A PHASE 1 DOSE ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF PF-06650808 IN PATIENTS WITH ADVANCED SOLID TUMORS

Compound:	PF-06650808
Compound Name:	Not applicable
US IND Number:	120498
European Clinical Trial Database (EudraCT) Number:	Not applicable
Protocol Number:	B7501001
Phase:	1

[redacted]

Document History

Document	Version Date	Summary of Changes
Original protocol	19 March 2014	N/A
Amendment 1	07 May 2014	Section 1.4.1 Clarification that PF-06380101 is a P-glycoprotein substrate. Section 5.4 Recommendation to avoid co-administration of potent CYP3A/P-gp inhibitors and/or inducers and addition of Appendix 6: CYP3A and P-Glycoprotein Inducers and Inhibitors. Section 5.2.3 (Medication Error text), Section 8 (Adverse Event Reporting) and Section 15 (Publication of Study Results) updated to align with updated Protocol Template.

PROTOCOL SUMMARY

Background and Rationale:

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

PF-06650808 is an anti-Notch3 ADC for the treatment of patients with cancer. PF-06650808 is comprised of a humanized anti-Notch3 antibody linked to an auristatin-based cytotoxic agent with a peptide cleavable maleimidocapronic-valine-citruline-p-aminobenzyloxycarbonyl (vc) linker. The auristatin-based payload is a highly potent, cell-permeable, anti-mitotic agent that blocks tubulin polymerization resulting in cell cycle arrest, induction of apoptosis and inhibition of tumor growth in preclinical models.

The Notch3 receptor is a highly conserved transmembrane protein that undergoes ligand-dependent and independent internalization, and traffics to the lysosome for degradation (Jia, et al. 2009).[11] Notch3 is over-expressed or amplified in certain human tumors and regulates cell proliferation, differentiation, and survival (Bellavia et al., 2008; Park et al, 2006; Cancer Genome Atlas Research Network, 2011).[4,6,16] Constitutive activation of Notch3 signaling is oncogenic in many contexts and induces tumors in mouse models. Immunohistochemical studies showed the presence of Notch3 on a variety of human carcinomas, including breast, lung and ovary (Hirose et al., 2010; Haruki et al, 2005; Jung et al., 2010).[8,9,12] Further, in ovarian cancer, high levels of Notch3 messenger ribonucleic acid (mRNA) expression are associated with poorer survival. In lung cancer, Notch3 signaling has been linked with a tumor-initiating cell (cancer stem cell) phenotype (Zheng et al, 2013).[17] CCI [redacted]

Triple negative breast cancer (TNBC) is a heterogenous 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 (Andre et al., 2012).[1] 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 (Liedtke et al., 2008).[13] 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 (Pal et al., 2011).[15] Thus, novel therapeutic options are urgently needed.

Study Objectives and Endpoints:

Dose Escalation (Part 1) Objectives

Primary Objective:

- To assess safety and tolerability at increasing dose levels of PF-06650808 in patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available in order to determine the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives:

- To evaluate the overall safety profile.
- To characterize the single and multiple dose pharmacokinetics of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101).
- To evaluate the immunogenicity of PF-06650808.
- To document any preliminary evidence of anti-tumor activity.

CCI [redacted]**:**

- CCI [redacted]

Dose Expansion (Part 2) Objectives

Primary Objective:

- To confirm safety and tolerability and explore preliminary evidence of anti-tumor activity of PF-06650808 at the RP2D in patients with TNBC.

Secondary Objectives:

- To evaluate the overall safety profile at the R2PD.
- To characterize the single and multiple dose pharmacokinetics of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101).
- To evaluate the immunogenicity of PF-06650808.

CCI [redacted]:

- CCI [redacted].

Primary 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.

Study Design:

This is a Phase 1, open label, multi-center, single arm, non randomized, multiple dose, safety, pharmacokinetic (PK) and pharmacodynamic (PD) study of single agent PF-06650808 in sequential cohorts of adult patients with advanced solid tumors for whom no standard therapy is available. Successive cohorts of patients will receive escalating doses of PF-06650808 intravenously every 21 days starting at a dose of 0.2 mg/kg.

Approximately 55 patients are expected to be enrolled in the study at approximately 3-4 sites. The actual number of patients enrolled will depend upon tolerability of PF-06650808 and the number of dose levels required to identify the MTD.

The study will include two parts, a dose escalation phase (Part 1) followed by a dose expansion phase (Part 2). 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. Part 2 will include approximately 20 patients with TNBC enrolled at the MTD in order to explore benefit from treatment as suggested by preclinical findings, and will better define the safety profile at the RP2D. Additional safety information gathered in Part 2 may be used to modify the dose recommended for future Phase 2 studies.

The study is expected to be completed in approximately 24 months. The end of the study is the last visit of the last patient.

Study Treatment:

A modified continual reassessment method (mCRM) targeting a DLT rate of 25% will be utilized for Part 1 (dose escalation phase). Patients will be enrolled in cohorts of 2 to 4, starting with 0.2 mg/kg for the first cohort. The possible doses explored will be from a fine grid of doses ranging from 0.2 mg/kg to 6.4 mg/kg. If a high DLT rate is observed at the starting dose of 0.2 mg/kg, a lower dose such as 0.14 mg/kg or lower will be considered. The study may be stopped if the drug is deemed not tolerable at the lowest reduced dose.

Part 2 will include patients enrolled at the MTD in order to explore benefit from treatment and will better define the safety profile at the RP2D.

Patients will continue with study treatment every 21 days until disease progression, withdrawal of consent, unacceptable toxicity occurs, or the study is terminated. Patients experiencing a DLT may be managed with dose modification or discontinuation.

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.

Protocol Activity	Screen/ Baseline[1] (≤28 days)	Treatment Period								Post Treatment	
		Cycle 1 Only (Days 1 -21)					Cycle 2 and Subsequent Cycles (Days 1-21)			End of Treatment[22]	Follow-Up[23]
		Day 1	Day 2	Day 4	Day 8	Day 15	Day 1	Day 8	Day 15		
Visit Window (Days)				±1	±1	±2	±2	±2	±2		
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		
Baseline signs and symptoms[6]		X									
Height	X										
Weight	X	X								X	
Vital signs[7]	X	X		X		X	X	X	X	X	X
ECOG Performance status[8]	X	X					X			X	X
12-Lead ECG[9]	X	X			X		X	X		X	
Laboratory											
Hematology[10]	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X	
Coagulation[12]	X						X			X	
Urinalysis[13]	X					X	X			X	
Pregnancy test[14]	X	X					X			X	
Registration[15]		X									
Study treatment[16]		X					X				
CT or MRI scan or equivalent[17]	X						X (every 6 weeks)			X	

