A PHASE 1 STUDY OF PF-05082566 AS A SINGLE AGENT IN PATIENTS WITH ADVANCED CANCER, AND IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA (NHL)

Investigational Product Number:	PF-05082566
Investigational Product Name:	Utomilumab*
United States (US) Investigational New Drug (IND) Number:	109,154
European Clinical Trials Database (EudraCT) Number:	2011-002799-17
Protocol Number:	B1641001
Phase:	1

* Utomilumab is the proposed International Nonproprietary Name (INN) for PF-05082566 (4-1BB agonist monoclonal antibody)

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Document History

Document	Version Date	Summary of Changes
Amendment 9	06 January 2017	The Schedule of Activities for the expansion cohorts (Table 5) has been updated to include some additional assessments requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA), to reduce the number of PK and ADA sample collection, to clarify the requirements for tumor tissue collection [redacted] The background section has been updated to provide updated clinical data from the present study and to introduce a paragraph presenting explicitly the benefit/risk assessment for PF-05082566 as a single-agent or in combination with rituximab. The study objectives and endpoints have been updated to indicate that OR is the primary objective and endpoint for the expansion cohorts of Portion A and Portion B, [redacted] The study design of the Expansion Cohort of Portion A has been updated to introduce a randomized cohort testing 3 different dose levels of PF-05082566 (0.24, 0.6 and 1.2 mg/kg) in patients with melanoma who have had RECIST-defined disease progression on a previous treatment with an immune check-point inhibitor. This cohort is intended to provide additional data in support of the RP2D selection for PF-05082566 as a single-agent in patients with advanced solid tumors. The study design of the Expansion Cohort of Portion B has been updated to introduce the possibility to evaluate a lower dose level of

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		0.24 mg/kg of PF-05082566 in combination with rituximab in patients with follicular lymphoma (FL) refractory to treatment with rituximab. The overall data from the expansion cohort of Portion B will be used to select the RP2D for PF-05082566 in combination with rituximab in patients with CD20-positive non-Hodgkin's lymphoma. The inclusion criteria have been updated to: • Define better the prior treatment history required for eligibility in the expansion cohorts of Portions A and B; • Require measurable disease at study entry for patients with advanced solid tumor; • Indicate that vaccine administration is not allowed within 4 weeks prior to study entry (not applicable to inactivated vaccines). The administration section has been updated to allow the introduction of a different preparation of PF-05082566. Also the dose modification guidelines have been updated and simplified taking into account the clinical experience in the present study and that only 3 dose levels for PF-05082566 (0.24, 0.6 and 1.2 mg/kg) are currently under investigation. Administration of rituximab starting at Cycle 4 Day 0 until Cycle 10 Day 0 for patients enrolled in Portion B has been removed to obtain consistency with the rituximab dosing schedule among patients irrespective of whether local recommendations allow this re-treatment. The study procedures and assessments sections have been updated to align with the modifications introduced to the other parts of the protocol.

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		The data analysis/statistical methods section has been updated to align with and support the modifications introduced to the study design and to other parts of the protocol. Administrative updates and wording modifications have been introduced to improve readability.
Amendment 8	16 September 2015	Portion A Expansion Cohort will include other tumor types in addition to melanoma as described in Section 4.1 Inclusion Criterion 1. Under Section 4.1 Inclusion Criteria, Portion A Expansion Cohort patients must have documented disease progression on a checkpoint inhibitor (anti-CTLA-4, anti-PD1/PD-L1 antibodies) per RECIST criteria. Rationale for focusing on checkpoint inhibitor refractory disease is detailed in Section 1.4. Added a statement in the Inclusion Criterion 2 to specify that Portion B Expansion Cohort includes patients with FL that are refractory to previous rituximab therapy or DLBCL with relapsed and/or refractory disease. Total number of patients is increased to approximately 220. The following inclusion criteria were modified as below: • Baseline renal function requirements were changed from creatinine ≤ 1.5 x ULN) or estimated creatinine clearance (CrCl) ≥ 60 mL/min to creatinine ≤ 2 x ULN or CrCl ≥ 50 mL/min. • ALT/AST baseline value requirements were changed from ≤ 2.0 ULN to ≤ 2.5 ULN • Removed baseline Alkaline phosphatase requirements

