils	Sodium	Albumin	PTT
Absolute Lymphocytes	Potassium	Total Protein	PT or INR

Hematology	Chemistry		Urinalysis
Absolute Monocytes	Magnesium	Phosphorus	**Pregnancy Test**
Absolute Eosinophils	Chloride	Total Bilirubin***	For female patients of childbearing potential, serum or urine
Absolute Basophils	Calcium	LDH	
	Bicarbonate or carbon dioxide		
	BUN or Urea		

*** 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)/international normalized ratio (INR), alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

If urine dipsticks are not used by the institution, urine samples are acceptable for the urine protein and blood results.

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 as per the schedule of activities; height will be measured at baseline only.

A complete 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 and dermatological examination, genitourinary examination is optional), the measurement of body weight, height (measured at screening only), vital signs and assessment of ECOG performance status. 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.

Weight may be collected within 7 days prior to the PF 06647263 infusion for dose preparation on Day 1 of each cycle. The weight measurement taken for Day 1 of each cycle should be used to calculate the patient's dose of study treatment for all doses in that cycle. Abbreviated PEs should be performed as appropriate at each visit where complete 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 and include a dermatological examination.

Vital signs will include measurements of blood pressure, pulse rate and temperature (oral, tympanic or axillary). Sitting blood pressure (BP) and pulse rate will be measured with the patient's arm supported at the level of the heart and recorded to the nearest mmHg. 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 prior to the nominal time of the blood collection.

7.1.5. (12-Lead) ECG

12-Lead ECG (single at Screening, triplicate for all others) will be collected as per the Schedule of Activities 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. ECG results will not be centrally reviewed. For each triplicate ECG, three consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTc interval. If the mean QTc is prolonged (value of ≥501 msec, ie, ≥CTC AE Grade 3), the ECGs should be re-evaluated by a qualified person at the institution for confirmation, including verification that the machine reading is accurate. If manual reading verifies a QTc of ≥501 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 501 msec. If QTc interval reverts to less than 501 msec, and in the judgment of Investigator(s) and Sponsor is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 501 msec the study drug will be held until the QTc interval decreases to ≤501 msec. Patients will then re-start the study drug at the next lowest dose level. If the QTc interval has still not decreased to <501 msec after 2-weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study. If a patient experiences a Grade 4 QTc prolongation considered related to study treatment, the patient will be removed from the study. Additional ECGs should be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, 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 the 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 must be carried out before each PK sample drawing, such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). All efforts will be made to complete the ECG at the exact nominal time relative to dosing. However, ECGs obtained within the 15-minute window before the end of infusion and within 10% of the subsequent nominal times from dosing will be not be captured as a protocol deviation, as long as the exact time of the ECG is noted on the source document and data collection tool (eg, CRF).

7.2. Long Term Follow-Up (Part 2 Patients Only)

Patients who have permanently discontinued treatment with study drug will enter the long term follow-up period until death or for 12 months after the End of Treatment visit.

Long term follow up information will be collected by telephone call, email, or in person approximately every 2 months after the End of Treatment visit. The date of death and cause of death, if applicable will be collected.

7.3. Pharmacokinetics Assessments

7.3.1. Blood for PK analysis of PF-06647263, Total Antibody, and Unconjugated Payload CL-184538

One (9 mL whole blood) blood sample for PK analysis will be collected at each timepoint into appropriately labeled tubes at times specified in the Schedule of Activities and the Study Procedures section of the protocol.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AE, at the time of AE occurrence, and the date and time documented in the CRF.

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within the 15-minute window before the end of infusion for the 1-hour post-dose sample and within 10% of the nominal times from dosing for the other post-dose samples will be not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

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

Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. Drug concentrations of PF-06647263, total antibody, and unconjugated payload will be measured using validated methods. Specifically, total antibody concentrations will be measured using ELISA method, PF-06647263 concentrations will be measured as conjugated payload using a hybrid Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)method, and unconjugated payload concentrations will be measured using an LC-MS/MS method.

As part of understanding the PK disposition of the study drug, samples from the highest dose group will be retained after PK measurements have been completed for possible metabolite identification experiments. 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]

[redacted]

CCI [redacted]

[redacted]

7.5. Tumor Response Assessments

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

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

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule of Activities, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 6 weeks).

Assessment of response will be made using RECIST version 1.1. Changes in tumor size will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), the latter incorporating the appearance of new lesions.