Protocol Activity	Screen/ Baseline1 (≤28 days)	Treatment Period								Post Treatment	
		Cycle 1 Only (Days 1 -21)					Cycle 2 and Subsequent Cycles (Days 1-21)			End of Treatment[22]	Follow-Up[23]
		Day 1	Day 2	Day 4	Day 8	Day 15	Day 1	Day 8	Day 15		
Visit Window (Days)				±1	±1	±2	±2	±2	±2		
CCI [redacted]											
CCI [redacted]											
Blood Samples for PK		See Pharmacokinetic and Pharmacodynamic Sampling Schedule Table below									
Blood Sample for Anti-PF-06650808 Antibody[19]		See Pharmacokinetic and Pharmacodynamic Sampling Schedule Table below									
CCI [redacted]		[redacted]									
Adverse Events[20]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and non drug supportive interventions[21]	X	X	X	X	X	X	X	X	X	X	X

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.
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. **Complete Physical Examination:** No need to repeat on C1D1 if baseline assessment performed within 72 hours of dosing.
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 AE CRF page.
7. **Vital Signs:** Includes temperature, blood pressure (BP), and pulse rate (PR) to be recorded in the sitting position after approximately 5 minutes of rest. On Day 1 of each cycle, vital signs should be measured prior to infusion start (pre-dose) and 1 hour after the start of infusion (ie, just prior to the end of the infusion).
8. **Performance Status:** per ECOG scale (see Appendix 3).
9. **12 Lead ECG:** ECGs will be collected during Screening and at the End of Treatment visit. Additional ECGs will be collected prior to dosing, at end of infusion and at Day 8 following administration of each dose of study treatment. If the mean QTc is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs should be performed if clinically indicated.
10. **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 hour prior to dosing. Hematology to be collected weekly through Cycle 6. Beginning at Cycle 7, hematology will be collected on Day 1 of the cycle only.
11. **Blood Chemistry:** Should include sodium, potassium, chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, 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 dosing. Chemistry to be collected weekly through Cycle 6. Beginning at Cycle 7, chemistry will be collected on Day 1 of the cycle only.
12. **Coagulation:** Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT).
13. **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).

14. **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 on Day 1 of Cycle 1 before 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.
15. **Registration:** Patient number and dose level allocation will be provided by Pfizer Inc. Treatment should begin no longer than 3 days from registration.
16. **Study Treatment:** PF-06650808 will be administered once every 21 days as an infusion over approximately 60 minutes.
17. **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 should be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out CNS metastases. CT or MRI scans are to be done every 6 weeks (±5 days) for the first two assessments (Week 6 and Week 12) and will then be collected every 12 weeks thereafter until disease progression by RECIST (v1.1) or death, or until permanent discontinuation of study treatment. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. For patients enrolled in Part 2, responses of CR or PR must be confirmed by repeat assessment no more than 4 weeks after the criteria for response are first met. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.

CCI [redacted].

19. **Anti PF-06650808 Antibodies:** Collection of serum to detect the presence of antibodies to PF-06650808 is to be obtained prior to the start of study drug infusion. Patients having an unresolved adverse event that is possibly related to anti-PF-06650808 antibodies at their last assessment will be asked to return to the clinic for ADA and drug concentration blood sampling at up to 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.
20. **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. 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 study drug are to be reported to the Sponsor.
21. **Concomitant Medications and Non Drug Supportive Interventions:** All concomitant medications and non drug supportive interventions should be recorded in the CRF.
22. **End of Treatment Visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
23. **Follow-up:** At least 28 days, and no more than 35 days, after discontinuation of treatment, patients will return to undergo review of concomitant medications, performance status, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

PHARMACOKINETIC, ANTI-DRUG ANTIBODY AND PHARMACODYNAMIC SAMPLING SCHEDULE

Protocol Activity	Screen (≤28 days)	Treatment Period																	Post Treatment
		Cycle 1 Only (Days 1 to 21)							Cycles 2 and 3		Cycle 4							Every Cycle Thereafter		EOT (+7)
		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 PK sample for PF-06380101[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood PK sample for PF-06650808 and PF-06460005[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Anti-PF-06650808 Antibody [3]		X						X	X		X							X		X
CCI [redacted]	[redacted]	[redacted]			[redacted]		[redacted]		[redacted]		[redacted]									[redacted]

*** Sampling times are related to the start of the infusion; 1 hr samples should be collected immediately before the infusion ends**

1. **Blood PK sample for PF-06380101:** 4 mL of whole blood will be collected for PK analysis of unconjugated payload (PF-06380101).
2. **Blood PK sample for PF-06650808 and PF-06460005:** Approximately 6 mL of whole blood will be collected for PK analysis of ADC (PF-06650808) and total antibody (PF-06460005).
3. **Anti PF-06650808 Antibodies:** Collection of serum to detect the presence of antibodies to PF-06650808 is to be obtained prior to the start of treatment. Patients having an unresolved adverse event that is possibly related to anti-PF-06650808 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.

CCI [redacted]

TABLE OF CONTENTS

LIST OF FIGURES

APPENDICES

CCI [redacted]

1. INTRODUCTION

1.1. Indication

PF-06650808 is intended to be used for the treatment of adult patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available.

1.2. Background and Rationale

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

PF-06650808 is an anti-Notch3 ADC for the treatment of patients with cancer. The Notch3 receptor is a highly conserved, 244 kDa, type I transmembrane glyoprotein that is over-expressed or amplified in certain human tumors and regulates cell proliferation, differentiation, and survival (Bellavia et al., 2008; Park et al, 2006; Cancer Genome Atlas Research Network, 2011).[4,6,16] Constitutive activation of Notch3 signaling is oncogenic in many contexts and induces tumors in mouse models. The Notch3 receptor undergoes ligand-dependent and independent internalization, and traffics to the lysosome for degradation (Jia, et al. 2009).[11] Immunohistochemical studies demonstrated the presence of Notch3 on a variety of human carcinomas, including breast, lung and ovary (Hirose et al., 2010; Haruki et al, 2005; Jung et al., 2010).[8,9,12]

In ovarian cancer, high levels of Notch3 mRNA expression are associated with poorer survival. In lung cancer, Notch3 signaling has been linked with a tumor-initiating cell (cancer stem cell) phenotype (Zheng et al, 2013).[17] CCI [redacted] In non-tumor tissues, Notch3 is expressed primarily in vascular smooth muscle cells (vSMC), various thymocyte subpopulations and the developing nervous system (Bellavia, 2008).4 Consistent with its restricted normal tissue distribution, targeted deletion of murine Notch3 does not lead to embryonic lethality. Instead, Notch3-null mice are viable, but have defects in the maturation and differentiation of vSMCs (Domenga et al, 2004).[5]

Triple negative breast cancer (TNBC) is a heterogenous 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 (Andre et al, 2012).[1] 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 (Liedtke et al., 2008).[13] 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 (Pal et al., 2011).[15] Thus, novel therapeutic options are urgently needed.

