A PHASE 1 DOSE ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF PF-06671008 IN PATIENTS WITH ADVANCED SOLID TUMORS

Compound:	PF-06671008
Compound Name:	Not applicable
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	Not applicable
Protocol Number:	B7831001
Phase:	Phase 1

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PROTOCOL SUMMARY

Background and Rationale:

Bispecific redirected T-cell-engaging therapies have demonstrated proof of concept (POC) in hematological malignancies with the recent US FDA (United States Food and Drug Administration) approval of the bispecific agent blinatumomab[4] for the treatment of acute lymphoblastic leukemia (ALL). This modality has also shown promise for the treatment of solid tumors with several bispecific agents targeting solid tumors in early clinical studies.

Bispecific redirected T cell molecules are typically recombinant bispecific antibody fragments with one binding domain targeting a specific tumor antigen of choice and the other binding domain targeting the T cell receptor complex, most often the cluster of differentiation 3 epsilon (CD3ε) molecule. Similar to a standard synapse formation, once a threshold of bispecific mediated-immune synapses have formed, CD3ε signals the T cell to initiate a cytotoxic response toward the adjacent tumor cell expressing the specific antigen. The most clinically advanced bispecific platforms that have been reported are typically smaller protein molecules, around 50 kilodalton (kD), with short circulating half-lives ($t_{1/2}$ ~1 hour) that require constant infusion through the use of a pump to achieve a stable exposure to the therapeutic molecule.

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Study Objectives and Endpoints:

Dose Escalation (Part 1) Objectives

Primary Objective

- To assess safety and tolerability of increasing dose levels of PF-06671008 administered in patients with advanced solid tumors for whom no standard therapy is available in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile;
- To characterize the single and multiple dose pharmacokinetics (PK) of PF-06671008;
- To evaluate the immunogenicity of PF-06671008;
- To document any anti-tumor activity.

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Dose Expansion (Part 2 Objectives)

Primary Objective

- To confirm safety and tolerability and explore preliminary evidence of anti-tumor activity of PF-06671008 at the RP2D in patients with P-cadherin expressing advanced CRC, TNBC or NSCLC.

Secondary Objectives

- To evaluate the overall safety profile at the RP2D;
- To characterize the single and multiple dose PK of PF-06671008;
- To evaluate the immunogenicity of PF-06671008;
- To evaluate preliminary anti-tumor activity through time to event endpoints.

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Primary Endpoints

Primary Endpoint (Part 1)

- First cycle Dose-Limiting Toxicities (DLTs).

Primary Endpoint (Part 2)

- Objective response (OR) as determined by the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 (Appendix 4) criteria.

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03), (Appendix 6) timing, seriousness, and relationship to study therapy;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;
- Vital sign abnormalities;
- Pharmacokinetic parameters of PF-06671008 Single Dose (SD) - C_{max}, T_{max}, $AUC_{sd,\tau}$, $t_{1/2}$, AUC_{inf}, and CL for intravenous (IV) administration or apparent clearance (CL/F) for subcutaneous (SC) administration as data permit. Multiple Dose (MD) (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, CL for IV or CL/F for SC, volume of distribution (V_{ss}) for IV or volume of distribution at steady state (V_{ss}/F) for SC, and R_{ac} ($AUC_{ss,\tau}$,/$AUC_{sd,\tau}$) as data permit;
- Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies against PF-06671008;
- Objective response, as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 – Part 1 only;
- Progression Free Survival (PFS) and Overall Survival (OS) – Part 2 only.

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Study Design

This is a Phase 1, open-label, multi-center, multiple-dose, safety, PK CCI [redacted] study of single-agent PF-06671008. This study contains two parts, dose escalation (Part 1) followed by dose expansion (Part 2). Sequential cohorts of patients with tumor types with the potential to have P-cadherin expression (see Appendix 2), and that are not candidates for regimens known to provide clinical benefit, will receive escalating doses of PF-06671008, in Part 1 of the study. In addition, at clinically relevant dose levels with the IV or SC route of administration of 100 ng/kg or higher (ie, doses where the exposure is near the target effective exposure) where the safety is confirmed in the first 2-4 patients dosed, approximately up to 5 additional patients with colorectal, triple negative breast, non-small cell lung cancer or squamous cell carcinoma of the head and neck may be enrolled. Pfizer internal data shows high level of P-cadherin is frequently found in these tumors. Paired biopsies will be required for these additional patients. Part 2 will evaluate the dose selected from Part 1 in patients with P-cadherin expressing TNBC, CRC or NSCLC.

Up to approximately 152 patients are expected to be enrolled in the study overall. The actual number of patients enrolled will depend on the tolerability of PF-06671008 and the number of dose levels required to identify the MTD.

PF-06671008 will be administered as a weekly intravenous (IV) infusion in 21-day cycles with a starting dose of 1.5 ng/kg. There will be a minimum 72-hour interval between the first dose administered to each of the initial patients (ie, patients contributing to initial DLT evaluation) enrolled at a new dose level due to the unknown time course of possible infusion-related reaction or cytokine release. All patients will be observed in-patient for at least 24 hours after the first dose on Cycle 1 Day 1 (C1D1). At doses of 100 ng/kg or higher, especially when the total dose exceeds 10,000 ng, additional in-patient overnight observation for subsequent doses beyond C1D1 may be considered based on the investigator's discretion and should be discussed with Pfizer.

In addition, PF-06671008 will be administered in cohorts as a weekly subcutaneous (SC) injection in 21-day cycles with a starting dose equal to the dose level selected as the IV Dose Prime (See Section Evaluation of a Priming Dose). Dose escalation cohorts with PF-06671008 SC administration will be evaluated in parallel with dose escalation cohorts evaluating PF-06671008 IV administration (See Section Criteria for Dose Escalation). For cohorts where a SC route of administration will be evaluated, there will also be a minimum 72-hour interval between the first dose administered to each of the initial patients (ie, patients contributing to initial DLT evaluation) enrolled at a new dose level due to the unknown time

course of possible cytokine release. All patients who will be dosed subcutaneously will be observed in-patient for at least 48 hours after the first dose on Cycle 1 Day 1 (C1D1). Additional in-patient observation for subsequent cycles beyond C1D1 may be considered based on the investigator's discretion and should be discussed with Pfizer.

Evaluation of either the IV or SC route of administration may be discontinued based on emerging clinical and safety data.

Study Treatment

Increasing dose levels of PF-06671008 administered weekly will be evaluated using a modified toxicity probability interval (mTPI) method that targets a MTD associated with a 27.5% probability of DLT. Part 1 will follow a mTPI method initially with cohorts of 1-2 patients each and a primary DLT observation period of 21 days following the first dose (C1D1).

Based on the toxicity study results, the evaluation of a priming dose to allow subsequent higher level dose administration may be instituted in this study. The initial priming dose will be defined to facilitate subsequent dose escalation towards establishing the MTD of a dosing regimen that includes a priming dose. The study aims to determine a MTD for an IV dose regimen that does not include a priming dose, and an independent MTD for an IV dose regimen that includes a priming dose. In addition, the study aims to similarly determine a MTD for PF-06671008 administered subcutaneously that may or may not include a priming dose.

If a dose level induces symptoms consistent with cytokine release syndrome (CRS) of Grade 3 lasting >24 hours considered not to be due to an infusion related reaction (IRR), allergic reaction, anaphylaxis or other causes in a cohort of 2-4 patients after the initial infusion, an additional 1-4 patients (up to approximately 6 patients overall) will be enrolled at that dose to confirm implementation of a priming dose (Dose Prime) for subsequent cohorts. If an additional confirmed CRS of Grade 3 lasting >24 hours is observed at that dose, then a lower dose, which has been evaluated in at least 2-4 patients will be chosen as a priming dose (Dose Prime) for subsequent cohorts. If a dose level induces confirmed CRS of Grade 4 in a cohort of 2-4 patients, then a lower dose, which has been evaluated in at least 2-4 patients, will be chosen as a priming dose (Dose Prime) for subsequent cohorts. If a Dose Prime is selected, dose escalation will continue to determine the MTD of a dose regimen that includes a priming dose. The evaluation of a Dose Prime may be implemented for both the IV and/or SC routes of administration.

After confirmation of the safety of Dose Prime, the treatment schedule will implement the inclusion of the fixed priming dose as the first dose (C1D1) followed by a second dose (C1D8) that will continue to be escalated in subsequent cohorts following an mTPI method in cohorts of 2-4 patients. The primary DLT observation period for cohorts that include Dose Prime will be 21 days following the first dose (C1D1).

SCHEDULE OF ACTIVITIES FOR INTRAVENOUS ADMINISTRATION

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

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

		Treatment Period							Post Treatment	
		Cycle 1 (1 cycle = 21 days)				Cycles ≥2				
Visit Identifier	**Screen[1] (≤28 days prior to registration)**	**Day 1**	**Day 4**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Treatment[21]**	**Follow-up[22]**
Visit Window (days)				**(±1)**	**(±1)**	**(±1)**	**(±2)**	**(±2)**		
Informed consent[2]	X									
Tumor history	X									
Medical history	X									
Complete physical examination	X	X[3]							X	
Abbreviated physical examination				X	X	X	X	X		X
Height	X									
Weight	X	X				X			X	
Vital signs[4]	X	X	X	X	X	X	X	X	X	X
Performance status[5]	X	X				X			X	X
Contraception check	X	X				X			X	
Laboratory										
Unique screening laboratory tests[6]	X									
Hematology[7]	X	X	X	X	X	X	X	X	X	X
Blood Chemistry[8]	X	X	X	X	X	X	X	X	X	X
Coagulation[9]	X	X		X	X	X			X	X
Urinalysis[10]	X	X		X	X	X			X	X
Pregnancy test[11]	X	X				X			X	

		Treatment Period							Post Treatment	
		Cycle 1 (1 cycle = 21 days)				Cycles ≥2				
Visit Identifier	**Screen[1] (≤28 days prior to registration)**	**Day 1**	**Day 4**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Treatment[21]**	**Follow-up[22]**
Visit Window (days)				**(±1)**	**(±1)**	**(±1)**	**(±2)**	**(±2)**		
(12 lead) ECG[12]	X	X		X	X	X	X (Cycle 2 only)	X (Cycle 2 only)	X	
Registration and Treatment										
Registration[13]		X								
Study treatment[14]		X		X	X	X	X	X		
Inpatient Monitoring[15]		X		X[15]						
Tumor assessments										
CT or MRI scan or equivalent[16]	X					X (every 6 weeks beginning at Cycle 3 and then every 12 weeks beginning at Cycle 8)			X[16]	
Other samplings										
CCI [redacted]										
CCI [redacted]										
Blood samples for PF-06671008	Refer to Schedule of Pharmacokinetic CCI [redacted] Assessments for Intravenous Administration									
Blood sample for Anti-PF-06671008 Antibody										
CCI [redacted]										
Other clinical assessments										
Adverse events[18]		X	X	X	X	X	X	X	X	X
Concomitant Treatments[19]	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[20]	X									

* Visit windows are calculated off the first day of each cycle. See Dose Delays section for calculation of visit windows for Cycle 1.

Abbreviations: CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

1. **Screening:** to be obtained within 28 days prior to registration.
2. **Informed Consent:** must be obtained prior to undergoing any study specific procedures. May be obtained more than 28 days prior to registration.
3. **Complete Physical Examination:** No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment is performed within 3 days of dosing.
4. **Vital Signs:** Includes temperature (oral, tympanic, temporal or axillary), blood pressure (BP) and pulse rate to be recorded in a supine or seated position. On each dosing day, vitals should be measured prior to infusion start (pre-dose) and at the end of the PF-06671008 infusion. In addition, pulse oximetry is to be collected on dosing days prior to infusion start (pre-dose) and at the end of the PF-06671008 infusion as part of the vital sign evaluation.
5. **Performance Status:** Use Eastern Cooperative Oncology Group (ECOG). – see Appendix 3.
6. **Unique Screening Laboratory Tests:** Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and human immunodeficiency virus (HIV) as well as follicle stimulating hormone (FSH) for post-menopausal women who are amenorrheic for at least 12 consecutive months only. Samples will be analyzed locally.
7. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, white blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils and basophils. No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing. Assessments performed at all subsequent dosing visits should be performed within 48 hours prior to dosing. Samples will be analyzed locally.
8. **Blood Chemistry:** Should include sodium, potassium, chloride, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), and C-reactive protein (CRP). Measurement of CRP not required after C2D1 if within normal range or similar to baseline levels; however, CRP should be measured anytime cytokine release syndrome is suspected and not already scheduled to be measured (eg, Cycle 2). No need to repeat on C1D1 if baseline assessment performed within 3 days prior to dosing. Assessments performed at all subsequent dosing visits should be performed within 48 hours prior to dosing. Samples will be analyzed locally.
9. **Coagulation:** Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing. Samples will be analyzed locally.
10. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing. Samples will be analyzed locally.
11. **Pregnancy Test:** 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 treatment – once at the start of screening and once on C1D1 immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment and additional whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board (IRB) or if required by local regulations.
12. **Triplicate 12-Lead ECG:** Triplicate ECGs to be collected before dosing and at the end of the PF-06671008 infusion on dosing days as outlined above. At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
13. **Registration:** Patient enrollment number and dose level allocation provided by Pfizer Inc. Registration should occur before any other Day 1 activities are performed.
14. **Study Treatment:** PF-06671008 will be administered once every 7 days as an intravenous (IV) infusion. For Cohort 1 only, the infusion will be given over 60 minutes (±5 minutes). For Cohort 2 and beyond, the infusion will be given over 120 minutes (±15 minutes).
15. **Inpatient Monitoring:** Patients receiving PF-06671008 intravenously will be admitted for inpatient monitoring for at least 24 hours following the first administration of study treatment (C1D1). For patients enrolled in cohorts where Dose Prime will be given on C1D1 followed by a higher dose on C1D8, patients will also be admitted for inpatient monitoring for at least 24 hours (for cohorts evaluating IV route of administration) following the second dose (C1D8). Patients may be released only after the investigator has confirmed the patient has not exhibited signs of a cytokine reaction. Patients should complete the required study specific laboratory assessments as detailed in the Schedule of Pharmacokinetic, CCI [redacted] Assessment table and should be monitored per local standard practice for inpatient monitoring. At doses of 100 ng/kg or higher, especially when the total dose exceeds 10,000 ng, additional in-patient overnight observation for subsequent doses beyond C1D1 may be considered based on the investigator's discretion and should be discussed with Pfizer.

16. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans or equivalent. The same modality should be completed, if possible throughout the study. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases; patient ineligible if positive for CNS metastases. CT or MRI scans to be done every 6 weeks (±7 days) from the start of study treatment until disease progression by irRECIST or death, or until permanent discontinuation of study treatment. The frequency will change to every 12 weeks (±7 days) beginning at Cycle 8. Response (complete response (CR)/partial response (PR)) and disease progression will be confirmed with two consecutive timepoints at least 4 weeks apart (in the absence of rapid clinical deterioration for progression). Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.
17. **Tumor Tissue Samples:** Patients enrolled in Part 1 and Part 2 will provide archival formalin-fixed paraffin embedded material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or fresh pre-treatment biopsy if the archival tumor is not available (tissue blocks are preferable, but freshly-cut paraffin sections are acceptable and must comprise 10 paraffin section, 4-microns in thickness, cut within 1 week of submission, and place individually on unstained, unbaked charged glass microscope slides) for evaluation of P-cadherin expression level. The mandated archival tumor sample will be assayed for P-cadherin expression levels retrospectively in Part 1 and prospectively for eligibility for Part 2. Additionally, fresh pre-treatment biopsy (ie, collected during screening) and on-treatment biopsy samples on Cycle 3 Day 1 (±5 days) are optional for the initial 2-4 patients enrolled in each cohort in Part 1. Fresh pre- treatment biopsy (ie, collected during screening) and on-treatment biopsy samples on Cycle 3 Day 1 (±5 days) will be mandatory for patients enrolled in Part 1 in cohorts with clinically relevant dose levels of 100 ng/kg or higher where the safety has been confirmed in the initial 2-4 patients and a decision is made to expand a dose for further evaluation and for patients enrolled in Part 2. Additional unscheduled on-treatment biopsies may be collected, if indicated, and agreed upon by the sponsor and investigator and agreed to by the patient. The screening biopsy should preferably be completed after all eligibility criteria have been verified. Fresh pre-treatment and on-treatment biopsies should be taken from the same lesion, not previously irradiated, if possible. An archival biopsy collected ≤6 months prior to study start may be substituted for the pre-treatment biopsy if the patient received no treatment between the collection of this tumor biopsy and study start. If the patient discontinues the study before the scheduled on treatment biopsy (C3D1), the patient will be asked to provide a fresh biopsy at the End of Treatment visit.
18. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Patients must be followed for AEs for 28 days after the last study 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 serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last study treatment administration. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
19. **Concomitant Treatments:** All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
20. **Ophthalmic Examination:** An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes Best Corrected Visual Acuity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic Exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow up.
21. **End of Treatment Visit (EOT):** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
22. **Follow-Up:** At least 28 days, and no more than 35 days, after discontinuation of treatment, patients will return to obtain these assessments as well as an evaluate the 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. Subsequent to the Follow-Up visit, patients should be contacted by telephone every 8 weeks (±7 days) to obtain information on subsequent anti-cancer treatment and overall survival for up to two years from the date of randomization.

Schedule of Pharmacokinetic, CCI [redacted] Assessments for Intravenous Administration – Cohort 1 Only

Visit Identifier	Screen	Cycle 1															Cycle 2										Subsequent Cycles						EOT
Study Day		1					2	4	8					9	11	15		1			2	4	8		15		1		8		15		
Hours Pre-/Post-Dose*		0	1	2	4	8	24	72	0	1	2	4	8	24	72	0	1	0	1	4	24	72	0	1	0	1	0	1	0	1	0	1	
CCI [redacted]																																	
Blood samples for PF-06671008		X	X		X		X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for Anti-PF-06671008 Antibody		X														X		X										X					X
CCI [redacted]																																	
CCI [redacted]																																	

Schedule of Pharmacokinetic, CCI Assessments for Intravenous Administration – Part 1 Cohort 2 and Beyond and Part 2

Visit Identifier	Screen	Cycle 1														Cycle 2										Subsequent Cycles						EOT
Study Day		1				2	4	8			9	11	15			1		2	4	8		15				1		8		15		
Hours Pre-/Post-Dose*		0	2◊	4	8	24	72	0	2◊	4	8	24	72	0	2◊	0	2◊	4	24	72	0	2◊	0	2◊	0	2◊	0	2◊	0	2◊	
CCI																																
Blood samples for PF-06671008		X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for Anti-PF-06671008 Antibody[3]		X												X		X										X						X
CCI																																
CCI																																

SCHEDULE OF ACTIVITIES FOR SUBCUTANEOUS ADMINISTRATION

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

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

		Treatment Period										Post Treatment	
		Cycle 1 (1 cycle = 21 days)						Cycles ≥2					
Visit Identifier	**Screen[1] (≤28 days prior to registration)**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**End of Treatment[22]**	**Follow-up[23]**
Visit Window (days)						**(±1)**	**(±1)**	**(±1)**		**(±2)**	**(±2)**		
Informed consent[2]	X												
Tumor history	X												
Medical history	X												
Complete physical examination	X	X[3]										X	
Abbreviated physical examination						X	X	X		X	X		X
Height	X												
Weight	X	X						X				X	
Vital signs[4]	X	X			X	X	X	X		X	X	X	X
Performance status[5]	X	X						X				X	X
Contraception check	X	X						X				X	
Laboratory													
Unique screening laboratory tests[6]	X												
Hematology[7]	X	X			X	X	X	X		X	X	X	X
Blood Chemistry[8]	X	X			X	X	X	X		X	X	X	X
Coagulation[9]	X	X				X	X	X				X	X
Urinalysis[10]	X	X				X	X	X				X	X
Pregnancy test[11]	X	X						X				X	

		Treatment Period										Post Treatment	
		Cycle 1 (1 cycle = 21 days)						Cycles ≥2					
Visit Identifier	**Screen[1] (≤28 days prior to registration)**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**End of Treatment[22]**	**Follow-up[23]**
Visit Window (days)						**(±1)**	**(±1)**	**(±1)**		**(±2)**	**(±2)**		
(12 lead) ECG[12]	X	X	X					X (Cycle 2 only)	X (Cycle 2 only)			X	
Registration and Treatment													
Registration[13]		X											
Study treatment[14]		X				X	X	X		X	X		
Injection Site Tolerability Assessment[15]		X	X			X	X	As clinically indicated					
Inpatient Monitoring[16]		→				X[16]							
Tumor assessments													
CT or MRI scan or equivalent[17]	X							X (every 6 weeks beginning at Cycle 3 and then every 12 weeks beginning at Cycle 8)				X[17]	
Other samplings													
CCI													
CCI													
Blood samples for PF-06671008	Refer to Schedule of Pharmacokinetic, CCI Assessments for Subcutaneous Administration												
Blood sample for Anti-PF-06671008 Antibody													
CCI													

		Treatment Period										Post Treatment	
		Cycle 1 (1 cycle = 21 days)						Cycles ≥2					
Visit Identifier	**Screen[1] (≤28 days prior to registration)**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**End of Treatment[22]**	**Follow-up[23]**
Visit Window (days)						**(±1)**	**(±1)**	**(±1)**		**(±2)**	**(±2)**		
Other clinical assessments													
Adverse events[19]		X		X	X	X	X	X		X	X	X	X
Concomitant Treatments[20]	X	X		X	X	X	X	X		X	X	X	X
Ophthalmic Examination[21]	X												

* Visit windows are calculated off the first day of each cycle. See Dose Delays section for calculation of visit windows for Cycle 1.
Abbreviations: CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

1. **Screening:** to be obtained within 28 days prior to registration.
2. **Informed Consent:** must be obtained prior to undergoing any study specific procedures. May be obtained more than 28 days prior to registration.
3. **Complete Physical Examination:** No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment is performed within 3 days of dosing.
4. **Vital Signs:** Includes temperature (oral, tympanic, temporal or axillary), blood pressure (BP) and pulse rate to be recorded in a supine or seated position. On each dosing day, vitals should be measured prior to the PF-06671008 injection. In addition, pulse oximetry is to be collected on dosing days prior to the PF-06671008 injection as part of the vital sign evaluation.
5. **Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 3.
6. **Unique Screening Laboratory Tests:** Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and human immunodeficiency virus (HIV) as well as follicle stimulating hormone (FSH) for post-menopausal women who are amenorrheic for at least 12 consecutive months only. Samples will be analyzed locally.
7. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, white blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils and basophils. No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing. Assessments performed at all subsequent dosing visits should be performed within 48 hours prior to dosing. Samples will be analyzed locally.
8. **Blood Chemistry:** Should include sodium, potassium, chloride, BUN (or urea), uric acid, creatinine, glucose, calcium, magnesium, phosphorus, albumin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), and C-reactive protein (CRP). Measurement of CRP not required after C2D1 if within normal range or similar to baseline levels; however, CRP should be measured anytime cytokine release syndrome is suspected and not already scheduled to be measured (eg, Cycle 2). No need to repeat on C1D1 if baseline assessment performed within 3 days prior to dosing. Assessments performed at all subsequent dosing visits should be performed within 48 hours prior to dosing. Samples will be analyzed locally.
9. **Coagulation:** Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing. Samples will be analyzed locally.

10. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing. Samples will be analyzed locally.
11. **Pregnancy Test:** 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 treatment – once at the start of screening and once on C1D1 immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment and additional whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board (IRB) or if required by local regulations.
12. **Triplicate 12-Lead ECG:** Triplicate ECGs to be collected before dosing and at 24 hours post the Cycle 1 Day 1 and Cycle 2 Day 1 PF-06671008 injections. At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
13. **Registration:** Patient enrollment number and dose level allocation provided by Pfizer Inc. Registration should occur before any other Day 1 activities are performed.
14. **Study Treatment:** PF-06671008 will be administered once every 7 days as a subcutaneous injection.
15. **Injection Site Tolerability Assessment:** Assessment of each injection should be conducted for at least 1 hour following each treatment administration in Cycle 1. In addition, an assessment should be performed 24 hours (±1 hour) after the Cycle 1 Day 1 dose. Injection site tolerability assessments should continue after each dosing visit in Cycle 2 and beyond, only if injection site pain or injection site reaction (ISR) characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve.
16. **Inpatient Monitoring:** Patients receiving PF-06671008 subcutaneously will be admitted for inpatient monitoring for at least 48 hours following the first administration of study treatment (C1D1). For patients enrolled in cohorts where Dose Prime will be given on C1D1 followed by a higher dose on C1D8, patients will also be admitted for inpatient monitoring for at least 48 hours (for cohorts evaluating SC route of administration) following the second dose (C1D8). Patients may be released only after the investigator has confirmed the patient has not exhibited signs of a cytokine reaction. Patients should complete the required study specific laboratory assessments as detailed in the Schedule of Pharmacokinetic, CCI [redacted] for Cohorts Where PF-06671008 Will Be Administered Subcutaneously table and should be monitored per local standard practice for inpatient monitoring. At doses of 100 ng/kg or higher, especially when the total dose exceeds 10,000 ng, additional in-patient overnight observation for subsequent doses beyond C1D1 may be considered based on the investigator's discretion and should be discussed with Pfizer.
17. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans or equivalent. The same modality should be completed, if possible throughout the study. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases; patient ineligible if positive for CNS metastases. CT or MRI scans to be done every 6 weeks (±7 days) from the start of study treatment until disease progression by irRECIST or death, or until permanent discontinuation of study treatment. The frequency will change to every 12 weeks (±7 days) beginning at Cycle 8. Response (complete response (CR)/partial response (PR)) and disease progression will be confirmed with two consecutive timepoints at least 4 weeks apart (in the absence of rapid clinical deterioration for progression). Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Tumor assessments should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.
18. **Tumor Tissue Samples:** Patients enrolled in Part 1 and Part 2 will provide archival formalin-fixed paraffin embedded material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or fresh pre-treatment biopsy if the archival tumor is not available (tissue blocks are preferable, but freshly-cut paraffin sections are acceptable and must comprise 10 paraffin section, 4-microns in thickness, cut within 1 week of submission, and place individually on unstained, unbaked charged glass microscope slides) for evaluation of P-cadherin expression level. The mandated archival tumor sample will be assayed for P-cadherin expression levels retrospectively in Part 1 and prospectively for eligibility for Part 2. Additionally, fresh pre-treatment biopsy (ie, collected during screening) and on-treatment biopsy samples on Cycle 3 Day 1 (±5 days) are optional for the initial 2-4 patients enrolled in each cohort in Part 1. Fresh pre- treatment biopsy (ie, collected during screening) and on-treatment biopsy samples on Cycle 3 Day 1 (±5 days) will be mandatory for patients enrolled in Part 1 in cohorts with clinically relevant dose levels of 100 ng/kg or higher where the safety has been confirmed in the initial 2-4 patients and a decision is made to expand a dose for further evaluation and for patients enrolled in Part 2. Additional unscheduled

on-treatment biopsies may be collected, if indicated, and agreed upon by the sponsor and investigator and agreed to by the patient. The screening biopsy should preferably be completed after all eligibility criteria have been verified. Fresh pre-treatment and on-treatment biopsies should be taken from the same lesion, not previously irradiated, if possible. An archival biopsy collected ≤6 months prior to study start may be substituted for the pre-treatment biopsy if the patient received no treatment between the collection of this tumor biopsy and study start. If the patient discontinues the study before the scheduled on treatment biopsy (C3D1), the patient will be asked to provide a fresh biopsy at the End of Treatment visit.

19. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Patients must be followed for AEs for 28 days after the last study 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 serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last study treatment administration. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
20. **Concomitant Treatments:** All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
21. **Ophthalmic Examination:** An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes Best Corrected Visual Acuity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic Exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow up.
22. **End of Treatment Visit (EOT):** 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 obtain these assessments as well as an evaluate the 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. Subsequent to the Follow-Up visit, patients should be contacted by telephone every 8 weeks (±7 days) to obtain information on subsequent anti-cancer treatment and overall survival for up to two years from the date of randomization.

Schedule of Pharmacokinetic, CCI [redacted] Assessments for Subcutaneous Administration

Visit Identifier	Screen	Cycle 1												Cycle 2								Subsequent Cycles			EOT
Study Day		1			2	3	5	8			9	10	15	1			2	3	8	15		1	8	15	
Hours Pre-/Post-Dose*		0+	4	8	24	48	96	0	4	8	24	48	0	0	4	8	24	48	0	0		0	0	0	
CCI [redacted]																									
Blood samples for PF-06671008		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Blood samples for Anti-PF-06671008 Antibody[3]		X											X	X								X			X

CCI [redacted]

CCI [redacted]

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06671008 is a bi-specific T-cell-engaging therapy being developed 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

Bispecific redirected T-cell-engaging therapies have demonstrated proof of concept (POC) in hematological malignancies with the recent United States Food and Drug Administration (US FDA) approval of the bispecific agent blinatumomab[4] for the treatment of acute lymphoblastic leukemia (ALL). This modality has also shown promise for the treatment of solid tumors with several bispecific agents targeting solid tumors in early clinical studies.

Bispecific redirected T cell molecules are typically recombinant bispecific antibody fragments with one binding domain targeting a specific tumor antigen of choice and the other binding domain targeting the T cell receptor complex, most often the cluster of differentiation 3 epsilon (CD3ε) molecule. Similar to a standard synapse formation, once a threshold of bispecific mediated-immune synapses have formed, CD3ε signals the T cell to initiate a cytotoxic response toward the adjacent tumor cell expressing the specific antigen. The most clinically advanced bispecific platforms that have been reported are typically smaller protein molecules, around 50 kD, with short circulating half-lives ($t_{1/2}$ ~1 hour) that require constant infusion through the use of a pump to achieve a stable exposure to the therapeutic molecule.

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The cadherin superfamily includes classical cadherins, protocadherins, and desmosomal cadherins. Classical cadherins constitute a family of molecules that mediate calcium-dependent cell-cell adhesion and are localized at the adherens junctions. Their intracellular domains directly interact with cytoplasmic catenins that link to the actin cytoskeletal network, providing the molecular basis for stable cell interactions. The cadherin/catenin complex, as well as the signaling pathways controlled by this structure, represent a major regulatory mechanism that guide cell fate decisions, through its influence on cell growth, differentiation, motility, and survival. Classical cadherins include the E-cadherin (CDH1), N cadherin (CDH2) and P-cadherin (CDH3). P-cadherin expression has been reported to correlate with increased tumor cell motility and invasiveness when overexpressed. Elevated expression of P-cadherin has been reported in various tumors, including breast, gastric, endometrial, colorectal, lung and pancreatic cancers, and is correlated with poor survival of breast cancer patients.[7,10,16,19,20,22] In contrast, significantly lower levels of the P-cadherin gene expression have been detected in normal tissues.[10]

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TNBC is a heterogeneous disease constituting approximately 15-20% of breast cancers and is characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PgR), and the absence of human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification. It occurs more frequently in women less than 50 years old and generally behaves more aggressively than other breast cancer subtypes.[3] 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.[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.[15] Thus, novel therapeutic options are urgently needed.

NSCLC is the most commonly fatal malignancy in the US accounting for nearly 30% of all cancer related deaths, and a frequent cause of mortality throughout the world. In the US in 2013, there were over 200,000 new cases. Approximately 80% of lung cancer is histologically defined as non-small cell and the remaining 20% as small cell. The majority of patients with NSCLC present with inoperable locally advanced (Stage IIIB) or metastatic

(Stage IV) disease for which no curative treatment is available. Platinum-based doublet combination chemotherapy regimens have become the clinical and regulatory standard of care for these patients. Patients with disease progression on or after first-line treatment may be candidates for second-line treatment. Second-line treatment options are limited and are of limited benefit.[8] NSCLC continues to be an area of high unmet medical need.

CRC also continues to be an area of unmet medical need despite advances in cytotoxic chemotherapies and newer targeted agents. In the US, nearly 150,000 new cases are diagnosed each year, and it results in the death of nearly 50,000 people annually.[1] Currently, treatment options include combinations of a fluoropyrimidine with either oxaliplatin or irinotecan as a backbone. Targeted agents have shown added benefit when added to these regimens, including monoclonal antibodies directed against the Epidermal Growth Factor Receptor (EGFR; cetuximab and panitumumab) and vascular endothelial growth factor (VEGF; bevacizumab, aflibercept).[9,18,5] Recently, the first oral multikinase inhibitor regorafenib has been approved for the treatment of refractory CRC.[6] However, despite advances in the treatment of CRC, the metastatic disease will ultimately progress and patients will die due to the advanced CRC.

1.2.1. P-cadherin Expression in Human Cancers

Bioinformatics, expression profiling and immunohistochemistry (IHC) data indicated that P-cadherin is over-expressed in triple negative breast, non-small cell lung and colorectal cancers. These findings have been confirmed using preclinical cell line and patient-derived xenograft models representing these three indications. PF-06671008 mediated activity in vivo has been observed in all three indications.

1.3. PF-06671008

PF-06671008 is a heterodimeric diabody Fc fusion protein comprised of two recombinant scFv domains, one against P-cadherin (human) and the other against the CD3ε chain (humanized), fused to the human Fc domain of IgG1. PF-06671008 allows the T cell to circumvent the need for the interaction of the TCR and MHC class I in complex with antigen, and instead redirects T cells to target cells through direct co-engagement of CD3ε expressed on the T cell and P-cadherin expressed on the tumor. The subsequent CD3ε signaling cascade directs T cell mediated killing of cells expressing P-cadherin through the release and transfer of granzyme B and perforin from the T cell to the target cell.

1.3.1. Efficacy

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1.5. Starting Dose Rationale

1.5.1. Intravenous Administration

The selection of the starting dose for this first-in-patient (FIP) study was based on the MABEL in accordance with the International Conference on Harmonization (ICH) S9 Guidance, given that PF-06671008 is a bi-specific T cell-engaging agent with immune agonistic properties. CCI [redacted]

Based on this MABEL approach, the clinical starting dose selected for the study is 1.5 ng/kg given as a 1-hour intravenous infusion weekly. CCI [redacted]

Prediction of clinical efficacious dose was based on efficacious concentration (C_{eff}) estimated from mouse PK CCI studies and predicted human PK. CCI [redacted]

[redacted]

CCI [redacted]

Body weight-based dosing approach (mg/kg) will be applied for the FIP study of PF-06671008 with the goal to reduce inter-individual variations in PK exposure. Pfizer intends to conduct population PK analysis of PF-06671008 after sufficient data have been collected to inform optimal dosing approach for future studies.

1.5.2. Subcutaneous Administration

Based on emerging safety, tolerability, and PK data from the initial IV administration cohorts, the study will be expanded to evaluate the safety and tolerability of PF-06671008 with SC administration. CCI [redacted] The SC administration dose escalation cohorts are planned to commence after the IV priming dose level is declared and the SC cohort will proceed in parallel with the IV dose escalation cohorts (See Section Criteria for Dose Escalation).

CCI [redacted]

Once the IV Dose Prime (according to the criteria specified in Section Evaluation of a Priming Dose) is declared, the SC administration cohort will be started at the IV priming dose level. The SC starting dose selection takes into consideration the clinical safety, tolerability and PK data from the initial IV administration cohorts, and the expected drug exposure with SC administration.

A SC starting dose at the IV priming dose level is projected to result in lower systemic exposure of study drug relative to IV priming dose. CCI [redacted]

Safety measures for monitoring potential toxicities following SC drug administration are planned, including AE and CRS evalatuion along with serial assessment of the injection site (See Section 7.1). In the SC cohorts in Part 1, there will be a minimum 72-hour separation of the first dose administered to each of the initial patients (ie, patients contributing to initial DLT evaluation.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Dose Escalation (Part 1) Objectives

Primary Objective

- To assess safety and tolerability of increasing dose levels of PF-06671008 administered in patients with advanced solid tumors for whom no standard therapy is available in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile;
- To characterize the single and multiple dose PK of PF-06671008;
- To evaluate the immunogenicity of PF-06671008;
- To document any anti-tumor activity.

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[redacted]

2.1.2. Dose Expansion (Part 2) Objectives

Primary Objective

- To confirm safety and tolerability and explore preliminary evidence of anti-tumor activity of PF-06671008 at the RP2D in patients with P-cadherin expressing advanced CRC, TNBC or NSCLC.

Secondary Objectives

- To evaluate the overall safety profile at the RP2D;
- To characterize the single and multiple dose PK of PF-06671008;
- To evaluate the immunogenicity of PF-06671008;
- To evaluate preliminary anti-tumor activity through time to event endpoints.

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2.2. Endpoints

Primary Endpoint (Part 1)

- First cycle Dose-Limiting Toxicities (DLTs).

Primary Endpoint (Part 2)

- Objective response (OR) as determined by the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 criteria (Appendix 4).

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03) (Appendix 6), timing, seriousness, and relationship to study therapy;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;
- Vital sign abnormalities;
- Pharmacokinetic parameters of PF-06671008 Single Dose (SD) - C_{max}, T_{max}, $AUC_{sd,\tau}$, $t_{1/2}$, AUC_{inf}, and CL for IV administration or CL/F for SC administration as data permit. Multiple Dose (MD) (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, CL for IV or CL/F for SC, V_{ss} for IV or V_{ss}/F for SC, and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$) as data permit;
- Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies against PF-06671008;
- Objective response, as assessed using the RECIST version 1.1 – Part 1 only;
- Progression Free Survival (PFS) and Overall Survival (OS) – Part 2 only.

CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open-label, multi-center, multiple-dose, safety, PK CCI [redacted] study of single-agent PF-06671008. This study contains two parts, dose escalation (Part 1) followed by dose expansion (Part 2). Sequential cohorts of patients with tumor types with the potential to have P-cadherin expression (see Appendix 2), that are resistant to standard therapy or for whom no standard therapy is available, will receive escalating doses of PF-06671008 in Part 1 of the study. In addition, at clinically relevant dose levels of 100 ng/kg or higher (ie, doses where the exposure is near the target effective exposure) where the safety is confirmed in the initial 2-4 patients dosed, approximately up to 5 additional patients with CRC, TNBC, NSCLC or squamous cell carcinoma of the head and neck (SCCHN) may be enrolled. CCI [redacted]

Up to approximately 152 patients are expected to be enrolled in the study overall. The actual number of patients enrolled will depend on the tolerability of PF-06671008 and the number of dose levels required to identify the MTD.

PF-06671008 will be administered as a weekly IV infusion in 21-day cycles with a starting dose of 1.5 ng/kg. There will be a minimum 72-hour interval between the first dose administered to each of the initial patients (ie, patients contributing to initial DLT evaluation) enrolled at a new dose level due to the unknown time course of possible infusion-related reaction or cytokine release. All patients will be observed in-patient for at least 24 hours after the first dose on C1D1. At doses of 100 ng/kg or higher, especially when the total dose

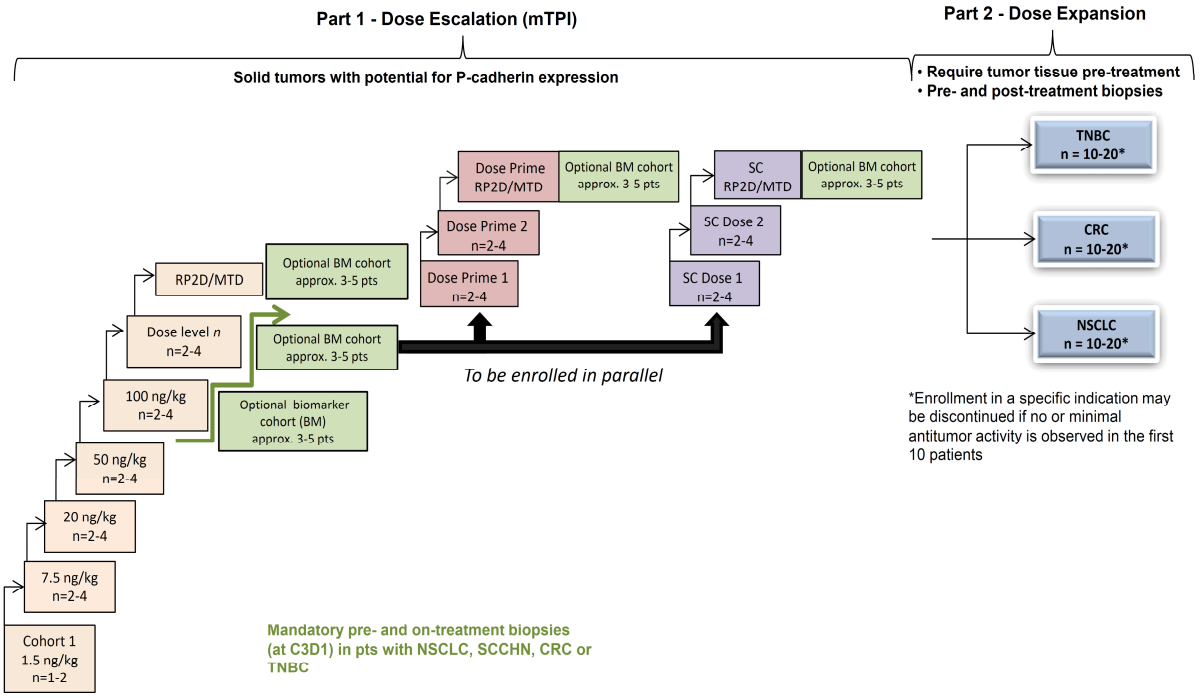
exceeds 10,000 ng, additional in-patient overnight observation for subsequent doses beyond C1D1 may be considered based on the investigator's discretion and should be discussed with Pfizer.