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

CT or MRI scan images for patients enrolled into Part 2 may be collected for an independent assessment of response. Details for the collection of the images will be provided in the Study Manual.

CCI [redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

7.7. Immunogenicity Evaluations

Assays to assess for anti-drug (anti-PF-06647263) antibodies (ADA) will be performed. All samples that are positive in a screening assay will be further characterized in terms of antibody specificity. Samples tested positive for ADA may also be analyzed for neutraling activity in a neutralizing anti-PF-06647263 antibody (Nab) assay. Patients found to have anti-PF-06647263 antibodies at their final study visit and an ongoing AE possibly related to ADA will be asked to return to the clinic for ADA assessment at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

Blood samples (5 mL) to provide approximately 2 mL of serum for ADA and Nab analysis will be collected into appropriately labeled tubes at times specified in the Schedule of Activities and Study Procedures sections of this protocol.

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

Samples that are determined to be positive for ADA may be tested for NAb. Samples for ADA and NAb will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. Samples may be further tested in order to further characterize the immune response to PF-06647263 and/or for evaluation of the bioanalytical methods.

[redacted]

7.8. Banked Biospecimens

7.8.1. Markers of Drug Response

Variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

CCI [redacted]

A 4 mL blood biospecimen CCI [redacted] will be collected at the Baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Banked Biospecimens will be collected from all patients **unless prohibited by local regulations or ethics committee decision.** Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

[redacted]

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

CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient

after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product [redacted] are to be reported to the Sponsor.

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

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

8.3. Definition of an Adverse Event

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

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

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

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

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

8.4. Medication Errors

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

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

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

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

8.5. Abnormal Test Findings

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

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

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

8.6. Serious Adverse Events

A Serious Adverse Event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);

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

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

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

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see Section 8.14.1 SAE Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin values ≥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 upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For patients with pre-existing AST or ALT baseline values above the normal range, AST or ALT ≥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 increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (whichever is smaller).

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

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute an 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 work-up 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;
- Pre-planned 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 non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

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

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

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse 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 an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

- 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 Report Form and Exposure in Utero (EIU) 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 EIU 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 EIU 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 EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

Additional information regarding the 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 Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

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

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

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

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe 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/her first awareness of the AE.

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Additional details of the analyses will be provided in the statistical analysis plan (SAP) and the clinical study report (CSR), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the preliminary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

The 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 Analysis 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 during the first cycle of treatment are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include failure to satisfy major entry criteria (eg, confirmation of the target disease; signed informed consent) or use of other anticancer treatments during the active treatment and disease follow-up phases other than as defined/allowed in this protocol.
4. Modified Intent-to-Treat (mITT) Population.
    - The modified intent-to-treat (mITT) is the analysis population that will follow the ITT principle and include subjects receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population may be used for interim analysis and conference presentations when the study is still ongoing.

5. PK analysis sets.

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

[redacted]

9.2. Statistical Methods and Properties

This study has been designed to establish the Maximum Tolerated Dose (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 and is considered appropriate based on simulations and expert input. Since mTPI algorithms are known to assign more patients above the target dose compared to 3+3 designs, the target was chosen below the maximum acceptable DLT rate of 33% (in order to protect study patients from exposure to doses with DLT rate higher than 30%). For similar reasons the prior distribution of DLT is set as a beta (0.75,0.65) (instead of beta (1,1) as suggested in the original mTPI method) and the threshold probability for early termination and dose exclusion is set to 0.975 (instead of 0.95 as suggested in the original mTPI method).[12] Similarly, doses with an incidence of DLT>33% (eg, 4 out of 10) cannot be selected as MTD although is allowed by the mTPI method.

The modified toxicity probability interval (mTPI) design 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 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 trials with different toxicity parameters. More importantly, all the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table (Table 5). In this table, 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% (eg, 4 out of 10) will not be declared the MTD but will be allowed by the mTPI method.

The decision rules to “dose escalate” (E), “no change in dose” (S), “dose de-escalate” (D) or “dose de-escalate, unacceptable toxicity” (U) are described on Table 5. Cohorts of patients could receive doses already tested but a dose that is associated with decision “Dose de-escalate, unacceptable toxicity” cannot be revisited and no more patients should be treated at this dose or higher doses for the remainder of the trial.