CCI [redacted]

1.3. PF-06650808

PF-06650808 is comprised of the hu28 humanized IgG1 antibody linked to an auristatin-based cytotoxic agent with a peptide cleavable maleimidocapronic-valine-citruline-p-aminobenzyloxycarbonyl (vc) linker. Hu28 is a non-inhibitory antibody that binds to Notch3 but does not neutralize Notch3 signaling. The auristatin-based payload is a highly potent, cell-permeable, anti-mitotic agent that blocks tubulin polymerization resulting in cell cycle arrest, induction of apoptosis and inhibition of tumor growth in preclinical xenograft studies. CCI [redacted].

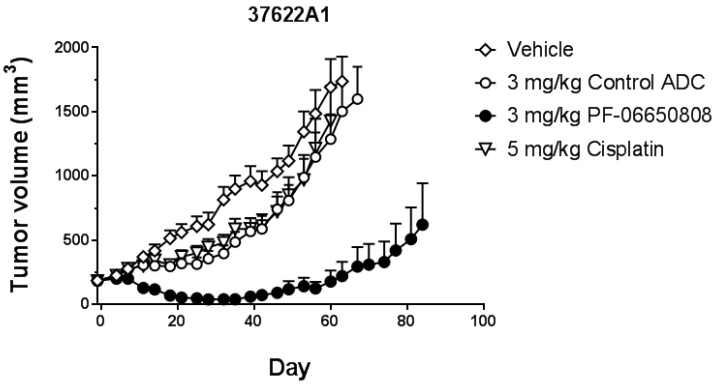
1.3.1. Efficacy

Efficacy studies were carried out in immune-compromised mice harboring subcutaneously (lung, ovarian) or orthotopically (breast) implanted human tumor cells. The panel of tumor models represented a broad range of tumor types and included both PDX and cell line xenografts (CLX). High levels of target expression were assessed in tumor extracts by immunoblot and immunohistochemistry on formalin-fixed paraffin embedded xenografts.

PF-06650808 treatment resulted in long-term tumor regressions and/or tumor-free mice at a dose of 3 mg/kg when given every four days for a total of four treatments (q4dx4).

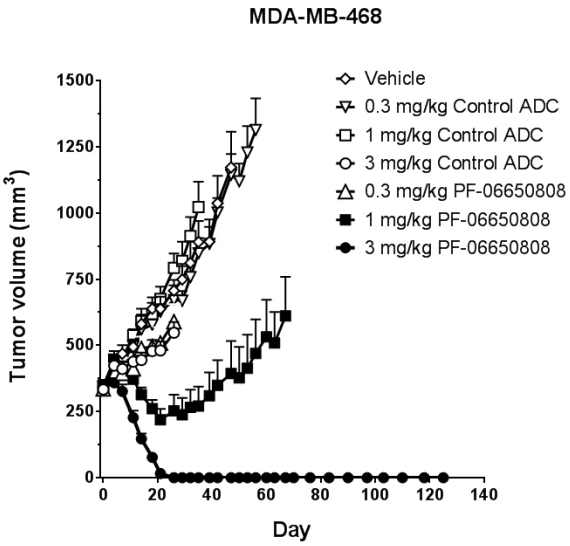
37622A1 is a PDX model of human non-small cell lung cancer (NSCLC) (Squamous Cell Carcinoma). PF-06650808 completely suppressed tumor growth up to Day 60 at which time 5 out of the 9 treated tumors slowly began to regrow (4 of the 9 animals remained tumor-free by Day 84). The non-targeted control-ADC did not inhibit tumor growth in any meaningful manner. Further, 37622A1 xenografts failed to respond to cisplatin administered at 5 mg/kg when dosed q4dx4, thus PF-06650808 outperformed standard-of-care and inhibited the growth of cisplatin-resistant tumors Figure 1.

Figure 1. Effect of PF-06650808 on the Growth of 37622A1 NSCLC PDX



MDA-MB-468 is an orthotopic CLX model of TNBC. The 3 mg/kg dose of PF-06650808 completely regressed tumors and all 8 animals remained tumor-free through study end on Day 125. At the 1 mg/kg dose of PF-06650808, tumor growth was inhibited by 66%. No activity was observed at the 0.3 mg/kg dose of PF-06650808. The non-targeted control-ADC did not inhibit tumor growth in any meaningful manner Figure 2.

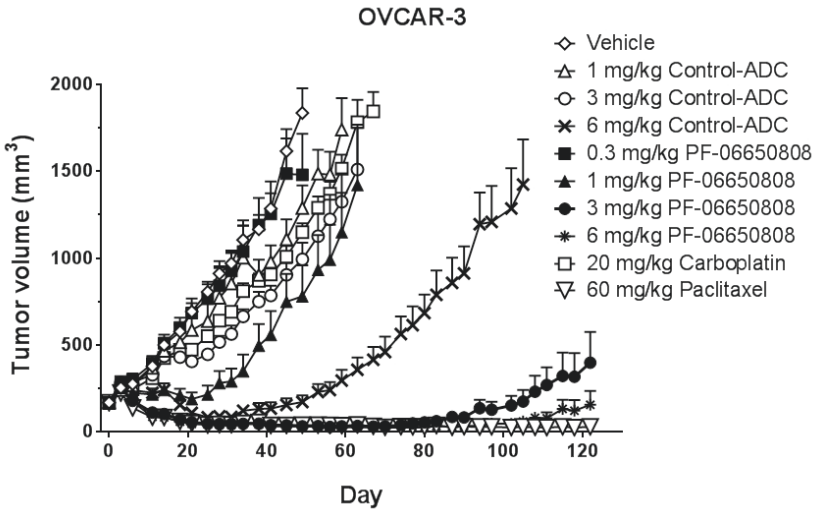
Figure 2. Effect of PF-06650808 on the Growth of TNBC CLX Model



OVCAR-3 is a CLX model of ovarian cancer. Mice bearing OVCAR-3 ovarian cancer xenografts were dosed q4Dx4 with PF-06650808, control ADC or vehicle. PF-06650808 inhibited tumor growth in a dose-dependent manner. At the 6 mg/kg dose of PF-06650808, tumors regressed and did not regrow larger than mean staging volume by 122 days (relative to the first dose) or study end. At the 3 mg/kg dose of PF-06650808, tumors regressed and then slowly regrew (slightly larger than mean staging volume) after 102 days (relative to the first dose). At the 1 mg/kg dose of PF-06650808, tumor growth was inhibited by 57%. No significant tumor growth inhibition was observed at the 0.3 mg/kg

dose of PF-06650808. At the 6 mg/kg, 3 mg/kg and 1 mg/kg dose of control ADC, tumor growth was non-specifically inhibited by 91%, 46% and 30%, respectively, by Day 49. Tumors from control ADC treated groups quickly regrew into large tumors that were similar in volume to vehicle treated group by study end. At the maximum tolerated dose of Paclitaxel (60 mg/kg) dosed q7Dx4, tumors regressed and did not regrow for at least 122 days, which was the end of the study. Further, OVCAR-3 tumors failed to respond to carboplatin administered at 20 mg/kg when dosed q7dx8, thus PF-06650808 outperformed a standard-of-care chemotherapy and inhibited the growth of carboplatin-resistant tumors Figure 3.