In addition, PF-06671008 will also be administered in cohorts as a weekly SC injection in 21-day cycles with a starting dose equal to the dose level selected as the IV Dose Prime (See Section Evaluation of a Priming Dose). Dose escalation cohorts with PF-06671008 SC administration will be evaluated independently in parallel with dose escalation cohorts evaluating PF-06671008 IV administration (See Section Criteria for Dose Escalation). For cohorts where a SC route of administration will be evaluated, there will also be a minimum 72-hour interval between the first dose administered to each of the initial patients (ie, patients contributing to initial DLT evaluation) enrolled at a new dose level due to the unknown time course of possible cytokine release. All patients who will be dosed subcutaneously will be observed in-patient for at least 48 hours after the first dose on Cycle 1 Day 1 (C1D1). Additional in-patient observation for subsequent cycles beyond C1D1 may be considered based on the investigator's discretion and should be discussed with Pfizer. Evaluation of either the IV or SC route of administration may be discontinued based on emerging clinical and safety data.

In the event study treatment administration is delayed due to toxicities during Cycle 1, the day when the patient receives their 4th dose of study drug will be counted as Day 1 of Cycle 2.

Treatment with investigational product will continue until either disease progression, patient refusal, or unacceptable toxicity occurs, whichever is earliest, unless the investigator and medical monitor agree to treatment beyond disease progression based on individual benefit/risk assessments.

Figure 3. Overall Study Design



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

3.2. Dose Escalation Phase (Part 1)

Increasing dose levels of PF-06671008 administered weekly will be evaluated using a modified toxicity probability interval (mTPI) method that targets a MTD associated with a 27.5% probability of DLT. Part 1 will follow a mTPI method initially with cohorts of 1-2 patients each and a primary DLT observation period of 21 days following the first dose (C1D1).

If a DLT or other toxicities occur (ie, those that have the potential to be DLTs if more severe) during Cycle 1 but prior to the observation of Grade ≥3 cytokine release syndrome (as described below in Evaluation of a Priming Dose), dose escalation will continue to follow a mTPI design but with cohorts of 2-4 patients each. The primary DLT observation period will continue to be 21 days following the first dose (C1D1).

Additional patients may be entered at any dose level in the IV and/or SC routes of administration at or below the MTD, after discussion with and permission by the sponsor, to obtain additional safety, PK [redacted] and anti-tumor activity data. [redacted] These additional patients will require paired biopsies. Because these additional patients will receive a dose lower than the concurrent dose escalation cohort or will be enrolled at dose following the DLT evaluation period in the first 2-4 patients enrolled, their potential DLT observations may not be strictly used in the mTPI algorithm for the ongoing dose finding. However, the safety profile from these additional patients will be used to establish the MTD or recommended Phase 2 dose (RP2D).

3.2.1. Evaluation of a Priming Dose

Based on toxicity study results, the evaluation of a priming dose to allow subsequent higher level dose administration may be instituted in this study. In addition, blinatumomab, an approved bispecific agent for the treatment of ALL, has been able to overcome symptoms of cytokine release syndrome (CRS) with the implementation of a priming dose (Topp et al, 2014).[21] Therefore, this study may implement the evaluation of a priming dose during the escalation phase.

The initial priming dose will be defined to facilitate subsequent dose escalation towards establishing the MTD of a dosing regimen that includes a priming dose. The study aims to determine a MTD for an IV dose regimen that does not include a priming dose, and an independent MTD for an IV dose regimen that includes a priming dose. In addition, the study aims to similarly determine a MTD for PF-06671008 administered subcutaneously that may or may not include a priming dose.

The decision to evaluate a regimen that includes a priming dose may be made by the investigators and sponsor prior to reaching a MTD using the following criteria as guidance:

If a dose level induces symptoms consistent with Grade 3 CRS as defined in Appendix 8 lasting for >24 hours considered not to be due to an infusion related reaction (IRR), allergic reaction, anaphylaxis or other causes in a cohort of 2-4 patients after the initial infusion, an additional 1-4 patients (up to approximately 6 patients overall) will be enrolled at that dose to confirm implementation of a priming dose (Dose Prime) for subsequent cohorts. If an additional confirmed CRS of Grade 3 lasting for >24 hours is observed at that dose, then a lower dose, which has been evaluated in at least 2-4 patients, will be chosen as a priming dose (Dose Prime) for subsequent cohorts. If a Dose Prime is selected, dose escalation will continue to determine the MTD of a dose regimen that includes a priming dose. The evaluation of a Dose Prime may be implemented for both the IV and/or SC routes of administration.

If a dose level induces confirmed CRS of Grade 4 considered not to be due to an IRR, allergic reaction, anaphylaxis or other causes, then a lower dose, which has been evaluated in at least 2-4 patients, will be chosen as a priming dose (Dose Prime) for subsequent cohorts.

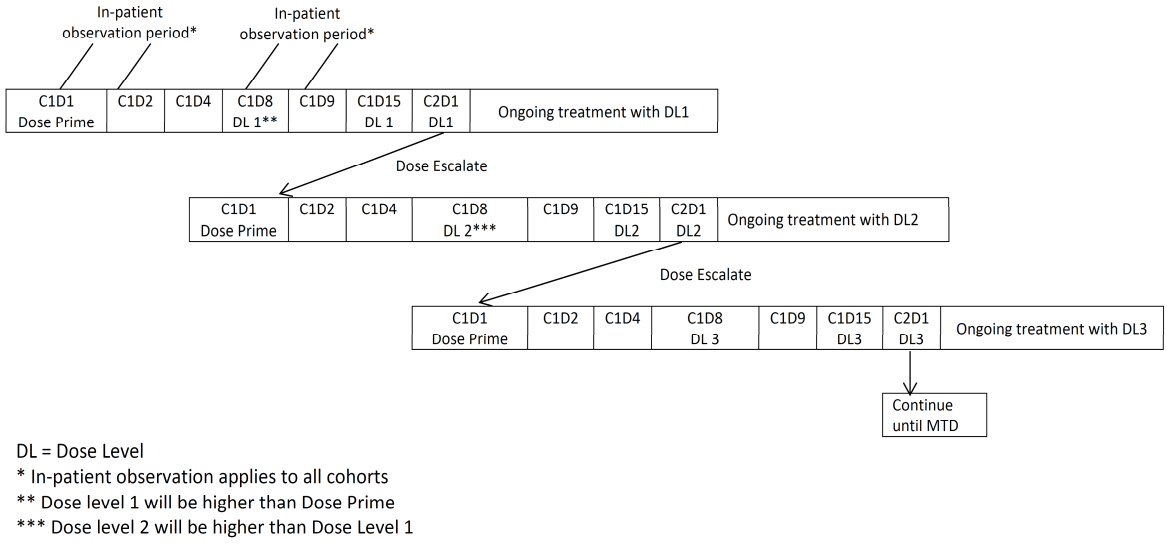
In addition, observation of a confirmed CRS event that meets the above qualifications following later infusions (ie, after Cycle 1 Day 1) or CRS events that are approaching the limit of tolerablity may prompt the investigators and sponsor to include evaluation of a Dose Prime for subsequent cohorts.

After confirmation of the safety of Dose Prime, the treatment schedule will implement the inclusion of the fixed priming dose as the first dose (C1D1) followed by a second dose (C1D8) that will continue to be escalated in subsequent cohorts following an mTPI method in cohorts of 2-4 patients. After the MTD has been established, the priming dose may potentially be further verified in connection to the established MTD/RP2D, including consideration of more than one priming step, if indicated, using information from all patients who were included in the initial priming dose determination as well as those enrolled in subsequent dosing cohorts.

The primary DLT observation period for cohorts that include Dose Prime will be 21 days following the first dose (C1D1). The dose escalation should a Dose Prime be instituted is depicted in Figure 4.

For cohorts instituting a Dose Prime, there will be a 72 hour observation period between the first dose administered to each of the initial patients enrolled (ie, patients contributing to initial DLT evaluation) at a new dose level. In addition to in-patient observation following the C1D1 dose, patients enrolled in cohorts instituting a Dose Prime must also undergo in-patient observation for at least 24 hours (for cohorts where PF-06671008 will be administered IV) or 48 hours (for cohorts where PF-06671008 will be administered SC) following the C1D8 dose.

Figure 4. Study Schematic Should Dose Prime Be Explored



DL = Dose Level
* In-patient observation applies to all cohorts
** Dose level 1 will be higher than Dose Prime
*** Dose level 2 will be higher than Dose Level 1

3.2.2. Criteria for Dose Escalation

The study has been designed to establish the MTD defined as the dose that yields approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) 22.5% to 32.5%.

Typically patients will be enrolled in cohorts of 2 to 4, but patients could be initially enrolled in cohorts of 1-2 for the lower doses (see section Dose Escalation Phase (Part 1)). The initial 2-4 patients to be included in a cohort will be open to any of the tumor types outlined in Appendix 2. When required to expand a cohort for further evaluation of the MTD, enrollment of patients may be limited to those with NSCLC, SCCHN, CRC or TNBC.

For IV administration cohorts, initial dose levels are provided in Table 1 and will be followed if no DLTs are observed; intermediate doses may be evaluated based on clinical findings. Subsequent maximum dose increases will be a maximum of 2-fold (100%) if no DLTs are observed. For SC administration cohorts, during the initial dose escalation levels, maximum dose increases will be up to 3-fold if no DLTs or safety events that are approaching the limit of tolerability are observed. The initial dose to be evaluated for SC administration will be equal to the dose level selected as the IV Dose Prime. The evaluation of the IV and SC routes of administration will proceed through dose escalation independently according to the mTPI method. Once the first DLT is observed, the maximum increase would follow a modified Fibonacci series in case of dose escalation (ie, 67%, 50%, 33%, etc.). Patients will be assigned to a dose that is closest to the current MTD prediction based on the mTPI method. The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level to determine (Decision Rules) where future cohorts should involve dose escalation, no change in dose, or dose de-escalation as presented in Table 2 (see also Section Statistical Methods and Properties).

Table 1. Dose Escalation Levels for IV Administration

Dose Level	Dose (ng/kg)
1 (Starting Dose)	1.5
2	7.5
3	20
4	50
5	100
6	200
7	300
8	400

* Intermediate doses may be evaluated based on clinical findings (eg, a dose between 20 and 50 ng/kg).

Table 2. Decision Rules

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

D: De-escalate the dose; E: Escalate the dose; S: Stay at the dose; U: Unacceptable toxicity
Note: If one patient has a DLT event observed in a dose cohort with 1 patient enrolled, additional patients (eg, 1 or 2) may be enrolled for dose escalation assessment.

Dose escalation will stop under any of the following conditions:

- The maximum sample size has been achieved;
- 6-12 patients have been enrolled at a dose that is predicted to be the MTD;
- All doses explored appear to be overly toxic and the MTD cannot be determined.

Intrapatient dose escalation, other than the potential inclusion of priming doses, will not be permitted in this study.

3.3. DLT Definition

Severity of adverse events will be graded according to CTCAE version 4.03 (Appendix 6). For the purpose of dose escalation, any of the following adverse events occurring in the first cycle of treatment (21 days after the first dose) will be classified as DLTs, unless there is a clear alternative explanation (eg, related to underlying disease/progression):

Hematologic:

- Grade 4 neutropenia lasting ≥5 days;
- Febrile neutropenia defined as an absolute neutrophil count (ANC) <1.0 x 10^9/L with a single temperature of >38.3°C, or 101°F, or a sustained temperature of ≥38°C, or 100.4°F, for more than one hour;
- Grade ≥3 neutropenia with infection;
- Grade 3 thrombocytopenia with Grade ≥2 bleeding;

- Grade 4 thrombocytopenia.

Non-hematologic:

- Grade 4 toxicities (not attributed to CRS) that are considered clinically significant;
- Grade 3 toxicities (not attributed to CRS) that are considered clinically significant despite maximal supportive care (eg, nausea, vomiting, diarrhea, easily corrected electrolyte abnormalities) that last >72 hours;
- Grade ≥3 CRS considered not to be due to an IRR, allergic reaction or anaphylaxis, except those i) not maximally treated or ii) events that are maximally treated, (eg, including the use of tocilizumab and/or vasopressors), and resolve to ≤ Grade 2 within 72 hours;
- Delay by more than 2 weeks in receiving the next scheduled dose due to persisting treatment related toxicities.

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 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. MTD Definition

The estimated MTD is the dose level associated with approximately 27.5% of DLT-evaluable patients experiencing a DLT. The target interval for the DLT rate is (22.5%-32.5%). Due to the discreteness of the dose levels and in the interest of the safety of patients, the estimated MTD is the highest tested dose level with DLT rate ≤0.325 in at least 6-12 evaluable patients for DLT. The study aims to determine a MTD for a dose regimen that does not include a priming dose administered IV, and an independent MTD for an IV dose regimen that includes a priming dose. In addition, the study aims to determine a MTD for PF-06671008 administered SC and may also determine an independent MTD for a SC dose regimen that includes a priming dose.