Patients will be enrolled in cohorts of 2 to 4, starting with 0.015 mg/kg Q3W in the first cohort. Evaluation of a weekly (QW) regimen will be initiated when the first patient treated with the Q3W regimen experiences a DLT or Grade 2 thrombocytopenia related to study treatment. The starting dose of the QW regimen will not exceed one-third of the highest Q3W dose evaluated. The maximum sample size would be N=70 but actual sample size will depend on the underlying dose toxicity profile and variability in actual data realization. Once initiated, the 2 regimens will be evaluated independently based on the same dose-escalation criteria as described below.

A minimum of 9 patients treated at the MTD is required to establish such dose as the RP2D. The study will continue accruing until one of the three stopping conditions below is triggered.

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

1. The maximum sample size has been achieved.

2. MTD has been identified with sufficient accuracy: at least 9 patients have been accumulated on a dose that is currently estimated to be the MTD; or

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

Due to binomial data variability in small samples, DLTs may be observed in a first cohort(s) assigned 0.015 mg/kg simply by chance even when the true Pr (DLT at 0.015 mg/kg) is fairly low. This could result in the estimated posterior DLT rate at 0.015 mg/kg (and all higher doses) to exceed the targeted 25% very early in the trial, triggering an early stop when very few patients (2-4) have been treated. To prevent stopping the trial prematurely in such cases, a step-down option with dose of 0.010 mg/kg is added to the dose grid. This dose will be explored only if a high DLT rate occurs in the first cohort assigned to 0.015 mg/kg, ie, it will not be used as a starting dose and the algorithm will always assign the first cohort of patients to 0.015 mg/kg.

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

Probability of Escalating Dose

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

9.3. Sample Size Determination

9.3.1. Part 1:

This First In Patient study is divided into 2 parts. In Part 1, patients will participate in a dose escalation phase aimed at estimating the MTD. The sample size for this component of the study will vary depending on the number of DLTs observed. It is anticipated that the maximum sample size of approximately 70 patients are expected to be enrolled in Part 1 of the study at 3 - 4 sites. The actual number of patients enrolled will depend upon tolerability of PF-06647263 and the number of dose levels required to identify the MTD in the Q3W and QW dosing regimens. Simulations under several toxicity scenarios estimated sample size ranging between 15 and 35 patients.

The minimum and maximum sample sizes after which Part 1 can be stopped and MTD declared are approximately 9 and approximately 70 patients, respectively. 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. However, since variable cohort size is allowed, the actual number of subjects treated at each dose will vary from 2 to 12. For example, N=12 is achieved if 4 additional patients are enrolled in a cohort of n=8.

Subsequent patients will enter Part 2, an expansion component aimed at evaluating PF-06647263 at the MTD.

9.3.2. Part 2:

A sample size of n=24 unselected Triple Negative Breast Cancer (TNBC) "response evaluable" patients are proposed. Assuming a noninformative prior for the TNBC patients (ie, uniform distribution in the interval 0% to 100%), a 42% response rate (10 out of 24) would provide a 92% posterior probability for the Overall Response Rate (ORR) to exceed 30% in TNBC patients. Suppose we look at the data after n=10 patients and find 6 responders in the TNBC group. It will provide a 91% chance that the ORR >30% at the end of the trial if we continue to enroll another 14 TNBC patients to a total of n=24 patients. Ongoing assessment of EFNA4 expression and efficacy of the unselected TNBC cohort will occur and continually feedback to the status of enrollment. Depending on the outcome of this assessment one option for the unselected TNBC cohort after determining the lack of expression and efficacy might be to pause unselected enrollment and enroll patients with moderate to high EFNA4 expressing TNBC and reassess the activity after the next 8 evaluable patients Additionally, the sample size proposed should be sufficient to assess if the concordance between EFNA4 positive/negative results in archival and fresh biopsy samples is different from perfect concordance (Kappa Cohen's statistic equal to 1) if the true Kappa value is <0.5.

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 rate, progression-free survival, and clinical benefit response rate will be summarized and presented (stratifying for EFNA4 expression Part 2 only) if data permits.

9.4.1. Analysis of Overall Response (CR or PR)

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. In Part 2, at the MTD, 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.

Objective Overall Response and Response Rate (RR) includes CR and PR.

Clinical Benefit Response (CBR) is defined as a CR, PR or SD ≥6 cycles.