Figure 3. Effect of PF-06650808 on the Growth of OVCAR-3 CLX Model



[redacted]

CCI

CCI

CCI

CCI [redacted]

[redacted].

1.5. Starting Dose Rationale

The selection of the starting dose for the human Phase 1 trial was based on the preclinical safety study results following 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 0.2 mg/kg given as an IV infusion every three weeks (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 C_{avg} for PF-06650808 at the proposed starting dose of 0.2 mg/kg is expected to be approximately $1/20^{th}$ of the observed monkey C_{avg} at HNSTD.

CCI [redacted]

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Dose Escalation (Part 1) Objectives

Primary Objective

- To assess safety and tolerability at increasing dose levels of PF-06650808 in patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available in order to determine the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile.
- To characterize the single and multiple dose pharmacokinetics of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101).
- To evaluate the immunogenicity of PF-06650808.
- To document any preliminary evidence of anti-tumor activity.

CCI

- CCI

2.1.2. Dose Expansion (Part 2) Objectives

Primary Objectives

- To confirm safety and tolerability and explore preliminary evidence of anti-tumor activity of PF-06650808 at the RP2D in patients with triple negative breast cancer.

Secondary Objectives

- To evaluate the overall safety profile at the R2PD.
- To characterize the single and multiple dose pharmacokinetics of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101).
- To evaluate the immunogenicity of PF-06650808.

CCI

- CCI .

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

- Adverse Events (AEs) as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study treatment.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.
- Vital Signs.
- Systemic pharmacokinetic (PK) exposure of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101) will be determined with validated methods. Standard noncompartmental PK parameters will be determined from the respective concentration-time data.
- Immunogenicity of ADC (PF-06650808); Human serum ADA (anti-PF-06650808 antibody) samples will be analyzed for the presence or absence of anti-PF-06650808 antibodies, following a tiered approach using screening, confirmation and titer/quantitation.
- Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 by calculating the Overall Response Rate (ORR), Progression Free Survival (PFS), and Overall Survival (OS) – Part 2 only.

CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted].
- CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open label, multi-center, single arm, non randomized, multiple dose, safety, PK and PD study of single agent PF-06650808 in sequential cohorts of adult patients with advanced solid tumors for whom no standard therapy is available. Successive cohorts of patients will receive escalating doses of PF-06650808 intravenously every 21 days starting at a dose of 0.2 mg/kg.

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

Approximately 55 patients are expected to be enrolled in the study at approximately 3-4 sites. The actual number of patients enrolled will depend upon tolerability of PF-06650808 and the number of dose levels required to identify the MTD.

Patients will participate in the study for approximately 6 months. This includes a 28 days screening period and approximately 4 month treatment period and a 28 day post dose follow-up period. Treatment with study drug will continue until: disease progression, patient refusal or unacceptable toxicity occurs. Patients who demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study treatment will be given the opportunity to continue treatment upon agreement between investigator and sponsor. Therefore, participation may be longer than 6 months for some patients.

The study will include two parts, a dose escalation phase (Part 1) followed by a dose expansion phase (Part 2). 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. Part 2 will include approximately 20 patients with TNBC enrolled at the MTD in order to explore benefit from treatment as suggested by preclinical findings by providing an estimate of the likely response rate in this patient population and will better define the safety profile at the RP2D. Additional safety information gathered in Part 2 may be used to modify the dose recommended for future Phase 2 studies.

The study is expected to be completed in approximately 24 months. The end of the study is the last visit of the last patient.

3.2. Dose Escalation Phase (Part 1)

A modified continual reassessment method (mCRM) targeting a DLT rate of 25% will be utilized for Part 1 (dose escalation phase) (Goodman et al, 1995; O'Quigley et al, 1990).[7,14] Patients will be enrolled in cohorts of 2 to 4, starting with 0.2 mg/kg for the first cohort. The possible doses explored will be from a fine grid of doses ranging from 0.2 mg/kg to 6.4 mg/kg. If a high DLT rate is observed at the starting dose of 0.2 mg/kg, a lower dose such as 0.14 mg/kg (a 30% reduction from starting dose) or lower will be considered. The study may be stopped if the drug is deemed not tolerable at the lowest reduced dose. The mCRM model will determine the next dose level based on the DLT rate using a 30%, 69% and 100% dose increment for 0, 1 or 2 dose skips respectively.

Starting with the second cohort, patients will be assigned to a dose that is closest to the current MTD prediction based on a model that mCRM utilized to learn about overall dose-toxicity relationship. This model is updated after DLT assessment of each cohort. At any given point in this phase, doses can be escalated, deescalated, unchanged or revisited, but always aiming towards the target MTD. To prevent overly aggressive dose-escalation, the maximum allowed dose increase will be limited to 2 increments at a time (ie, no more than 100% dose increase at a time). In addition, if two clinically significant Grade 2 toxicities of the same type are seen in a cohort, dose escalation will be limited to no greater than 69% for the next cohort. If there is one additional case of the same Grade 2 toxicity or two other cases of clinically significant Grade 2 toxicities of the same type, dose escalation will again be limited to no greater than 69% for the next cohort; otherwise dose escalation following the mCRM algorithm will resume. Grade 2 toxicities will not be considered clinically significant if a corresponding Grade 3 toxicity exists (by NCI CTCAE v 4.03); Grade 2 toxicities without a corresponding Grade 3 toxicity will be considered clinically significant (eg, Grade 2 alopecia, dry skin, libido decrease). In addition, Grade 2 nausea, vomiting, and diarrhea will not be considered clinically significant unless it has been optimally medically managed.