3.5. Dose Expansion Phase (Part 2)

The maximum sample size for each tumor indication (ie, TNBC, CRC and NSCLC) will be in the range n=10 to n=20. Enrollment of patients in one indication may be discontinued if minimal or no anti-tumor activity (eg, 0 or 1 response) is observed in the first 10 evaluable patients for that indication (see section Sample Size Determination).

3.6. Recommended Phase 2 Dose (RP2D) Definition

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

result in a RP2D dose lower than the MTD (eg, if in the expansion part >25% of patients require a dose reduction due to toxicity, then the sponsor may convene a safety committee to determine if a lower RP2D needs to be determined).

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

1. For dose escalation (Part 1): Histological or cytological diagnosis of a tumor type with the potential to have P-cadherin expression (see Appendix 2). Patients with tumor types other than those listed in Appendix 2 may be allowed to enroll based on emerging data and with the agreement of the sponsor. Patients must be refractory to, intolerant of established therapy known to provide clinical benefit for their condition, ie, patients must not be candidates for regimens known to provide clinical benefit.

2. For dose escalation (Part 1): Must have tumor tissue available for submission to the sponsor. Patients enrolled in Part 1 should have access to their archival formalin-fixed paraffin embedded material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy or consent to undergo a biopsy during screening.

3. For dose expansion (Part 2): Histological or cytological diagnosis of previously treated CRC, TNBC or NSCLC with at least one measurable lesion, not previously irradiated, as defined by RECIST version 1.1 (Appendix 4). Patients must be refractory to, intolerant of established therapy known to provide clinical benefit for their condition, ie, patients must not be candidates for regimens known to provide clinical benefit.

4. For dose expansion (Part 2): Must have tumor tissue available for P-cadherin expression evaluation and must meet minimum required P-cadherin expression level (to be determined prior to activation of Part 2). Patients enrolled in Part 2 should have access to their archival formalin-fixed paraffin embedded material containing tumor that is of diagnostic quality and representative of their diagnosed malignancy.

5. For dose expansion (Part 2): Must have at least one tumor lesion, not previously irradiated, that is amenable to biopsy and must agree to undergo biopsies required per the Schedule of Activities.

6. Age ≥18 years.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) must be 0 or 1.
8. Total body weight ≥70 kg (154 lbs) for IV starting dose level only.
9. Adequate bone marrow function, including:
    a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
    b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
    c. Hemoglobin ≥10 g/dL.
10. Adequate renal function, including:
    a. Estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.
11. Adequate liver function, including:
    a. Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome;
    b. Aspartate and Alanine transaminase (AST and ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement secondary to tumor;
    c. Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in case of bone metastasis).
12. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for adverse events (AEs) not constituting a safety risk by investigator judgment.
13. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.
14. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective method(s) of contraception throughout the study and for at least 28 days after the last dose of study treatment.

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

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or

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

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

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

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Patients with known CNS disease including, but not limited to, metastases.

2. Current or history of seizure disorder.

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

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

5. Bleeding esophageal or gastric varices within 2 months prior to registration.

6. History of or current requirement for chronic blood product support.

7. Grade ≥2 peripheral neuropathy.

8. Pregnant female patients; breastfeeding female patients.

9. Major surgery within 4 weeks prior to registration.

10. Radiation therapy within 4 weeks prior to registration. Palliative radiotherapy to a limited field is allowed after consultation with the sponsor's medical monitor unless it is clearly indicative of disease progression.

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

12. Previous high-dose chemotherapy requiring stem cell rescue.

13. Requirement for systemic immune suppressive medication [eg, ≥10 mg of prednisone or equivalent (≥1.5 mg of dexamethasone)].

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

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

16. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.

17. Participation in other studies involving investigational drug(s) within 28 days prior to registration.

18. 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.

19. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

4.3. Lifestyle Guidelines

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive PF-06671008, a compound for which the teratogenic risk is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 28 days after the last dose of study treatment. The investigator or his or her designee, in consultation with the patient, will confirm the patient has selected two appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected in the patient or the patient's partner.

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

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
6. Female partner who meets the criteria for non-childbearing potential, defined as:
    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or
    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.

4.4. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace,

the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference of Harmonisation (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

Patient enrollment number and dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will email a complete Registration Form to the designated sponsor study team member. The sponsor will assign a patient identification number documenting patient enrollment. IV and SC routes of administration will be enrolled in parallel. Patients will be allocated to a dose escalation cohort and route of administration based on the sequential available slots.

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

- confirmation of the patient's enrollment;
- specification of the dose level and route of administration for that patient and;
- permission to proceed with dosing the patient.

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

5.2. Patient Compliance

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

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

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

PF-06671008 solution for injection, 1 mg/mL is presented as a sterile solution for IV or SC administration. Each vial contains 1 mg of PF-06671008 in 1 mL of aqueous buffered solution, is sealed with a coated stopper and an overseal, and is labeled according to local regulatory requirements.

5.3.2. Preparation and Dispensing

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

Vials are for single-use, single-patient only.

5.4. Administration

CCI

[redacted]

CCI

[redacted]

[redacted]

5.4.1. Cytokine Release Syndrome

Symptoms associated with CRS vary greatly and may be difficult to distinguish from other conditions. The more common symptoms include fever, nausea, headache, tachycardia, hypotension, rash and shortness of breath. The severity of symptoms can be mild to life threatening and thus, there should be a high suspicion for CRS if these symptoms occur. Grade 1 CRS does not require any intervention but patients should be monitored closely. Grade ≥2 CRS requires PF-06671008 infusion interruption and prompt symptomatic treatment per local standard of care. For CRS not rapidly responsive to supportive care or CRS of Grade ≥3, treatment with corticosteroids and/or tocilizumab,[2] an anti-human IL-6R mAb, should be considered.[12] A suggested treatment algorithm for the management and grading of CRS based on a revised CRS grading system by Lee et al. is provided in Appendix 8.

The decision to incorporate pre-medication (ie, corticosteroids) for CRS prophylaxis in all patients will be made following discussions between the sponsor and the investigators. The pre-treatment medication will not be supplied by Pfizer.

5.4.2. Infusion Reactions

In the case of infusion related reactions, characterized by fever and chills, and less commonly hypotension, the sponsor should be notified and adjustment of infusion rate may be considered, which could include interrupting the infusion or slowing the infusion rate to a previously acceptable rate by increasing duration of the infusion. When the infusion rate is adjusted to a previously acceptable rate for 2 or more patients at the current cohort, the sponsor should be notified and the infusion rates for current and subsequent cohorts should be maintained at the previously acceptable rate.

In addition, pre-treatment medication should be administered prior to subsequent infusions (in the case that the patient is able to continue on treatment). The decision to incorporate pre-medication for infusion related reaction prophylaxis 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-06671008 administration. The pre-treatment medication 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 additional doses of acetaminophen may be administered approximately every 4 hours after the initial pre-treatment or as needed.

5.4.3. Hypersensitivity Types 1 and 3

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

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

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

5.4.4. Extravasation

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

5.4.5. Recommended Dose Modifications

Every effort should be made to administer investigational product on the planned dose and schedule.

In the event of significant toxicity dosing may be delayed 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 one of three ways:

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

5.4.6. Dosing Interruptions

Patients experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment interrupted.

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in the Dose Delays section.

Doses may be held as needed until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions section, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

5.4.7. Dose Delays

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

- ANC ≥1,000/mm^3.
- Platelets count ≥50,000/mm^3.
- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator discretion, Grade ≤2 if not considered a safety risk for the patient).

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 14 days of treatment interruption or cycle delay, PF-06671008 may be resumed. Refer to Section Dose Reductions for AEs requiring dose reduction at the time of treatment resumption.

If treatment interruption due to toxicity exceeds 14 days, treatment with this agent should be permanently discontinued.

The day when the patient receives their 4^{th} dose of study drug will be counted as Day 1 of the next cycle. Subsequent cycles will be 21 days in length regardless of treatment delays.

5.4.8. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-06671008 dose may need to be reduced when treatment is resumed.

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

Dose reduction of PF-06671008 by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Patients enrolled in the first cohort should be discontinued from the study if more than 1 dose reduction is required. Patients requiring more than 2 (or 1 for the first cohort) dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and CRF.

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

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

Recommended dose reductions are described in Table 3.

Table 3. Dose Reductions

Event	Action
Grade 3 or 4 non-hematologic toxicity (except CRS) considered **related** to PF-06671008 per investigator judgment (including persistent nausea, vomiting, diarrhea despite optimal medical therapy), excluding clinically manageable electrolyte abnormalities.	• Hold PF-06671008 until recovery to Grade 0-1 or baseline and reduce by 1 dose level. • If toxicity (Grade 3-4) reoccurs despite reduction, patient may be dose reduced again by 1 more dose level (except for the first cohort) upon recovery to Grade 0-1 or baseline. • Prompt palliative and supportive measures mandated per local standard of care (eg, antiemetic). • Patients who experience Grade 4 non hematologic toxicities despite intervention should be discontinued from study treatment, unless restarting treatment at reduced dose level is in the patient's best interest per investigator judgment and after consultation with Pfizer's medical monitor (eg, clear clinical benefit and no alternative treatment options).
Cytokine Release Syndrome	• Grade 2: Hold PF-06671008 until resolved and resume at same dose level. If Grade 2 CRS reoccurs, hold PF-06671008 until resolved and consider reduction by 1 dose level based on the investigator's discretion. • Grade 3: Hold PF-06671008 until resolved and consider reduction by 1 dose level based on the investigator's discretion. If Grade 3 CRS recurs despite reduction, permanently discontinue PF-06671008. • Grade 4: Permanently discontinue PF-06671008.
Hematologic toxicity considered **related** to PF-06671008 per investigator judgment • Grade 4 neutropenia, ie, ANC <500 mm^3 (1.0 x 10^9/L) for more than 5 days or • Febrile neutropenia, ie, fever >38.3°C (101°F)or a sustained temperature of ≥38°C (100.4°F) with ANC <1000/mm^3 or • Grade ≥3 neutropenic infection or • Grade 4 Thrombocytopenia, ie, PLTS <25,000 mm^3 (25.0 x 10^9/L) or • Grade 3 Thrombocytopenia, ie, PLTS <50,000 mm^3 (50.0 x 10^9/L) with bleeding.	• Hold PF-06671008 until recovery of ANC to ≥1.0 x 10^9/L (1,000 cells/mm^3) and platelets ≥75 x 10^9/L (75,000 cells/mm^3). • Reduce PF-06671008 by 1 dose level. • If toxicity reoccurs (grades as described on the left side) despite dose reduction, patients may either be held until recovery and continuation at same dose, or undergo further dose reduction by 1 more dose level (except for the first cohort).
Other grade 4 hematologic toxicity considered **related** to PF-06671008 per investigator judgment	• Hold PF-06671008 until recovery to Grade 0-1 or baseline and reduce PF-06671008 dose by 1 dose level. • If toxicity reoccurs (Grade 4) despite dose reduction, patient may either be held until recovery and continuation at same dose, or undergo further dose reduction by 1 more dose level.
No recovery of toxicities within 4 weeks of scheduled PF-06671008 infusion	• Discontinue treatment, unless restarting treatment at reduced dose level is in the patient's best interest per investigator judgment and after consultation with Pfizer's medical monitor (eg, clear clinical benefit and no alternative treatment options).

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational product is stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the investigational product label for storage conditions of the product.

Storage conditions stated in the SRSD (ie, IB) will be superseded by the storage conditions stated in the labeling.

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

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

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

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

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

Refer to the investigational product manual for any additional guidance on storage conditions and actions to be taken when conditions are outside of the specified range.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

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

All concomitant treatments, including supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat AEs or chronic disease, blood products, as well as non-drug interventions (eg, transfusions) received by patients from screening until the Follow-up visit will be recorded on the CRF.

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

No additional anti-tumor treatment will be permitted while patients are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided 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. In view of the current lack of data about the interaction of PF-06671008 with radiotherapy, PF-06671008 treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment after recovery to baseline.

5.7.2. Supportive Care

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

5.7.3. Hematopoietic Growth Factors

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

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

5.7.4. Anti-Diarrheal, Anti Emetic Therapy

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

5.7.5. Anti-inflammatory Therapy

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

5.7.6. Corticosteroids

Chronic, systemic corticosteroid use for palliative or supportive purposes is not permitted in cases other than those discussed in the Cytokine Release Syndrome section. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

5.7.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06671008 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06671008 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-06671008 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see Schedule of Activities and Assessments section. Screening to be obtained within 28 days prior to registration. The informed consent document must be obtained prior to undergoing any study specific procedures. Informed consent may be obtained more than 28 days prior to registration.

6.2. Study Period

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

6.3. Follow-up Visit

For follow-up procedures see Schedule of Activities and Assessments section. The EOT assessments are to be obtained if they are not completed in the last week (last 6 weeks for tumor assessments). The Follow-Up visit should be conducted at least 28 days, and no more than 35 days, after discontinuation of treatment. Patient will return to undergo assessments per the Schedule of Activities and will be evaluated for the 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. Subsequent to the Follow-Up visit, patients should be contacted by telephone every 8 weeks (±7 days) to obtain information on subsequent anti-cancer treatment and overall survival for up to two years after randomization.

6.4. Patient Withdrawal

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 by irRECIST (see Appendix 5). Disease progression will be confirmed with two consecutive timepoints at least 4 weeks apart in the absence of rapid clinical deterioration;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

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

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

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

7. ASSESSMENTS

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

7.1. Safety Assessment

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

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment-once at the start of screening and once at C1D1, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit within 5 days after the first day of the menstrual period counting the first day as Day 1 before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive human chorionic gonadotropin (hCG) test, the patient will be withdrawn from treatment and will be withdrawn from the study. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

7.1.2. Adverse Events

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

Adverse events that occur during the study will be recorded on the adverse events CRF page.