9.5. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, CCI [redacted]
Data will also be displayed graphically, where appropriate. Additional details of the analysis are outlined in the SAP.

9.5.1. Analysis of Pharmacokinetics

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 PF-06647263 and total antibody, PK parameters including the maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and area under the plasma concentration versus time curve (AUC_{inf}, $AUC\tau$), clearance (CL), volume of distribution at steady state (Vss), terminal half-life ($t_{1/2}$), and accumulation ratio (R_{ac}) will be calculated. For unconjugated payload, PK parameters including Cmax, Tmax, AUC_{inf}, $AUC\tau$, $t_{1/2}$, and R_{ac} will be calculated.

Drug concentrations of PF-06647263, total antibody, and unconjugated payload will be summarized graphically and with descriptive statistics by dose, cycle, and the nominal PK sampling time. Noncompartmental PK parameters will be summarized descriptively by dose and cycle.

9.5.2. Pharmacokinetic/Pharmacodynamic Analysis

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

9.5.3. Immunogenicity

Listings and summary tabulations of the anti-PF-06647263 antibody and NAb data at baseline and post randomization will be generated. The percentage of subjects with positive ADA and NAb will be summarized by dosing cohort.

Potential impact of immunogenicity on PK and clinical responses including PD markers, safety/tolerability and efficacy of PF-06647263 will be explored, if 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, cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of patients.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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

Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 1.1 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 CTC grade definitions, results will be categorized as normal, abnormal or not done.

9.6.3. ECG

The analysis of ECG results will be based on Safety Population patients with baseline and on-treatment ECG data.

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

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Bazett's, Fridericia's and possibly a study specific factor). The adequacy of the correction method will be assessed graphically (plots of QT and QTc versus RR) and supplementary transformations may be considered, as appropriate. Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF and QTcB by treatment and dose. Individual QTc (all evaluated corrections) intervals will be listed by compound, time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment by compound, dose and by time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Outlier analysis of the QTc data will be conducted and summarized as follows:

- The number of patients with maximum change from baseline in QTc (<30, 30-60, and ≥60 ms);
- The number of patients with maximum post-dose (post-baseline) QTc (<450, 450-<480, 480- <500, and >500 ms).

Shift tables will be provided for baseline vs worst on study QTc (one or more correction method will be used) using Maximum CTC AE Grade. As well as tables of ECG abnormality at baseline (yes, no, not done: (n, %)). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

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

9.7. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee (DMC) 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

During study conduct, Pfizer or its agent will conduct periodic monitoring visits 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 is 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.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), 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.

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 is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

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

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

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

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

12.2. Ethical Conduct of the Study

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

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

12.3. Patient Information and Consent

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

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient.

In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

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

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

12.4. Patient Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

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

13.2. End of Trial in all other Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06647263 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a 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 for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial 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 primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. 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, Investigator is free to publish separately, subject to the other requirements of this Section.

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

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

[redacted]

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Appendix 1. Abbreviations

Ab	Antibody
ACD®	Advanced Cell Diagnostics
ARF	Acute renal failure
ADA	Anti drug antibodies
ADC	Antibody-drug conjugate
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALK/ROS	Anaplastic lymphoma kinase and c-**ros** oncogene
ALT	Alanin aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CBR	Clinical benefit response
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
CLL	Chronic lymphocytic leukemia
CLX	Cell line xenografts
Cmax	Maximum concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRO	Contract research organziation
CSA	Clinical study agreement
CSC	Cancer stem cells
CSR	Clinical study report
CT	Computed tomopgraphy
CTA	Clinical trial application
CTC	Circultating tumor cells
CTCAE	Common terminology criteria for adverse events
D	Dose de-escalate
DAB	Diaminobenzidine
DFS	Disease free survival
DLT	Dose limiting toxicity
DMC	Data safety monitoring committee
DMH	Dimethyl hydrazide
DNA	Deoxyribonucleic acid
E	Escalate
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EDTA	Ethylenediaminetetraacetic acid
EI	Equivalence Interval
EIU	Exposure in-utero
EFNA4	Ephrin-A4
ELISA	Enzyme-linked immunosorbent assay
ER	Estrogen receptor