The combination of a fine dose grid and the ability to skip doses allows rapid dose escalation if no DLTs are observed and small dose changes with exploration of adjacent doses once the observed DLT rate becomes noticeable. The algorithm will stop if any of the following criteria is met:

1. The maximum sample size has been achieved (approximately 35 patients total).

2. At least 6 patients have been accumulated on a dose that is predicted to be the MTD, or

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

Although dose levels are capped at 6.4 mg/kg, this mCRM will continue to operate subject to the constraints detailed above while allowing for doses higher than specified. Doses may continue to be skipped, visited more than once, or not visited at all. In addition, if necessary, doses beyond 6.4 mg/kg may be allowed in 30% increments.

All significant AEs and serious adverse events (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 sponsor clinical team and the investigators, can override the dose escalation increment determined by the algorithm if a more conservative approach is mandated.

Patients will continue with study treatment every 21 days until disease progression, patient refusal or unacceptable toxicity occurs. Patients experiencing a DLT may be managed with dose modification or discontinuation.

Subsequent dose levels may not be opened until all patients entered at the current dose level have been treated and observed for at least one complete cycle (through Day 21) and the number of DLTs among those patients in their first cycle has been determined.

3.3. DLT Definition

Severity of AEs will be graded according to 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 (21 days) 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:

- 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.

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

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

3.4. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further study based on Phase 1 results. If the MTD proves to be clinically feasible for long term administration in a reasonable number of patients, such dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower or higher than the MTD.

4. PATIENT SELECTION

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

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

2. For the dose expansion phase: Previously treated metastatic triple negative breast cancer that expresses Notch3 with at least one measurable lesion.

3. For the dose expansion phase: Archival core needle biopsy or prospectively collected core needle biopsy available for exploratory biomarker and Notch3 expression analysis.

4. Age ≥18 years.

5. ECOG Performance Status (PS) of 0 or 1.

6. Life expectancy ≥12 weeks.

7. Adequate Bone Marrow Function as defined by:

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

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

Hemoglobin ≥9 g/dL.

8. Adequate Renal Function as defined by:

    a. Serum creatinine ≤1.5 x upper limit of normal (ULN); or

    b. Estimated creatinine clearance ≥60 ml/min as calculated using the method standard for the institution.

9. Adequate Liver Function as defined by:

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

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

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

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

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

12. Male and female patients of childbearing potential must agree to use a highly effective method 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.

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

14. 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 or systemic anti-cancer therapy within 4 weeks of starting study treatment (6 weeks for mitomycin C or nitrosoureas).

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

4. Presence of ≥ Grade 2 peripheral neuropathy.

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

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

7. Pregnant or breastfeeding; males and females of childbearing potential who are unwilling or unable to use a highly effective method 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.
8. Currently active treatment in another clinical study.
9. Any of the following in the previous 12 months or currently: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism, as well as ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, or QTc interval >470 msec at screening.
10. Known or suspected hypersensitivity to recombinant human or murine proteins.
11. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
12. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.

4.3. Life Style Guidelines

In this study, patients of childbearing potential will received PF-06650808, a compound for which a 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 of investigational product. 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 intrauterine device (IUD) or intrauterine system (IUS).

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.

4.4. 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-06650808 in an open-labeled, unblinded manner. Patients will be successively assigned to the next available treatment slot at a dose level decided on after the previous cohort’s safety evaluation and ongoing observations of earlier enrolled patients. Treatment should begin no longer than 3 days from registration of the patient.

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

No patient shall receive study drug until the investigator or designee has received the following information in writing from the Sponsor:

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

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

5.2. Drug Supplies

PF-06650808 will be supplied for the study by Pfizer.

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

5.2.1. Formulation and Packaging

PF-06650808 for injection, 60 mg extractable per vial, is presented as a sterile lyophilized product, white to off white cake, packaged in a 6 mL type 1 tubing glass vial with a 13 mm rubber stopper and a 13 mm aluminum overseal. Each vial of PF-06650808 for injection is reconstituted with 2.2 mL of water for injection (WFI). The volume of the solution in the vial after reconstitution is 2.4 mL to ensure that 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 asceptic conditions.

The starting dose level will be 0.2 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 Dosage Administration Instruction (DAI) located in the Study Manual.

5.2.3. Administration

PF-06650808 will be administered on Day 1 of each 21-day cycle per the DAI as an IV infusion over approximately 60 minutes. A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 21 days. Each patient may receive PF-06650808 until disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

In the case of infusion related reactions, characterized by fever and chills, and less commonly hypotension, the sponsor should be notified and pre-treatment medication should be administered prior to subsequent infusions (in the case that the patient is able to continue on treatment as per Appendix 5). The decision to incorporate pre-medication in all patients will be made following discussions between the sponsor and the investigators. Patients should be pre-treated with acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each PF-06650808 administration. The pre-treatment medications will not be supplied by Pfizer.

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

PF-06650808 will be administered as a 60-minute (±5 minutes) IV infusion. 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 DAI for infusion rate and duration.

Medication errors may result, in this study, from the administration of the wrong drug, 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 case report form (CRF) which is a specific version of the AE page of the CRFs 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 should be captured on the medication error version of the adverse event (AE) page and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page.

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 toxicity in the previous cycle;
- In the next cycle: dose reduction based on worst toxicity 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.

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. A treatment delay or interruption of more than 14 days due to lack of recovery will result in discontinuation of the patient from the treatment.

A new cycle of treatment may begin only if:

- ANC $\geq$1,000/mm^3.
- Platelets count $\geq$75,000/mm^3.
- Non-hematologic toxicities have returned to baseline or Grade $\leq$1 severity (or, at the investigator discretion, Grade $\leq$2 if not considered a safety risk for the patient).

If these conditions are not met, treatment must be delayed by 1 week. If, after a 1-week delay, all toxicities have recovered within the limits described above treatment with PF-06650808 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-06650808 treatment resumption within 35 days of Day 1 of previous cycle, treatment with PF-06650808 will be permanently discontinued.

5.2.6. Dose Reductions

Dose reductions or delays in the administration of PF-06650808 are permitted as described below for PF-006650808 related toxicity. The sponsor should be notified when dose reductions are planned and consulted for any dose reduction related questions.

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. The reduced dose will be considered the maximum dose for all subsequent cycles for that patient. Doses should be reduced to the next lowest cohort dose level. Dose re-escalation is not allowed.

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. For patients experiencing an adverse

event related to PF-06650808 that fails to recover to CTCAE Grade 1 (or within 1 grade of starting values for pre-existing laboratory abnormalities) leading to treatment delay of >2 weeks should be discontinued unless discussed with the sponsor.