7.1.3. Laboratory Safety Assessment

Hematology, blood chemistry, coagulation and urinalysis will be evaulated at the time points described in the Schedule of Activities and analyzed at local laboratories. There is no need to repeat the C1D1 laboratory assessments if the baseline assessment is performed within 3 days prior to dosing. Assessments performed at all subsequent dosing visits should be performed within 48 hours prior to dosing. Additional local laboratory assessments outside of the timepoints outlined in the Schedule of Activities, (eg, additional local cytokine samples), may be obtained for patient safety evaluation at the discretion of the investigator.

Table 4. Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test	Unique Screening Labs
Hemoglobin	ALT/SGPT	PT or INR	Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine	Hepatitis B surface antigen
Platelets	AST/SGOT	PTT			Hepatitis B core antibody
WBC	Alk Phos				Hepatitis C antibody
Absolute Neutrophils	Sodium				HIV
Absolute Lymphocytes	Potassium				
Absolute Monocytes	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)		
Absolute Eosinophils	Chloride				
Absolute Basophils	Calcium				
	Total Bilirubin[1]				
	BUN or Urea				
	Creatinine				
	Uric Acid				
	Glucose (non-fasted)				
	Albumin				
	Phosphorous or Phosphate				
	LDH				
	CRP[2]				

* All samples will be analyzed locally.

1. For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.
2. Measurement of CRP is not required after C2D1 if within normal range or similar to baseline levels; however, CRP should be measured anytime CRS is suspected and not already scheduled to be measured (eg, Cycle 2).

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination (PE) to include vital signs, assessment of ECOG performance status and height; height will be measured at screening only. Weight will be measured at screening, the beginning of each cycle and the end of treatment. Weight does not need to be performed at each visit; however patients should be monitored throughout the study for significant weight change.

A complete PE will be performed at Screening, on Cycle 1 Day 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 Cycle 1 Day 1 PE does not need to be repeated if the screening assessment is performed within 3 days of the visit. 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 AE in the CRF.

Abbreviated PEs should be performed as appropriate per the Schedule of Activities (SOA), and on an as needed basis for assessment of AEs. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.

Vital signs will include measurement of temperature (oral, tympanic, temporal or axillary), blood pressure (BP) and pulse rate to be recorded in a seated or supine position. On dosing days, vital signs should be measured prior to administration of investigational product (pre-dose) and at the end of the PF-06671008 infusion (for cohorts where PF-06671008 is administered IV). For BP assessment, the same arm (preferably the dominant arm) should be used throughout the trial. A 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 is acceptable.

On dosing days, pulse oximetry should be measured prior to administration of investigational product (pre-dose) and at the end of the PF-06671008 infusion (for cohorts where PF-06671008 is administered IV) as part of the vital sign evaluation. Pulse oximetry should be collected prior to the collection of BP and pulse rate. Oxygen levels should be evaluated on the finger in accordance with the sites standard procedures. A single reading should be collected.

7.1.5. Ophthalmic Examination

An eye exam, to be performed by an ophthalmologist, will be performed at screening. The eye exam is to include Best Corrected Visual Activity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens,

and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow up.

7.1.6. (12-Lead) Electrocardiogram

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to <500 msec. Patients will then restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to 500 msec after 2-weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

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

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

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

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7.1.8. Injection Site Tolerability Assessment (SC Only)

Assessments of the injection sites in the abdominal fat fold to monitor local tolerability to PF-06671008 SC injections will be performed for at least 1 hour following study drug administration in Cycle 1, as per the Schedule of Activities. An assessment should also be performed 24 hours (±1 hour) after the Cycle 1 Day 1 dose. Injection site tolerability assessments for at least one hour post the PF-06671008 injection should continue after each dosing day visit in Cycle 2 and beyond, only if injection site pain or injection site reaction (ISR) characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve. The injection sites will be assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after PF-06671008 administration. The diameter of the affected area will be measured, and the condition of the injection site will be recorded on the CRF. Any observed abnormality at the injection site will be judged by the investigator to determine if the event should also be reported as an adverse event. ISRs should be immediately photographed in color, with scaled ruler placed by the reaction, and these photographs should be included in the patient's source documentation. When appropriate, at the discretion of the investigator, a patient with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR.

7.2. Pharmacokinetics Assessments

7.2.1. Blood for Assessment of PF-06671008 Pharmacokinetics

Blood samples (approximately 2 mL whole blood) will be collected for measurement of PF-06671008 PK as outlined 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 of blood sample collection and of last dosing prior to PK collection documented in the CRF.

Where noted in the Schedule of Activities, blood samples for PF-06671008 concentrations will be collected at approximately the same time as other assessments such as PD samples, ECGs etc., wherever possible.

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) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and CRF. The actual times may change but the number of samples will remain the same.

If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, patient, and sponsor. PF-06671008 PK samples will be assayed using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

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7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans or equivalent; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases. The same modality should be completed, if possible, throughout the study. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases; patient ineligible if positive for CNS metastases. CT or MRI scans to be done every 6 weeks (±7 days) from the start of study treatment until disease progression by irRECIST or death, or until permanent discontinuation of study treatment. The frequency will change to every 12 weeks (±7 days) beginning at Cycle 8.

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

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

Assessment of response will be made using RECIST version 1.1 (Appendix 4) and irRECIST (Appendix 5). Disease progression will be confirmed with two consecutive timepoints at least 4 weeks apart in the absence of rapid clinical deterioration. Responses of CR or PR must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met.

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

7.5. Immunogenicity Evaluations

Assays to assess for anti-drug (anti-PF-06671008) antibodies (ADA) will be performed. All samples that are positive in a screening assay will be further characterized in terms of antibody specificity. Samples tested positive for ADA may also be characterized for neutralized antibodies (Nab). Patients with an unresolved AE possibly related to ADA will be asked to return to the clinic for ADA and drug concentration assessments 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 3 mL of serum for ADA and Nab analysis will be collected into appropriately labeled tubes at the 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 validated analytical methods in compliance with Pfizer standard operating procedures.

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

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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 AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

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

reasonable possibility of being related to investigational product are to be reported to the sponsor.

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

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

8.3. Definition of an Adverse Event

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

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

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

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

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

8.4. Medication Errors

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

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

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

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

8.5. Abnormal Test Findings

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

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

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

8.6. Serious Adverse Events

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

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

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

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

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above;

- For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

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

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a

tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

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

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

8.9. Causality Assessment

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

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

8.10. Exposure During Pregnancy

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

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

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

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

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

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

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

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

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured

on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

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

9.1. Analysis Sets

Data analysis will be performed on the following analysis populations:

1. Safety analysis set.
    - The safety analysis set includes all enrolled patients who receive at least one dose of study treatment.
2. Full analysis set.
    - The full analysis set includes all enrolled patients.

3. Per-protocol analysis set (evaluable for MTD).

    - The per protocol analysis set includes all enrolled patients who receive at least one dose of study treatment and who do not have major treatment deviations during first cycle. Patients with major treatment deviations during the first cycle of treatment are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include failure to satisfy major entry criteria (eg, confirmation of the target disease; signed informed consent) or use of other anticancer treatments during the active treatment and disease follow-up phases other than as defined/allowed in this protocol.

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

    - The modified intent-to-treat (mITT) is the analysis population that will follow the ITT principle and include patients receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population may be used for interim analysis and conference presentations when the study is still ongoing.

5. PK analysis sets.

    - The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest and who have no major protocol deviations influencing the PK assessment.

6. CCI [redacted]

7. Immunogenicity analysis sets.

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

9.2. Statistical Methods and Properties

This study has been designed to establish the Maximum Tolerated Dose (MTD) defined as the dose that yields approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) 22.5% to 32.5%. The 27.5% target was chosen based on safety considerations and is considered appropriate based on simulations and expert input. The prior distribution of DLT is set as a beta (0.5,0.5) and the threshold probability for early termination and dose exclusion is set to 0.95 as suggested

in the original mTPI method.[11] Similarly, doses with an incidence of DLT>32.5% (eg, 4 out of 10) cannot be selected as MTD although is allowed by the mTPI method.

The modified toxicity probability interval (mTPI) design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of three dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.275) (See Appendix 7). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model. Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different trials with different toxicity parameters. More importantly, all the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table. The decision rules to "dose escalate" (E), "no change in dose" (S), "dose de-escalate" (D) or "dose de-escalate, unacceptable toxicity" (U) are described in Table 2.

Table 6. Dose Escalation Levels for IV Administration

Dose Level	Dose (ng/kg)
1 (Starting Dose)	1.5
2	7.5
3	20
4	50
5	100
6	200
7	300
8	400

* Intermediate doses may be evaluated based on clinical findings (eg, a dose between 20 and 50 ng/kg).

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

The maximum sample size for Part 1 would be N=92 but actual sample size will depend on the underlying dose toxicity profile and variability in actual data realization.

The study will continue accruing until one of the three stopping conditions below is triggered.

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

1. The maximum sample size has been achieved.

2. MTD has been identified with sufficient accuracy: 6 to 12 patients have been accumulated on a dose that is currently estimated to be the MTD; or

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

Due to binomial data variability in small samples, DLTs may be observed in a first cohort(s) by chance even when the true Probability (DLT) is fairly low. This could result in the estimated posterior DLT rate to exceed the targeted 27.5% very early in the trial, triggering an early stop when very few patients (2-4) have been treated. To prevent stopping the trial prematurely in such cases, a step-down option with a lower dose of 1.0 ng/kg is added to the dose grid. This dose will be explored only if a high DLT rate occurs in the first cohort assigned to 1.5 ng/kg, ie, it will not be used as a starting dose and the algorithm will always assign the first cohort of patients to 1.5 ng/kg.

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

Probability of Escalating Dose

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

9.3. Sample Size Determination

This first in patient study is divided in to two parts. Up to approximately 152 patients are expected to be enrolled in the study overall.

In Part 1, patients will participate in a dose escalation phase aimed at estimating the MTD. The sample size for this component of the study will vary depending on the number of DLTs observed. It is anticipated that the maximum sample size of approximately 92 patients are expected to be enrolled in Part 1 of the study at approximately 6 sites. The actual number of patients enrolled will depend upon tolerability and the number of dose levels required to identify the MTD.

The minimum and maximum sample sizes after which Part 1 can be stopped and MTD declared are approximately 6-12 and approximately 92 patients, respectively. As for the number of patients treated at each dose, it is expected that the typical number will be 1 to 4 patients for the doses actually studied. However, since variable cohort size is allowed, the actual number of patients treated at each dose will vary from 1 to 12.

In **Part 2** the maximum sample sizes for each tumor indication (ie, TNBC, CRC and NSCLC) will be in the range n=10 to n=20. Enrollment of patients in one indication may be discontinued if minimal or no anti-tumor activity (eg 0 or 1 response) is observed in the first 10 evaluable patients for that indication. Assuming a non-informative prior (ie, Jeffrey's prior) if 1 out of 10 patients have tumor response, this would predict a posterior probability

(Beta-Binomial) equal to 0.93 that the true response is inferior to 30%. On the other hand, if 7 out of 20 patients have tumor response, this would predict a posterior probability equal to 0.70 that the true response is not inferior to 30% and a posterior probability equal to 0.05 (5%) that the true response is inferior to 20%. In addition, posterior probabilities may be calculated by using informative priors based on the antitumor activity that may be observed during Part 1 (eg 2 out of 3 TNBC patients experience tumor response in Part 1). These posterior probabilities will be assessed for each indication during Part 2 when at least the first 10 Pts are enrolled in that indication. Posterior Probabilities >0.75 of an ORR<20% (eg, 0,1 out of 10; 0,1,2 out of 16) may provide evidence of no substantial anti-tumor activity for that indication.

Assuming a Kappa statistic equal to 0.7, N=20 would determine a 90% CI lower bound equal to 0.44 if Kappa is calculated as a measure of concordance between positive/negative P-cadherin results in different samples when the proportion of P-cadherin positive is 80%.

9.4. Efficacy Analysis

In this First In Patient study anti-tumor activity is a primary objective for Part 2 of the study.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor response at each visit, and best overall response. In addition, progression date, death date, date of first response and last tumor assessment date, and date of last contact will be listed.

The definition of each response category is provided in Appendix 4 (RECIST v1.1) CCI [redacted]

9.5. Analysis of Pharmacokinetics CCI [redacted]

9.5.1. Analysis of Pharmacokinetics

PK parameters for single dose including the maximum concentration (C_{max}), time to maximum concentration (T_{max}), and area under the concentration versus time curve (AUC_{last}, $AUC_{sd,\tau}$) will be estimated using non-compartmental analysis. PK parameters for multiple dose (assuming steady state is achieved) including the maximum concentration ($C_{ss,max}$), time to maximum concentration ($T_{ss,max}$), and area under the concentration versus time curve ($AUC_{ss,\tau}$) will be estimated using non-compartmental analysis. If data permit or if considered appropriate, area under the concentration versus time curve to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), clearance (CL) for IV administration or apparent clearance (CL/F) for SC administration, volume of distribution at steady state (V_{ss}) for IV administration or apparent volume of distribution at steady state (V_{ss}/F) for SC administration, and accumulation ratio ($R_{ac} = AUC_{ss,\tau}/AUC_{sd,\tau}$) will be also estimated. Actual sample collection times will be used for the parameter calculations. The PK parameters will be summarized descriptively by dose, cycle, dosing day and route of administration.