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Document	Version Date	Summary of Changes
		Exclusion criteria were modified as below: • Systemic immunosuppressive regimens were reduced from 28 days to 14 days. • Therapeutic or experimental monoclonal antibodies were reduced from 60 days to 28 days. • Radiation therapy was reduced from 28 days to 14 days. • Exclusion of patients with unstable or serious concurrent medical conditions in the previous 12 months is changed to previous 6 months. • In the exclusion #18, patients with prior therapy with any anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4, was removed. Pharmacokinetic sampling requirements were updated based on requirements according to escalation and expansion cohorts for both Portions. CCI [redacted] Off treatment follow up period and intervals were updated under Section 6.3, allowing 1 month window for survival follow up. Section 5.4.7 was added to allow palliative radiotherapy during study treatment. Statement regarding palliative radiotherapy under Section 5.4.1 is removed. Off treatment criteria is updated to clarify loss of clinical benefit, allowing patients to continue study treatment who continue to demonstrate clinical benefit despite disease progression. Patients must reconsent confirming

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Document	Version Date	Summary of Changes
		understanding that they may be forgoing approved therapy with possible clinical benefit(s) by continuing with the study treatment beyond objective disease progression. Under Portion B, rituximab maintenance dosing beginning at the 4th cycle is now optional and at the discretion of the investigator. CCI [redacted] Sample Size Determination was updated to include rationale for expansion cohort sample size. CCI [redacted] Schedule of Activities (SOA) tables were updated to align with the changes described as above. References and Appendix 1 list of abbreviations were updated. Minor editorial changes were made for consistencies throughout the document.
Amendment 7	29 April 2015	Schedule of Activities was revised as follows: • Study visits were reduced to q4 weeks from Cycle 2 for expansion cohorts. • On-treatment biopsy requirement was removed for the Portion B expansion cohort. Baseline biopsy requirement was replaced with existing archival tissue sample. • Portion B patients will repeat rituximab dosing. Rituximab (375 mg/m^2) will be

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Document	Version Date	Summary of Changes
		administered every 8 weeks, in accord with the local and institutional Standard of Care, starting at Cycle 4 Day 0 until Cycle 10 Day 0 (or until discontinuation of study treatment due to progression, unacceptable toxicity, or consent withdrawal, whichever occurs earlier). To better inform a decision on the RP2D, expansion cohort A will enroll patients with previously treated metastatic melanoma in each of 3 different doses (0.24 mg/kg, 1.2 mg/kg and 10 mg/kg). Patients enrolled under Portion B expansion cohort will receive PF-05082566 1.2 mg/kg in combination of rituximab. Under this amendment, patients who are rituximab refractory or resistant CD-20+ FL or DLBCL will be enrolled. CCI [redacted] Added clarification to Inclusion Criteria 1, 2 and 3, and corrected Inclusion Criterion 13 from Amendment 6. Exclusion criterion 1 was revised to allow enrollment of patients with stable brain metastases. Exclusion criterion 3 was revised to provide clarity to the steroid administration prior to study entry. Section 4.3, Lifestyle guidelines was updated to align with the current standard language. Dose hold, resumption and reduction scheme for expansion cohorts were added. To reduce radiation exposure, the frequency of tumor assessments were reduced for patients who remain on study therapy for >10 months. CCI [redacted]

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Document	Version Date	Summary of Changes
		Added details on the analysis of immunogenicity data. Clarification was made to specify Fridericia's QT correction formula for exclusion criterion 10. Clarification was made to distinguish patients enrolled in Japan from Japanese (ethnic) patients who are enrolled from the sites outside of Japan. CCI [redacted] Several administrative changes were made throughout the document to clarify language associated with the Schedule of Activities and to resolve inconsistencies. Adverse Events and Communication of Results by Pfizer sections were updated to match current Pfizer standards. Administrative changes were made to enhance readability.
Amendment 6	21 November 2014	Main changes are to add Japan cohort(s) in Portion A to evaluate safety, tolerability and PK profile of PF-05082566 as a single-agent in patients enrolled in Japan. <u><Japan specific changes></u> <u>General Study Design</u> Additional Japan cohorts with paired tumor biopsy in Portion A were added. Standard 3+3 design is applied to the Japan cohort(s). Japan specific changes required by local regulation were added. <u>Patient Selection</u>