FDA	US Food and Drug Administration
FDAAA	Food and drug administration amendments act of 2007
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle stimulating hormone
GCP	Good clinical practices
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practices
GnRH	Gonadotropin-releasing hormone agonist
HBV	Hepatitis B
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
HER2	Hman epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
IB	Investigator Brochure
ICH	International conference on harmonisation
IEC	Independent ethics committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
ISH	In situ hybridization
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function test
LSLV	Last subject last visit
MCL	Mantle cell lymphoma
MedRA	Medical dictionary for regulatory activities
mITT	Modified intent-to-treat
Ml	Mililiters
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSD	MesoScale Discovery
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interaval method
NA	Not applicable
Nab	Neutralizing antibody
NCI	National cancer institute
NS	Sample not evaluated
NSAID	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
OVCA	Ovarian cancer
PCD	Primary completion date
pCR	Pathological complete response
PD	Pharmacodynamic
PD	Progressive disease
PDX	Patient-derived xenograft

PE	Physical examination
PFS	Progression free survival
PJC	Premature junctional complex
PK	Pharmacokinetics
PR	Pulse Rate
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial Thromboplastin Time
PVC	Premature ventricular contraction
qRT-PCR	Quantitative polymerase chain reaction
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate Fridericia's
QW	Once weekly
Q3W	Every 3 weeks
R_{ac}	Accumulation ratio
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumor
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RR	Response rate
S	No change in dose
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of care
SRSD	Single reference study document
STD	Severely toxic dose in 10% of animals
$T_{1/2}$	Terminal elimination half-life
TLDA	Taqman low density array
Tmax	Maximum concentration
TNBC	Triple negative breast cancer
TSC	Tumor static concentration
U	Dose de-escalate, unacceptable toxicity
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
US	United States
UTI	Urinary tract infection
Vd	Volume of distribution
CCI	[redacted]
WBC	White blood cell
WFI	Water for injection

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

Normal sites

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

Recording Tumor Assessments

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

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 progressionPatients 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	NewLesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table 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. National Cancer Institute (NCI) common Terminology Criteria for Adverse Events (CTCAE)

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

Appendix 4. 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 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 5.2.3.

NCI-CTCAE Grade 2 allergic reaction or cytokine release syndrome

- Stop PF-06647263 infusion.
- Administer bronchodilators, oxygen, acetaminophen, etc. as medically indicated.
- Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop infusion. Institute premedication for subsequent infusions as per Section 5.2.3.

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

- A Grade 3 anaphylaxis (hypersensitivity reaction) consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or hypotension.
- A Grade 4 anaphylaxis (hypersensitivity reaction) is a life-threatening event requiring urgent intervention.

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

- Stop the PF-06647263 infusion immediately and disconnect infusion tubing from the patient.
- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically indicated.
- Telephone Sponsor or designated representative to report an SAE as per Section 8.

- 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-06647263 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-06647263.

- 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-06647263.

- 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.

[redacted]

Appendix 6. Detailed Dose Escalation/De Escalation Scheme for mTPI design

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

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

- With 10 patients treated at current dose level
  1-0 DLTs > escalate
  2-3 DLTs > remain at the same dose
  4-5 DLTs > de-escalate
  6-10 DLTs > de-escalate and consider current dose as intolerable
- With 11 patients treated at current dose level
  1-0 DLTs > escalate
  2-3 DLTs > remain at the same dose
  4-5 DLTs > de-escalate
  6-11 DLTs > de-escalate and consider current dose as intolerable
- With 12 patients treated at current dose level
  0-1DLTs > escalate
  2-4 DLTs > remain at the same dose
  5-6 DLTs > de-escalate
  >6 DLTs > de-escalate and consider current dose as intolerable
- With 13 patients treated at current dose level
  0-2 DLTs > escalate
  3-4 DLTs > remain at the same dose
  5-6 DLTs > de-escalate
  >6 DLTs > de-escalate and consider current dose as intolerable
- With 14 patients treated at current dose level
  0-2 DLTs > escalate
  3-4 DLTs > remain at the same dose
  5-6 DLTs > de-escalate
  >6 DLTs > de-escalate and consider current dose as intolerable
- With 15 patients treated at current dose level
  1-0 DLTs > escalate
  3-5 DLTs > remain at the same dose
  6-7 DLTs > de-escalate
  >7 DLTs > de-escalate and consider current dose as intolerable
- With 16 patients treated at current dose level
  0-2 DLTs > escalate
  3-5 DLTs > remain at the same dose
  6-7 DLTs > de-escalate
  >7 DLTs > de-escalate and consider current dose as intolerable
- With 17 patients treated at current dose level
  0-2 DLTs > escalate
  3-5 DLTs > remain at the same dose
  6-7 DLTs > de-escalate
  >7 DLTs > de-escalate and consider current dose as intolerable
- With 18 patients treated at current dose level
  0-2 DLTs > escalate
  3-6 DLTs > remain at the same dose
  7-8 DLTs > de-escalate
  >8 DLTs > de-escalate and consider current dose as intolerable