PF-06671008 concentrations will be summarized descriptively (n, mean, SD, coefficient of variation(CV), median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time. Median profiles of the concentration-time data will be plotted by dose, cycle and day (single dose and steady state) using nominal times, for dosing intervals with full PK profile. Median profiles will be presented on both linear-linear and log-linear scales.

Dose normalized AUC_{inf} (AUC_{τ} at steady state), AUC_{last} and C_{max} will be plotted against dose (using a logarithmic scale) by cycle and dosing day. These plots will include individual patient values and the geometric means for each dose level. These plots will be used to help understand the relationship between the PK parameters and dose.

The observed accumulation ratio and the linearity ratio will be summarized descriptively. Each will be analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation and linearity ratios for each dose.

Trough concentrations will be plotted for the first 2 cycles using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady state.

9.5.2. Population Pharmacokinetic Analysis or Pharmacokinetic[redacted] (PK[redacted]) Modeling

PK, efficacy, [redacted], and safety data from both Part 1 and Part 2 may be pooled for PK[redacted] analyses using appropriate modeling to explore any association between PF-06671008 exposure [redacted] or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

[redacted]

CCI [redacted]

9.5.4. Immunogenicity

The development of anti-PF-06671008 antibodies will be measured using validated assays. Listings and summary tabulations of the anti-PF-06671008 antibody data at baseline and post-treatment will be generated.

Potential impact of immunogenicity on PK, clinical responses, and safety/tolerability will be explored, if data warranted.

9.6. Safety Analysis

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

9.6.1. Analysis of the Primary Endpoint

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

9.6.2. Analysis of Secondary Safety Endpoints

Adverse Events

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

Laboratory Test 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). Shift tables will be provided to examine the distribution of laboratory toxicities.

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

9.6.3. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data.

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

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

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

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

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 serious adverse events (SAEs) according to regulatory guidelines.

Discussions between the investigators and the sponsor of AEs and laboratory test alterations seen at each dose level will be conducted in an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the

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

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

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

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

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

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

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

12. ETHICS

12.1. Institutional Review Board /Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

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

12.3. Patient Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

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

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

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

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

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as the last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06671008 at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

adult populations or within 6 months of the primary completion date for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.	
Abbreviation	**Term**
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
BUN	Blood urea nitrogen
C	Cycle
C1D1	Cycle 1 Day 1
C_{ave}	Average concentration
CBC	Complete blood count
CD3ε	Cluster of differentiation 3 epsilon
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
CLIA	Clinical laboratory improvement amendments
C_{max}	Maximum concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
D	Day
DART	Dual affinity re-targeting
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure during pregnancy
ELISA	Enzyme-linked immunosorbent assay
EOT	End of treatment

F	Absolute bioavailability
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
irPFS	Immune-related progression free survival
IRR	Infusion Related Reaction
irRECIST	Immune-related response criteria in solid tumor
IV	Intravenous
K_2EDTA	Dipotassium ethylene diamine tetraacetic acid
kD	Kilodalton
kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver function test
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
MABEL	Minimally anticipated biologic effect level
MHC	Major histocompatibility class
mTPI	Modified toxicity probability interval
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
Nab	Neutralizing antibody
NCI	National Cancer Institute
ng	Nanogram

CCI	
NSCLC	Non-small cell lung cancer
OR	Overall response
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PE	Physical examination
CCI	
PD	Progressive disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PLTS	Platelets
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
QT	Time between the start of the Q wave and the end of the T wave
RECIST	Response Evaluation Criteria in Solid Tumors
RO	Receptor occupancy
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOA	Schedule of activities
SRSD	Single reference safety document
T	Time
$T_{1/2}$	Terminal elimination half-life
TCR	T cell repertoire
TK	Toxicokinetic
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
TSC	Tumor static concentration
ULN	Upper limit of normal
US	United States
USPI	United States Package Insert
V_{ss}	Volume of distribution
V_{ss}/F	Volume of distribution at steady state
WBC	White blood cell count

Appendix 2. Tumor Types with Potential for P-cadherin Expression Eligible in Dose Escalation (Part 1)

Bladder urothelial carcinoma
Breast carcinoma
Colorectal adenocarcinoma
Head and neck squamous cell carcinoma
Non-small cell lung cancer
Ovarian (epithelial) carcinoma
Pancreatic adenocarcinoma
Prostate Adenocarcinoma

Appendix 3. EGOG 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.

Appendix 4. RECIST (Response Evaluation Criteria In Solid Tumors) Version 1.1 Guidelines

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

a. Categorizing Lesions at Baseline

1. Measurable Lesions

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

1. 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).

2. Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.

3. Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.

4. Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

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

2. Non-measurable Disease

1. 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.

2. 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.

3. Previous local treatment: A previously irradiated lesion (or lesion patientive to other local treatment) is non-measurable unless it has progressed since completion of treatment.

3. Normal Sites

1. 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.

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

4. Recording Tumor Assessments

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

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

5. Target Lesions

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

1. 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.

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

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

6. Non-target Disease

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

b. Objective Response Status at Each Evaluation

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

7. Target Disease

1. 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.

2. 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.

3. 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.

4. 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.

5. 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.

8. Non-target Disease

1. 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).

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

3. 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.

4. 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.

9. 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.

10. Supplemental Investigations

1. 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.
2. 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.

11. Subjective Progression

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

Table 7. Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 8. Objective Response Status at each Evaluation for Patients with Non Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Appendix 5. Immune-Related Response Criteria Derived from RECIST 1.1 (irRECIST)

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

This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD-1/anti-PD-L1 antibodies which exert the antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects (Hoos et al, 2010; Hodi et al, 2008).[1,2] Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria (Wolchok et al, 2009; Nishino et al, 2012).[3,4]

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria.(Wolchok et al, 2009; Nishino et al, 2012).[3,4]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST v1.1 (irRECIST). (Nishino et al, 2014).[5]

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

1. Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and

2. Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm longest diameter per non-nodal lesion and 15 mm shortest diameter per nodal lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial.

irRECIST is defined as follows:

1. Overall immune-related complete response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.

2. Overall immune-related partial response (irPR): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.

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

4. Overall immune-related progressive disease (irPD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (ie, added to the target lesion measurements). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

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

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

Table 9. Overall Response Derived from Changes in Index, Non-index and New Lesions

Measurable response	**Non-measurable Response**		**Overall response using irRECIST[b]**
Index and New Measurable Lesions (Tumor Burden)[a]	**Non-Index Lesions**	**Measurable Lesions**	
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

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

References:

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Appendix 6. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

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

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

Appendix 7. Detailed Dose Escalation/De-Escalation Scheme for mTPI Design

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

- With 1 patient treated at current dose level
  - 0 DLT -> escalate
  - 1 DLT or other toxicities occur (ie, those that have the potential to be DLTs if more severe) -> may add additional patients to asses safety on a cohort size of n=2-4
- With 2 patients treated at current dose level
  - 0 DLT -> escalate
  - 1 DLT -> remain at the same dose
  - 2 DLTs -> de-escalate and consider current dose as intolerable
- With 3 patients treated at current dose level
  - 0 DLT -> escalate
  - 1 DLT -> remain at the same dose
  - 2 DLTs -> de-escalate
  - 3 DLTs -> de-escalate and consider current dose as intolerable
- With 4 patients treated at current dose level
  - 0 DLT -> escalate
  - 1-2 DLTs -> remain at the same dose
  - 3-4 DLTs -> de-escalate and consider current dose as intolerable
- With 5 patients treated at current dose level
  - 0 DLT -> escalate
  - 1 DLT -> remain at the same dose
  - 2 DLTs -> remain at the same dose (mTPI suggests “escalate”)
  - 3 DLTs -> de-escalate

- 4-5 DLTs -> de-escalate and consider current dose as intolerable

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

- With 10 patients treated at current dose level
  - 0-1 DLT -> escalate
  - 2-3 DLTs -> remain at the same dose
  - 4 DLTs -> de-escalate (mTPI suggests “remain at the same dose”)
  - 5 DLTs -> de-escalate
  - 6-10 DLTs -> de-escalate and consider current dose as intolerable
- With 11 patients treated at current dose level
  - 0-2 DLT -> escalate
  - 3-4 DLTs -> remain at the same dose
  - 5 DLTs -> de-escalate (mTPI suggests “remain at the same dose”)
  - 6-11 DLTs -> de-escalate and consider current dose as intolerable
- With 12 patients treated at current dose level
  - 0-2 DLTs -> escalate
  - 3-4 DLTs -> remain at the same dose
  - 5 DLTs -> de-escalate (mTPI suggest “remain at the same dose”)
  - 6-12 DLTs -> de-escalate and consider current dose as intolerable

mTPI Operating Characteristics

This is a dose-escalation study primarily driven by safety. While efficacy endpoints will also be assessed, they will play only a supportive role. The primary safety endpoint will be presence or absence of DLT The simulation focuses on a follow-up period for DLT assessment and ignores non DLTs toxicities or DLTs occurring outside of this time frame. This simulation refer to the escalation phase after the selection of the priming dose as that will be based on non DLTs lower grade cytokine release (eg < Grade 2; see Evaluation of a Priming Dose).

This study has been designed to establish the Maximum Tolerated Dose (MTD) defined as the dose that yields approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLTs in the interval (Equivalence Interval) 22.5% to 32.5%. The 27.5% target was chosen based on safety considerations and is considered appropriate based on simulations and expert input. Since mTPI algorithms are known to assign more patients

above the target dose compared to 3+3 designs, the target was chosen slightly below the maximum acceptable DLT rate of 33.3% (in order to protect study patients from exposure to doses with DLT rate higher than 33%). Doses with an incidence of DLT>33% cannot be selected as MTD in the current protocol therefore the decision rules implemented in the actual study are more conservative of the ones used in this simulation, therefore results of these simulations represent more aggressive scenario. In addition, in the study patients will be enrolled in cohorts of size 2-4 but constant size of 3 was assumed for all simulations.

Table 10. Simulation Parameters Selected for the Final Design

	Final Design Value
Control Parameters	
Cohort size	3 patients
Max doses levels	5 levels
Minimum number of patients on MTD to stop for success	6,**9**,12 patients
Other parameters	
Max sample size for one regimen of part 1	50 patients
DLT target rate at MTD	pT= 0.275
Equivalence Interval for DLT target rate at MTD	EI: 0.225-0.325
Prior distribution of DLT	Beta(0.5,0.5)
Threshold probability for early termination and dose exclusion	$\xi = 0.95$

Simulation Scenarios

Simulations are created to summarize the operating characteristics of the proposed model based design under multiple scenarios. In order to simulate the design, assumptions have to be made about how the data are generated. These assumptions do not affect the design or the analysis, but they are necessary to simulate patient results. The simulations assume patients are accrued in cohorts of 3 and all patients within a cohort are enrolled at the same time. The next cohort of patients is available for enrollment immediately after the previous cohort's DLT responses are obtained.

For the two competing designs (ie, 3+3 and mTPI), the following operating characteristics were assessed, by scenario, to further quantify the trade-off between precision of MTD estimation and design cost:

- Probability to select MTD:
  - Correctly (dose with 22.5%-32.5% DLT rate);
  - Underestimate (dose with <22.5% DLT rate);
  - Overestimate (dose with >32.5% DLT rate);
  - N/A (all doses declared too toxic).

- Design cost:
  - Average Number of Treated Patients;
  - Average Number of DLTs;
  - Average proportion of DLTs.

The scenarios used in simulations are summarized in Table 11:

Table 11. Dose-toxicity Scenarios used in Simulations and Their Respective Target Dose Ranges

	Probability of DLT as a function of dose				
Dose Level	Sc. 1 *MTD: level 5*	Sc. 2 *MTD: level 5*	Sc. 3 *MTD: level 4*	Sc. 4 *MTD: level 2*	Sc. 5 *MTD: level 1*
1	0.01	0.05	0.05	0.125	0.32
2	0.02	0.1	0.1	0.275	0.45
3	0.05	0.15	0.175	0.425	0.575
4	0.08	0.2	0.275	0.6	0.7
5	0.12	0.25	0.425	0.8	0.85

Figure 5. Dose-toxicity Scenarios used in Simulations

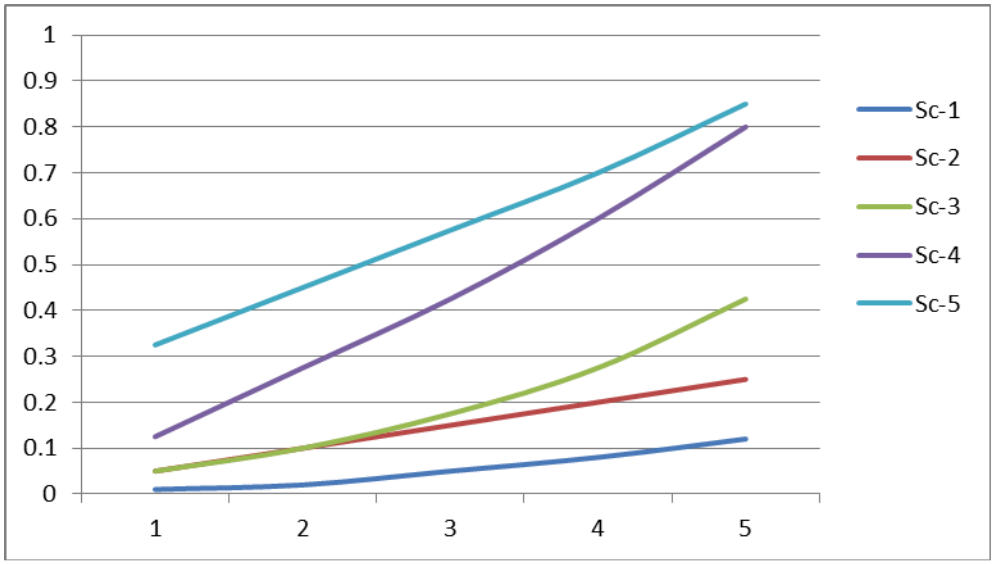

Figure 5 provides graphical summary of the same scenarios. These scenarios cover situations where the true MTD lies to the left, middle and to the right of the studied dose range and different levels of increased toxicity for each escalation step.