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

Event	Action
Grade 3 or 4 nonhematologic toxicity considered at least possibly related to PF-06650808 per investigator judgment (including persistent nausea, vomiting, diarrhea despite optimal medical therapy)	• Hold PF-06650808 infusion until recovery to Grade 0-1 or baseline and reduce by 1 dose level. • Discontinue PF-06650808 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 intervention should be discontinued from the study.
Hematologic toxicity considered at least possibly related to PF-06650808 per investigator judgment • Grade 4 neutropenia, ie, ANC <500/mm^3 (1.0 x 109/L) for more than 7 days. or • Febrile neutropenia, ie, fever with a single temp >38.3°C or sustained temp ≥38°C for more than 1 hour with ANC <1000/mm^3. or • Grade 4 Thrombocytopenia, ie, PLTS <25,000 mm^3 (25.0 x 109/L). or • Any grade Thrombocytopenia with bleeding.	• Hold PF-06650808 until recovery of ANC to ≥1.0 x 109/L (1,000 cells/mm^3) and platelets ≥75 x 109/L (75,000 platelets/mm^3). • Reduce PF-06650808 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.
Other grade 4 hematologic toxicity considered at least possibly related to PF-06650808 per investigator judgment	• Hold PF-06650808 until recovery to Grade 0-1 or baseline and reduce PF-06650808 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-06650808 infusion	• Discontinue treatment

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 monitor.

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

5.3. Drug Storage and Drug Accountability

The investigator, or an approved representative (eg, pharmacist), will ensure that all PF-06650808 is stored in a secure area, under recommended storage conditions and in accordance with applicable regulatory requirements. PF-06650808 should be stored at 2-8°C (36-46°F) and protected from light until ready to use. PF-06650808 should not be frozen. Specific instructions on storage and handling are provided in the DAI located in the Study Manual. To ensure adequate records, all PF-06650808 will be accounted for in the CRF and drug accountability inventory forms as instructed by the sponsor. Unless otherwise authorized by the sponsor, 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 the sponsor 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 the sponsor. Destruction must be adequately documented.

Storage conditions stated in the Investigator Brochure 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. Any temperature excursions should be reported immediately 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 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 the sponsor.

5.4. Concomitant Medication(s)

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

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. (Anonymous, 2006).[2]

CCI

All concomitant medications, blood products, as well as non drug interventions (eg, analgesic use or paracentesis) received by patients within 28 days prior to the first dose of study treatment until the Follow-Up Visit will be recorded on the CRF.

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 anticancer 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.

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 American Society of Clinical Oncology (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 American Society of Clinical Oncology (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 there is no known or expected drug-drug interaction. If so it must be approved by the sponsor.

5.4.5. 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.

5.4.6. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06650808 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06650808 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-06650808 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

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

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

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

6.2. Treatment Period

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

6.3. Follow-up Visit

For follow-up procedures see Schedule of Activities and Assessments section. Patients will return to the clinic at least 28 days, and no more than 35 days, after discontinuation of treatment to undergo review of concomitant medications, performance status, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience

toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

In the event a patient is unable to return to the clinic for the follow-up visit, telephone contact with the patient to assess 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.

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, or they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression according to RECIST 1.1;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- 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 for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

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

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the 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, electrocardiogram (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 on Day 1 of Cycle 1 before investigator product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced. 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. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

7.1.2. Adverse Events

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

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

7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories. On Day 1 of Cycle 1, the hematology and blood chemistry samples do not need to be repeated if the screening assessment is performed within 72 hours prior to dosing. Hematology and blood chemistry will be collected on Day 1, Day 8 and Day 15 of each cycle through Cycle 6. For subsequent cycles, hematology and blood chemistry will be collected on Day 1 of each cycle.

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

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

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

7.1.4. Vital Signs and Physical Examination

Patients will have a physical exam to include weight, vital signs, assessment of ECOG status and height; height will be measured at screening 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 examination, genitourinary examination is optional), the measurement of body weight, vital signs and assessment of ECOG performance status. The complete PE on Day 1 of Cycle 1 is not required if the screening complete PE is performed within 72 hours of dosing. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an adverse event in the CRF.

Abbreviated PEs, including skin assessment, 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.

Weight and body surface area (BSA) do not need to be performed at each visit; however patients should be monitored throughout the study for significant weight change. If, in the Investigator's opinion, clinically significant weight change occurs, BSA should be recalculated to determine appropriate dose.

Vital signs will include measurements of blood pressure, pulse rate and temperature (oral, tympanic or axillary). On Day 1 of each cycle, vital signs should be measured prior to infusion start (pre-dose) and 1 hour after the start of the infusion. Sitting blood pressure (BP) will be measured with the patient's arm supported at the level of the heart and recorded to the nearest mmHg sufficient. The same arm (preferably the dominant arm) should preferably be used throughout the trial. The blood pressure cuff, which has been properly sized and calibrated, should be used to measure blood pressure. The use of automated devices for measuring BP and pulse rate is acceptable. When the timing of the measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.1.5. (12-Lead) ECG

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

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

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

7.2. Pharmacokinetics Assessments

7.2.1. Blood for PK analysis of PF-06650808, Total Antibody (PF-06460005); and Unconjugated Payload (PF-06380101)

Blood samples (4 mL of whole blood for PK analysis of unconjugated payload (PF-06380101) analysis and 6 mL of whole blood for PK analysis of ADC (PF-06650808) and total antibody (PF-06460005) will be collected in appropriately labeled tubes at times specified in the Schedule of Activities. PK sampling schedule may be modified based on emerging PK data.

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

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

CCI [redacted]

CCI [redacted]. 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]

7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out central nervous system (CNS) metastases.

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

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule of Activity, 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 (Appendix 2). 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. For patients in Part 2, responses of CR or PR must be confirmed by repeat assessment no more than 4 weeks after the criteria for response are first met.

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

CCI [redacted]

7.6. Immunogenicity Evaluations

Assays to assess for anti-drug (anti-PF-06650808) antibodies (ADA) will be performed. All samples that are positive in a screening assay will be further characterized in terms of antibody specificity. Confirmed ADA responses may also be characterized for neutralizing antibodies (Nab). Patients found to have anti-PF-06650808 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 AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

Blood samples (6 mL) to provide approximately 5 mL of serum for ADA and Nab analysis will be collected into appropriately labeled tubes at times specified in the Schedule of Activities. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Study Manual.

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

CCI [redacted]. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.7. Banked Biospecimens

7.7.1. 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]

CCI [redacted]

A 4 mL blood sample 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.

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]

[redacted]

7.8. Other Assessments

7.8.1. Tumor and Medical History

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

7.8.2. Baseline Signs and Symptoms

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

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. 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 study drug 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 study treatment through last patient 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. 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.

8.5. Serious Adverse Events

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

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

8.5.1. 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 Serious Adverse Event Reporting Requirements).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (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 ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X UNL with no evidence of hemolysis and an alkaline phosphatase ≤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 by 1 X ULN **or** if the value reaches ≥3 X ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel

history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.6. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to 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 lab 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.