Document	Version Date	Summary of Changes
		Japan specific changes required by local regulation were added. <Common changes> Exclusion of >4 cm liver lesions was removed for the patients who enrolled in expansion cohorts since no severe drug-related AEs related to hepatotoxicity have been observed based on current study safety data. CCI [redacted] Mandatory study visits are reduced for patients in expansion cohorts to Day 1 of each cycle from Cycle 4, at the discretion of the investigator. Administrative Changes Multiple administrative changes were made throughout the document to clarify language associated with the Schedule of Activities to resolve inconsistencies and to incorporate changes in the Pfizer clinical protocol template.
Amendment 5	05 February 2014	General Study Design Added language to allow another Portion B expansion cohort at any of the previously tested dose escalation dose levels. Study Treatment Exclusion Criterion 18 was changed to allow the inclusion of patients who have previously received treatment with an immunotherapy regimen (including anti-PD-1 and anti-CTLA4) if such treatment was not associated with clinically significant adverse events. Based on current study safety data indicating that PF-05082566 infusion does not result in clinically significant infusion reactions. Therefore, after completion of the 0.6 mg/kg

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Document	Version Date	Summary of Changes
		dose level, there will no longer be a waiting period between the first dose of PF-05082566 for a patient and the first dose of rituximab for the next patient in the same dose cohort Administrative Changes Multiple administrative changes were made throughout the document to clarify language associated with the Schedule of Activities, resolve an inconsistency in stated dose levels in the Statistical Design section and to improve the readability of the protocol.
Amendment 4	24 May 2013	General Study Design The protocol indication is more detailed to incorporate changes in Pfizer clinical protocol template instructions. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] Study Treatment For portions A and B, patients clinically benefiting from study treatment without unacceptable toxicity, objective disease progression, or withdrawal of consent will be given the opportunity to continue treatment after 8 cycles of therapy following approval from Pfizer. Continued treatment will be on a reduced visit schedule, or as clinically indicated. Patient Selection

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Document	Version Date	Summary of Changes
		Inclusion Criterion 2 for Portion B the patient population for the expansion cohort will be CD20+ B cell NHL patients with a history of rituximab-refractory disease. Inclusion Criterion 3 changed to accurately reflect the Cheson criteria for disease assessment with least one extranodal tumor mass >1.0 cm in the greatest transverse diameter or in the case of malignant lymph nodes >1.5cm in the greatest transverse diameter. Exclusion Criterion 15 changed to include recent (within the past year) or active suicidal ideation or behavior per the updated Pfizer protocol template. Exclusion Criterion 17 added to exclude patients with a history of active ethanol abuse, hepatitis or liver lesions greater than 4 cm on the longest axis. Exclusion Criterion 18 added to exclude patients with previous therapies containing drugs that specifically target T cell costimulation or checkpoint pathways. <u>Administrative</u> A risk/benefit statement was added to the end of the Introduction to conform to the Pifzer protocol guidance changes. New Pfizer protocol Sections were added to incorporate changes in the Pfizer clinical protocol template changes. These include Section 4.4 on sponsor qualified medical personnel, Section 5.4.4 on the use of anti-inflammatory therapies, Section 5.2.5 on dose interruptions was added, and Section 8.5.1 Protocol-Specified Serious Adverse Events (which clarifies that there are no protocol-specified AEs in this protocol). In Section 8.2 and table footnotes, the SAE

Document	Version Date	Summary of Changes
		active reporting period was increased to 60 days based on the Pfizer protocol template changes. Section 9.2.2 (Simulations and Operating Characteristics in TITE-CRM) was removed as this material is covered in the Statistical Analysis Plan. Other edits were made to enhance readability and to clarify language throughout the protocol.
Amendment 3	25 July 2012	Detailed rituximab dose administration guidelines are provided for Portion B. Guidelines for management of rituximab related infusion reactions are also provided. Additional pregnancy testing as indicated in Schedule of Activities per the updated protocol template and guidelines for testing are provided per the updated protocol template. Clarification of measurable disease for Portion B. Clarification on B-cell neoplasms excluded from the study. Adequate bone marrow function, for Portion A defined as absolute neutrophil count (ANC) ≥1.5 x 10^9/L (≥1,500/μL), platelet count ≥100 x 10^9/L (≥100,000/μL), and hemoglobin >9.0 g/dL (>5.6 mmol/L), and for Portion B as ANC ≥1.0 x 10^9/L (≥1,000/uL), platelet count ≥75 x 10^9/L (≥75000/μL), and hemoglobin >9.0 g/dL (>5.6 mmol/L). Lifestyle guidelines detailed per the updated protocol template. Survival follow-up every 3 months. Record retention guidelines updated per the protocol template. Administrative changes due to the protocol template update and to enhance readability.
Amendment 2	13 February 2012	Definition of dose sought in Portion B redefined to be in line with Portion A (Optimal