Operating characteristics are summarized in Table 12 and Table 13. Based on 10000 trials simulated, on average, this particular mTPI design provides more accurate estimates of MTD versus the 3+3 design, with comparable overall proportion of toxicities. In certain dose-toxicity scenarios (eg, when DLT can be observed early in the trial), mTPI may require slightly larger sample size and, consequently, duration of the study. The magnitude of trade-off between quality of MTD information obtained and design costs (such as sample size, duration and observed toxicities) varies depending on the underlying dose-toxicity relationship. A specific variant of mTPI design (cohort size 3 and stopping rule with 9 patients on MTD) was chosen among several variants examined for comparison with the 3+3 design.

Scenarios #1-3 have a relatively flat dose-toxicity profile. Scenarios #4-5 assume a more aggressive dose-toxicity profile. Both groups of scenarios cover situations where the true MTD lies to the left, middle and to the right of the studied dose range. In case of Scenarios #2 and #3, there are small increases of DLT rate from dose-to-dose. As a result, there are several doses that could trigger a stopping rule and be selected as MTD for these scenarios. Such DLT profiles may present a challenge for the algorithms to find the right dose given a generally acceptable sample size, as there will be several "competing" MTD doses. On the other hand, Scenario 4 has noticeable changes in toxicity around the true MTD dose resulting in only 1 dose adequate to be selected as MTD). Even though the sample size required to find MTD in such cases may be smaller (compared to Scenarios 2 & 3), the consequences of missing the true MTD dose are more severe because all the neighboring doses have toxicities well below or above the acceptable range of 22.5%-32.5%. Scenarios #1-2 describe two situations where all tested doses are below the target toxicity.

Design Operating Characteristics

In this section, selected operating characteristics of the mTPI design are presented. In each scenario, 10000 simulated trials were conducted and the key operating characteristics that influenced the design selection are summarized in 3. We also report similar operating characteristics for the traditional 3+3 design at the same dose levels for comparison. Since both methods operate on the same dose space, these methods are 100% comparable and providing operating characteristics of the 3+3 design (under the same dose-toxicity scenarios) serves as a useful "benchmark" of performance.

The simulations in this report were performed using the R software.

The first column in 3 contains scenario name, labeled by location of the "true" MTD under such scenario. Second column is for "Design" mTPI (n at MTD=9) or 3+3. Four columns under "MTD dose selection decision" header summarize the proportion of times (out of 10000 trials) that MTD was identified correctly, underestimated, over-estimated or not identified at all, respectively. The following definition was used to specify the above four categories:

- Correct MTD: selected dose produces 22.5%-32.5% true DLT rate
- Underestimated MTD: selected dose produces <22.5% true DLT rate
- Overestimated MTD: selected dose produces >32.5% true DLT rate
- N/A: trial stopped early

The last three columns of 3 summarize the operating characteristics associated with trial "cost": average sample size, average number and proportion of patients experiencing DLTs. These operating characteristics played an important role in design selection process by quantifying the trade-off between precision of MTD selection and exposing more patients to doses with higher toxicity levels. The studied scenarios cover situations where the true MTD lies to the left, middle and to the right of the studied dose range.

As expected, those Scenarios in which there are small increases of DLT rate from dose-to-dose present a challenge for the algorithms to find the right dose in terms of sample size, as there will be many "competing" MTD doses. For example in Scenarios #1 and #2 mTPI selects the correct MTD 90% and 44% of the times respectively. Specifically in Scenario #1, mTPI selected the correct MTD 90% of the times compared to 79% by 3+3 but required approximately 5 more patients. Similarly, in Scenario #2, mTPI estimated the correct MTD more often than 3+3 with slight increase in sample size. Also the absolute and relative numbers of toxicity events were comparable. Scenario #5 represents a situation where the DLT curve is very steep and only one dose is within the EI. mTPI selected the correct MTD 66% of the times compared to 31% by 3+3 and required approximately 5 patients more. In all scenarios #1-2-3-4-5 the performance of the mTPI method was always superior to 3+3, selecting the correct MTD at least 13% more often (35% in Scenario #5) and requiring approximately 4 more patients on average.

Stopping rules with 6, 9 and 12 patients on MTD were considered for the mTPI design and compared via simulations. These results are summarized in Table 13. The stopping rule with 9 patients on MTD performed adequately for MTD estimation and required a study sample size comparable to that of 3+3 design (Table 13). A stopping rule with 12 patients had greater chance of identifying MTD correctly (scenarios 1,2,3,4). However this added benefit came at a price of additional patients. In cases of early toxicity (eg, Scenario 5), where the first tested dose is within the EI, there were no noticeable improvements in quality of correct MTD estimation if 12 patients were required on MTD to stop, rather than 6 or 9.

In summary, since there was no *a priori* knowledge about the likelihood of a particular toxicity scenario, performance of the mTPI design under all scenarios was taken into consideration in the choice of the final design. Across all scenarios examined, a design employing the mTPI algorithm with at least n=6 at MTD (up to n=12) will have a better chance to estimate MTD correctly compared to a traditional 3+3 design, while the overall proportion of toxicities observed within a study remains acceptable and similar between mTPI and 3+3. mTPI design may result in a longer trial duration compared to the duration of 3+3 design, however, this increase is off-set by a better performance of mTPI in all simulated scenarios. Among many design parameters examined, the stopping rule (number of patients on MTD) had the most impact on the design's performance. As expected, increasing the minimum number of patients treated on MTD prior to stopping leads to a more precise MTD estimation; however this requirement would also lead to larger overall sample size, longer trial duration and greater overall number of toxicities (but not necessarily the proportion of toxicities).

Table 12. Operating Characteristics of the mTPI Design (n at MTF=9) versus Conventional 3+3 Design

		MTD dose selection decision (proportion)						
DLT Scenario	Design	CORRECT	UNDER	OVER	NA	Av Size	Num Tox	Prop tox
1:	3+3	0.79	0.20	-	0.01	17.1	1.0	0.06
	mTPI	0.90	0.10	-	0.00	21.9	1.6	0.07
2:	3+3	0.31	0.66	-	0.03	17.3	2.4	0.14
	mTPI	0.44	0.56	-	0.00	21.1	3.2	0.15
3:	3+3	0.23	0.71	0.03	0.03	17.2	2.9	0.17
	mTPI	0.38	0.45	0.17	0.00	20.9	4.1	0.20
4:	3+3	0.37	0.43	0.09	0.15	12.2	3.1	0.26
	mTPI	0.50	0.26	0.23	0.005	16.2	4.5	0.27
5:	3+3	0.31	-	0.07	0.62	7.7	2.8	0.38
	mTPI	0.66	-	0.18	0.17	11.5	4.3	0.38

Table 13. Operating Characteristics of the mTPI Design by Minimum Number of Patients on MTD

mTPI: Dose selection decision (%) by Minimum number of patients on MTD (ie, n=6,9,12)

scenario	N at MTD	% CORRECT	% UNDER	% OVER	% NA	Av Size	Num. Tox	Prop Tox
1	6	0.893	0.108	0.000	0.000	18.837	1.214	0.064
1	9	0.900	0.101	0.000	0.000	21.943	1.564	0.071
1	12	0.956	0.044	0.000	0.000	25.802	2.012	0.078
2	6	0.437	0.563	0.000	0.000	17.600	2.562	0.146
2	9	0.437	0.563	0.000	0.000	21.051	3.233	0.154
2	12	0.544	0.456	0.000	0.000	26.637	4.364	0.164
3	6	0.374	0.434	0.192	0.000	17.277	3.154	0.183
3	9	0.378	0.448	0.174	0.000	20.919	4.109	0.196
3	12	0.460	0.342	0.198	0.000	26.728	5.700	0.213
4	6	0.470	0.266	0.260	0.004	12.333	3.334	0.270
4	9	0.504	0.263	0.228	0.005	16.235	4.469	0.275
4	12	0.560	0.189	0.245	0.006	21.146	6.033	0.285
5	6	0.676	0.000	0.221	0.103	8.496	3.193	0.376
5	9	0.656	0.000	0.178	0.166	11.459	4.322	0.377
5	12	0.616	0.000	0.176	0.208	14.765	5.531	0.375

Appendix 8. Suggested Cytokine Release Syndrome Management Algorithm and Revised CRS Grading System

Adapted from D.W.Lee, et al: Current Concepts in the Diagnosis and Management of Cytokine Release Syndrome. Blood 124 (2014) 188-195.

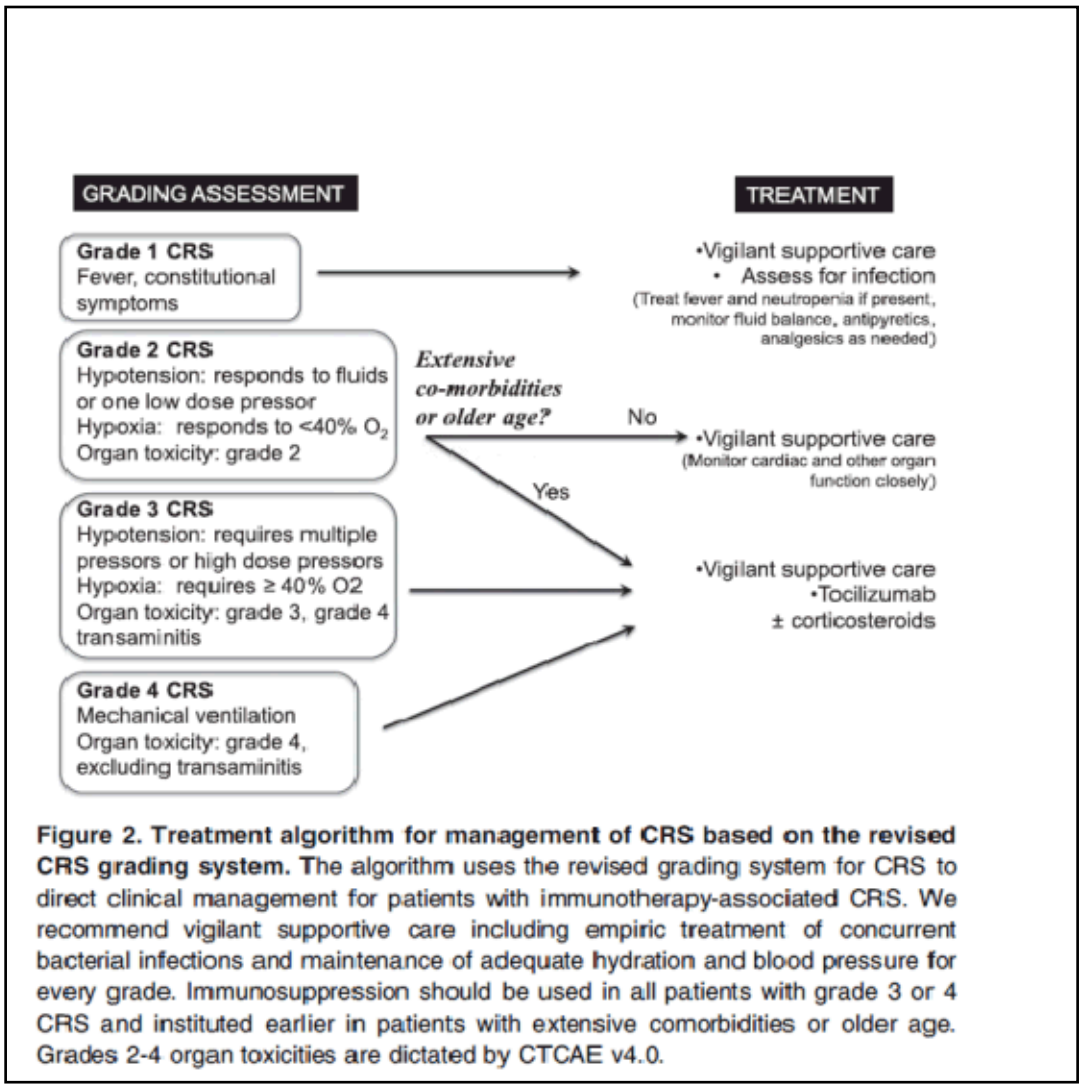

Figure 2. Treatment algorithm for management of CRS based on the revised CRS grading system. The algorithm uses the revised grading system for CRS to direct clinical management for patients with immunotherapy-associated CRS. We recommend vigilant supportive care including empiric treatment of concurrent bacterial infections and maintenance of adequate hydration and blood pressure for every grade. Immunosuppression should be used in all patients with grade 3 or 4 CRS and instituted earlier in patients with extensive comorbidities or older age. Grades 2-4 organ toxicities are dictated by CTCAE v4.0.

Suggested tocilizumab administration: 4 mg/kg over 1 hour; consider a second dose if no clinical improvement within 24 to 48 hours.

CRS Revised Grading System

Grade	Toxicity
1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
2	Grade 2 hypoxia* [decreased oxygen saturation with activity (eg, pulse oximeter <88%); intermittent supplemental oxygen] or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
3	Grade 3 hypoxia* [decreased oxygen saturation at rest (eg, pulse oximeter <88% or partial pressure of oxygen (PaO2) <=55 mm Hg)] or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
4	Life-threatening symptoms Grade 4 hypoxia* [life-threatening airway compromise; urgent intervention indicated (eg, tracheotomy or intubation)] Grade 4 organ toxicity (excluding transaminitis)
5	Death
*Modification to the Lee et al CRS Revised Grading System according to the CTCAE v4.03. Transient decreases in oxygen levels below 88% will not be considered to have met the criteria.	