8.7. 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 CTC 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.

8.8. 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.

8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

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

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant women (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

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

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless 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, 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 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 EDP Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.10. Occupational Exposure

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

An occupational exposure is reported to safety within 24 hours of 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 study master file.

8.11. Withdrawal Due to Adverse Events (See also Section Patient Withdrawal)

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

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

8.12. 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.

8.13. 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.

8.13.1. 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.

8.13.2. 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.

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

9.1. Analysis sets

Data analyses will be performed on the following analysis population.

1. Safety analysis set.

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

2. Full analysis set.

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

3. Modified Intent-to-Treat (mITT) Population.

    - The modified intent-to-treat (mITT) is the analysis population that will follow the ITT principle and include patients receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment or 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.

4. 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 at the dose level of RP2D and who do not have major treatment deviations during first cycle. Patients with major treatment deviations in cycle 1 are not evaluable for the RP2D assessment. Major 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. A baseline disease assessment and at least one post-baseline disease assessment are appropriate to allow efficacy analysis.

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.

6. PD/Biomarker analysis sets.

    - The PD/Biomarker analysis population is defined as all enrolled patients with at least 1 of the PD/Biomarker evaluated at pre- and/or post-dose.

9.2. Statistical Methods and Properties

9.2.1. Part 1

Part 1 of this study employs a modified continual reassessment method (mCRM) targeting a DLT rate of 25% to estimate the MTD. The mCRM algorithm utilizes Bayesian

methodology to consistently learn about dose-toxicity relationship after each cohort's DLT response becomes available. The underlying model assumption is that DLT rate at each dose can be expressed as Pr (DLT| x)=f(x, β), where x is a quantity associated with a dose, f is a monotonically increasing function, and β is an unknown parameter with prior distribution placed on it at the beginning of the trial. The first cohort of (2-4) patients will be assigned to 0.2 mg/kg. After the first cohort's response becomes available (all patients through Day 21), the prior distribution of β is updated based on their DLT responses and becomes a posterior distribution. The current estimate of MTD is as the dose corresponding to x= f^{-1} (0.25, β), given posterior information about β (ie, DLT data + modeling), and the next cohort's dose assignment is chosen as the dose closest to this estimated MTD but not exceeding it. This process is continued until 1 of the stopping rules below is triggered.

1. Maximum sample size of 35 patients has been reached.

2. MTD has been identified with sufficient accuracy: at least 6 patients have been accumulated on a dose that is currently estimated to be the MTD and there are at least 12 patients overall enrolled in the trial.

3. All doses appear to be overly toxic and the MTD cannot be determined in the current trial setting.

Starting from the second cohort and until the end of trial, the above described mCRM algorithm constantly incorporates additional information about dose-DLT relationship learned from the data via modeling and that is reflected on the projected MTD. By design, such dose allocation procedure will eventually cluster dose assignments around the dose yielding an approximately 25% DLT rate. Because CRM derives MTD estimate from all the data accumulated at a given time and not just the last cohort's response, the procedure is capable of incorporating DLT information occurring late in the trial, ie, after the minimum required DLT follow-up of 21 days.

Like all Bayesian methods, mCRM may be sensitive to prior information placed on the model parameter β at the beginning of the trial. However, as the trial progresses and DLT data accumulates, it eventually overrules the prior information and the latter becomes less important. Furthermore, a non-informative prior distribution is used for β in this study. Although simulation was performed assuming a maximum dose of 6.4 mg/kg, actual doses may be limited at this or a lower dose level until additional information is obtained to support a higher dose exposure.

Due to binomial data variability in small samples, DLTs may be observed in a first cohort at 0.2 mg/kg simply by chance even when the true Pr(DLT at 0.2 mg/kg) is fairly low. This could result in the estimated posterior DLT rate at 0.2 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 for futility in such cases, a step-down option with dose 0.14 mg/kg (a 30% reduction from starting dose) is added to the dose grid. This dose will be explored only if a high DLT rate occurs in the first cohort assigned to 0.2 mg/kg, ie, it will not be used as a starting dose.

9.2.2. Part 2

Part 2 of this study is intended to confirm the safety and tolerability of the dose selected in Part 1 while assessing the antitumor activity of PF-06650808 in patients with TNBC. The DLT rate and its 95% confidence interval at the selected dose may be estimated.

Analyses may be performed on data from both Part 1 and Part 2 to explore the relationships between PK parameters, safety endpoints, and efficacy endpoints.

9.3. Sample Size Determination

Approximately 55 patients are expected to be enrolled in this study.

The exact sample size of the mCRM design in Part 1 cannot be pre-specified in advance because it is a dynamic feature of the design. The minimum and maximum sample sizes after which the Part 1 can be stopped and MTD declared are approximately 12 and 35 patients, respectively. Also, a minimum of 6 patients on MTD dose at Part 1 is required to establish such dose as RP2D. The actual sample size of Part 1 will depend on the underlying dose toxicity profile and variability in actual data realization.

As for the number of patients treated at each dose, it is expected that the typical number will be 2 to 4 patients for the doses actually studied. For the dose declared as MTD at the end of Part 1, this number will be 6 or more patients. However, since not every dose listed will be studied and variable cohort size is allowed, the actual number of patients treated at each dose will vary.

The sample size in Part 2 is based on clinical consideration, rather than statistical justification. Upon identification of the MTD by the mCRM method, approximately 20 patients with triple negative breast cancer will be enrolled in Part 2 to further evaluate safety and preliminary efficacy parameters.

9.4. Efficacy Analysis

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

Objective tumor response rate, progression-free survival, overall survival and clinical benefit response rate will be summarized and presented if data permits.

9.4.1. Analysis of Overall Response

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

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

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

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Clinical benefit response (CBR) is defined as a CR, PR or SD ≥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 analyses are outlined in the SAP.

9.5.1. Analysis of Pharmacokinetics

Drug concentrations of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101) will be measured using validated methods. PK parameters will be determined from the respective concentration-time data using standard noncompartmental methods. Actual sample collection times will be used for the parameter calculations. For ADC (PF-06650808) and total antibody (PF-06460005), PK parameters including maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve (AUC_{inf}, and AUC_{τ}), clearance (CL), volume of distribution (Vss), terminal elimination half-life ($t_{1/2}$), and accumulation ratio (R_{ac}) will be calculated. For unconjugated payload (PF-06380101), PK parameters including maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve (AUC_{inf}, and AUC_{τ}), terminal elimination half-life ($t_{1/2}$), and accumulation ratio (R_{ac}) will be calculated.