Document	Version Date	Summary of Changes
		Biological Dose revised to Recommended Phase 2 Dose). CCI [redacted] Revision to PK schedule (addition of end of infusion draw). Addition of hepatitis B core antibody assessment to hepatitis status panel at baseline. Removal of several laboratory assessments in order to streamline data collection and review. Addition of instructions in the cases of mixed response. Revision of Adverse Event section to align with recently updated protocol template per CT3 guidance and US FDA Final Rule. Administrative changes and clarifications made throughout.
Amendment 1	21 January 2011	Revisions made per the FDA's request during the IND review period.
Original protocol	09 December 2010	Not Applicable

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

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PROTOCOL SUMMARY

Indication

PF-05082566, also known as utomilumab, as a single-agent is under investigation for the treatment of patients with advanced solid tumor malignancies or B cell lymphoma. PF-05082566 in combination with rituximab is also under investigation for the treatment of patients with relapsed or refractory CD20-positive non-Hodgkin's lymphoma (NHL).

Rationale

Study Rationale

PF-05082566 is a fully human IgG2 monoclonal antibody (mAb) and promising new molecular entity that binds to human 4-1BB with high affinity and specificity. In vitro and in vivo data demonstrated significant immunomodulatory activity and anti-tumor activity of PF-05082566 when dosed as a single-agent and in combination with therapeutic mAbs that have the potential to induce antibody dependent cell mediated cytotoxicity (ADCC). Preclinical studies have shown favorable pharmacokinetics (PK) and metabolic properties which suggest that it may be well tolerated when administered intravenously (IV). Based upon the above considerations, this first-in-human Phase 1 study will assess the safety and establish the maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) of single-agent PF-05082566 in patients with advanced solid tumors or B-cell lymphoma, and the MTD and RP2D of PF-05082566 given in combination with rituximab in patients with non-Hodgkin's B-cell lymphoma.

Consecutive cohorts of patients will receive PF-05082566 administered as a single-agent once every four weeks as an IV infusion (Portion A). Based on preclinical studies, the dosing will begin at 0.006 mg/kg. Once the safety of once every 4-week dosing of PF-05082566 as a single-agent is established at 0.06 mg/kg, dosing of PF-05082566 once every 4 weeks will be tested in combination with rituximab, given once weekly for 4 weeks, in patients with CD20-positive NHL (Portion B). Patients will be assessed for dose-limiting toxicities (DLTs) for the first 2 cycles of treatment in both Portions. PK properties of PF-05082566 and rituximab will be assesse CCI

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Taken these data together, 3 PF-05082566 dose levels will be further evaluated in Portion A

expansion cohorts: 0.24 mg/kg, 0.6 mg/kg and 1.2 mg/kg, and 2 dose levels may be further evaluated in Portion B expansion cohorts: 1.2 mg/kg and 0.24 mg/kg based on emerging data.

Portion A includes dose escalation cohorts and Japan cohort(s). The Japan cohort(s) will be conducted in Japanese patients at Japanese sites following the completion of enrollment of the dose escalation cohorts in Portion A of this study. Patients enrolled into the Japan cohort(s) will receive PF-05082566 administered as a single-agent once every 4 weeks as an IV infusion. Patients enrolled in Japan will follow the same eligibility criteria, study procedures (unless otherwise specified), and discontinuation criteria as those patients in the dose escalation cohort of Portion A. As of June 2016, seven (7) patients have been enrolled in the 2 cohorts in Japanese patients and the 2 tested dose levels of PF-05082566 (5.0 and 10 mg/kg) were well tolerated with no DLTs reported. Japanese sites are currently participating in the expansion cohorts of Portion A and Portion B.

Portion A expansion cohorts include patients with solid tumors who have documented disease progression on a previous immune checkpoint inhibitor therapy (anti-CTLA-4, anti-PD-1/PD-L1 antibodies) per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 criteria (see Section 4.1 for the definition of disease that progressed from previous immune checkpoint inhibitor therapy).

Portion B expansion cohorts include patients with follicular lymphoma (FL) refractory to rituximab (see Section 4.1 for the definition of FL disease refractory to rituximab) or diffuse large B-cell lymphoma (DLBCL) with relapsed or refractory disease.