- With 19 patients treated at current dose level
  0-2 DLTs > escalate
  3-6 DLTs > remain at the same dose
  7-8 DLTs > de-escalate
  >8 DLTs > de-escalate and consider current dose as intolerable
- With 20 patients treated at current dose level
  0-3 DLTs > escalate
  4-6 DLTs > remain at the same dose
  7-8 DLTs > de-escalate
  >8 DLTs > de-escalate and consider current dose as intolerable
- With 21 patients treated at current dose level
  0-3 DLTs > escalate
  4-7 DLTs > remain at the same dose
  8-9 DLTs > de-escalate
  >9 DLTs > de-escalate and consider current dose as intolerable
- With 22 patients treated at current dose level
  0-3 DLTs > escalate
  4-7 DLTs > remain at the same dose
  8-9 DLTs > de-escalate
  >9 DLTs > de-escalate and consider current dose as intolerable
- With 23 patients treated at current dose level
  0-3 DLTs > escalate
  4-7 DLTs > remain at the same dose
  8-9 DLTs > de-escalate
  >9 DLTs > de-escalate and consider current dose as intolerable
- With 24 patients treated at current dose level
  0-3 DLTs > escalate
  4-8 DLTs > remain at the same dose
  9-10 DLTs > de-escalate
  >10 DLTs > de-escalate and consider current dose as intolerable
- With 25 patients treated at current dose level
  0-3 DLTs > escalate
  4-8 DLTs > remain at the same dose
  9-10 DLTs > de-escalate
  >10 DLTs > de-escalate and consider current dose as intolerable
- With 26 patients treated at current dose level
  0-4 DLTs > escalate
  5-8 DLTs > remain at the same dose
  9-10 DLTs > de-escalate
  >10 DLTs > de-escalate and consider current dose as intolerable
- With 27 patients treated at current dose level
  0-4 DLTs > escalate
  5-9 DLTs > remain at the same dose
  10-11 DLTs > de-escalate
  >11 DLTs > de-escalate and consider current dose as intolerable

- With 28 patients treated at current dose level
  0-4 DLTs > escalate
  5-9 DLTs > remain at the same dose
  10-11 DLTs > de-escalate
  >11 DLTs > de-escalate and consider current dose as intolerable
- With 29 patients treated at current dose level
  0-4 DLTs > escalate
  5-9 DLTs > remain at the same dose
  10-11 DLTs > de-escalate
  >11 DLTs > de-escalate and consider current dose as intolerable
- With 30 patients treated at current dose level
  0-4 DLTs > escalate
  5-10 DLTs > remain at the same dose
  11-12 DLTs > de-escalate
  >12 DLTs > de-escalate and consider current dose as intolerable
- With 31 patients treated at current dose level
  0-5 DLTs > escalate
  6-10 DLTs > remain at the same dose
  11-12 DLTs > de-escalate
  >12 DLTs > de-escalate and consider current dose as intolerable
- With 32 patients treated at current dose level
  0-5 DLTs > escalate
  6-10 DLTs > remain at the same dose
  11-12 DLTs > de-escalate
  >12 DLTs > de-escalate and consider current dose as intolerable
- With 33 patients treated at current dose level
  0-5 DLTs > escalate
  6-10 DLTs > remain at the same dose
  11-12 DLTs > de-escalate
  >12 DLTs > de-escalate and consider current dose as intolerable
- With 34 patients treated at current dose level
  0-5 DLTs > escalate
  6-11 DLTs > remain at the same dose
  12-13 DLTs > de-escalate
  >13 DLTs > de-escalate and consider current dose as intolerable
- With 35 patients treated at current dose level
  0-5 DLTs > escalate
  6-11 DLTs > remain at the same dose
  12-13 DLTs > de-escalate
  >13 DLTs > de-escalate and consider current dose as intolerable