Drug concentrations of ADC (PF-06650808), total antibody (PF-06460005) and unconjugated payload (PF-06380101) 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 (ORR) data from both Part 1 and Part 2 will be pooled. PK/PD analyses will be conducted to explore the exposure-response relationship using appropriate model-based methods to assist MTD estimation.

CCI [redacted]

9.5.3. Immunogenicity

The development of anti-PF-06650808 antibodies will be measured using validated assays. Listings and summary tabulations of the anti-PF-06650808 antibody data at baseline and post randomization will be generated.

Potential impact of immunogenicity on PK and clinical responses including PD markers, safety/tolerability and efficacy of PF-06650808 will be explored, if data is warranted.

9.6. Safety Analysis

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

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

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

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

9.6.1. Analysis of Primary Endpoint

DLT is the primary endpoint of the dose escalation phase of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in Section Dose Escalation Phase (Part 1). AEs constituting DLTs will be listed per dose level. Because the intent is to find a desirable dose that meets the tolerability criteria based on DLT rate while demonstrating clinical activity based on response rate, descriptive statistics (n, frequency and percentage) will be reported. Corresponding listings of data will be generated.

9.6.2. Analysis of Secondary Safety Endpoints

9.6.2.1. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study 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 laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

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

9.6.3. ECG

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

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

Safety QTcF

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

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

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

9.7. Data Safety Monitoring Committee

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

- Surveillance for SAEs according to regulatory guidelines;
- Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level in an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

End of Trial is defined as Last Patient Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06650808 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), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

The timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, Food and Drug Administration (FDA)-approved products, Pfizer posts results within one year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last patient, last visit (LPLV);

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

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

www.pfizer.com

Pfizer posts clinical trial results on www.pfizer.com for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an FDA-approved Pfizer product with a LSLV on or after 27-Sep-2007 for which Basic Results were posted on www.clinicaltrials.gov.

<u>EudraCT</u>

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01-May-2004, regardless of the marketing status of the compound.

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.

16. REFERENCES

1. Andre F, and Zielinski CC. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. Ann Oncol 2012;23;vi46-vi51.

2. Anonymous. Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. *JCO Jul 1, 2006:3187-3205*

3. Bellavia D, Campese AF, Alesse E, et al. Constitutive activation of NF-kappaB and T-cell leukemia/lymphoma in Notch3 transgenic mice. EMBO J 2000; 19(13):3337-48.

4. Bellavia D, Checquolo S, Campese AF, et al. Notch3: from subtle structural differences to functional diversity. *Oncogene* 2008; 27(38):5092-8.

5. Domenga V, Fardoux P, Lacombe P, et al. Notch3 is required for arterial identity and maturation of vascular smooth muscle cells. *Genes Dev* 2004; 18(22):2730-5.

6. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011; 474:609-15.

7. Goodman SN, Zahurak ML, Piantadosi S. Some practical improvements in the Continual Reassessment Method for Phase 1 Studies. *Stat Med.* 1995;4:1149-1161.

8. Haruki N, Kawaguchi KS, Eichenberger S, et al. Dominant-negative Notch3 receptor inhibits mitogen-activated protein kinase pathway and the growth of human lung cancers. Cancer Res 2005; 65(9):3555-61.

9. Hirose H, Ishii H, Mimori K, et al. Notch pathway as candidate therapeutic target in Her2/Neu/ErbB2 receptor-negative breast tumors. *Oncol Rep.* 2010; 23(1):35-43.

10. Hu C, Dievart A, Lupien M, et al. Overexpression of activated murine Notch1 and Notch3 in transgenic mice blocks mammary gland development and induces mammary tumors. Am J Pathol 2006; 168(3):973-90.

11. Jia L, Yu G, Zhang Y, Wang MM. Lysosome-dependent degradation of Notch3. *Int J Biochem Cell Biol*. 2009; 41(12):2594-8.

12. Jung SG, Kwon YD, Song JA, et al. Prognostic significance of Notch 3 gene expression in ovarian serous carcinoma. *Cancer Sci.* 2010; 101(9):1977-83.

13. Liedtke C, Mazouni C, Hess KR, et. al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26:1275-1281.

14. O'Quigley J, Pepe M, Fisher L. Continual Reassessment Method. A practical design for phase 1 clinical trials in cancer. *Biometrics*. 1990;46:33-48.

15. Pal SK, Childs BH, and Pegram M. Triple negative breast cancer: unmet medical needs. Breast Cancer Res Treat 2011; 125:627-636.

16. Park JT, Li M, Nakayama K, et al. Notch3 gene amplification in ovarian cancer. Cancer Res 2006; 66(12):6312-8.

17. Zheng Y, de la Cruz CC, Sayles LC, et al. A rare population of CD24(+)ITGB4(+)Notch(hi) cells drives tumor propagation in NSCLC and requires Notch3 for self-renewal. *Cancer Cell* 2013; 24(1):59-74.

Appendix 1. Abbreviations

Abbreviation	Term
ADA	Anti-drug Antibody
ADC	Anti-Drug Congugate
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
C1D1	Cycle 1 Day 1
CBC	Complete Blood Count
CLX	Cell Line Xenograft
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DAI	Dosage Administration Instruction
DFS	Disease Free Survival
DLT	Dose Limiting Toxicities
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
HNSTD	Highest Non-Severely Toxic Dose
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IND	Investigational New Drug
ITT	Intent-to-Treat
IV	Intravenous
mg/kg	Milligram/kilogram
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
N/A	Not Applicable
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PDX	Patient Derived Xenograft
PK	Pharmacokinetic
PFS	Progression Free Survival
PR	Partial Response

PR	Pulse Rate
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
TNBC	Triple Negative Breast Cancer
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

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.

Patientive progression

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

Table 1. Objective Response Status at each Evaluation			
Target Lesions	**Non-target Disease**	**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

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

Appendix 3. ECOG Performance Status

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

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

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

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

Appendix 5. Management of Infusion Related Reactions Including Allergic Reactions, Cytokine Release Syndrome or Anaphylaxis

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

The following treatment guidelines should be employed:

If chills and fever occur, the infusion should be interrupted. Patients may be treated symptomatically and the infusion should be restarted at 50% of the original rate.

NCI-CTCAE Grade 1 allergic reaction or cytokine release syndrome

- Monitor for worsening condition. If the reaction worsens, stop the infusion. Institute premedication for subsequent infusions as per Section Administration.

NCI-CTCAE Grade 2 allergic reaction or cytokine release syndrome

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

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

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

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

- Stop the PF-06647263 infusion immediately and disconnect infusion tubing from the patient.
- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, and others as medically indicated.

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

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

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

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

- Once the PF-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.

CCI
[redacted]