STUDY OBJECTIVES AND ENDPOINTS

Objectives

Primary Objective – Dose Escalation Cohorts

Portion A:

- To assess safety and tolerability at increasing dose levels of single-agent PF-05082566 in patients with advanced solid tumors or B-cell lymphoma in order to estimate the MTD and select the RP2D.

Portion B:

- To assess safety and tolerability at increasing dose levels of PF-05082566 given in combination with rituximab in patients with relapsed or refractory CD20-positive NHL in order to estimate the MTD and select the RP2D.

Secondary Objectives – Dose Escalation Cohorts

Portion A:

All secondary objectives listed below are to be evaluated for PF-05082566 as a single-agent in patients with advanced solid tumors or B-cell lymphoma.

- To evaluate the overall safety profile;
- To characterize the pharmacokinetics of PF-05082566;
- To evaluate the immunogenicity of PF-05082566;
- To characterize the effects of PF-05082566 on QTc;
- To evaluate the anti-tumor effect of PF-05082566.

Portion B:

All secondary objectives listed below are to be evaluated for PF-05082566 in combination with rituximab in patients with relapsed or refractory CD20-positive NHL.

- To evaluate the overall safety profile;
- To characterize the pharmacokinetics of PF-05082566 and rituximab given in combination;
- To evaluate the immunogenicity of PF-05082566 and rituximab;
- To characterize the effects of PF-05082566 in combination with rituximab on QTc;
- To evaluate the anti-tumor effect of PF-05082566 in combination with rituximab.

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Primary Objective – Expansion Cohorts

Portion A:

- To estimate the objective response rate of PF-05082566.

Portion B:

- To estimate the objective response rate of PF-05082566 in combination with rituximab.

Secondary Objectives – Expansion Cohorts

Portion A:

All secondary objectives listed below are to be evaluated for PF-05082566 as a single agent in patients with advanced solid tumors or B cell lymphoma.

- To evaluate the overall safety profile;
- To characterize pharmacokinetics of PF-05082566;
- To evaluate the immunogenicity of PF-05082566;
- To characterize the effects of PF-05082566 on QTc;
- To evaluate the anti-tumor effect of PF-05082566.

Portion B:

All secondary objectives listed below are to be evaluated for PF-05082566 in combination with rituximab in patients with relapsed or refractory CD20-positive NHL.

- To evaluate the overall safety profile;
- To characterize pharmacokinetics of PF-05082566 and rituximab given in combination;
- To evaluate the immunogenicity of PF-05082566 and rituximab;
- To characterize the effects of PF-05082566 in combination with rituximab on QTc;
- To evaluate the anti-tumor effect of PF-05082566 in combination with rituximab.

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Endpoints

Primary Endpoint – Dose Escalation Cohorts

- First 2 cycles DLTs.

Secondary Endpoints – Dose Escalation Cohorts

Portion A:

- Safety: Adverse events as characterized by type, frequency, severity [as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03], timing, seriousness and relationship to study therapy PF-05082566; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; Vital signs (blood pressure and pulse rate);

- PK: PF-05082566 [C_{max}, C_{trough}, T_{max}, Area under the concentration vs time curve $(AUC)_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, AUC_{tau}, clearance (CL), and V_{ss}, as data permits];

- Anti-Drug Antibody levels for PF-05082566;

- QTc interval;

- Objective response as assessed by RECIST v1.1;

- Duration of response;

- Time to tumor response;

- Progression-free survival;

- Overall survival.

Portion B:

- Safety: Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566 in combination with rituximab; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; Vital signs (blood pressure, pulse rate, and body temperature);
- PK: PF-05082566 (C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ AUC_{tau}, CL and V_{ss}, as data permits) and rituximab (C_{max} and C_{trough});
- Anti-Drug Antibody levels for PF-05082566 and rituximab;
- QTc interval;
- Objective response as assessed using the Cheson 2007 criteria;
- Duration of response;
- Time to tumor response;
- Progression-free survival;
- Overall survival.

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Secondary Endpoints – Expansion Cohorts

Portion A:

- First 2 cycles DLTs;
- Safety: Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; Vital signs (blood pressure and pulse rate);
- PK: PF-05082566 (C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ AUC_{tau},CL, and V_{ss}, as data permits);
- Anti-Drug Antibody levels for PF-05082566;
- QTc interval;
- Duration of response;
- Time to tumor response;
- Progression-free survival;
- Overall survival.

Portion B:

- First 2 cycles DLTs;
- Safety: Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566 in combination with rituximab; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; Vital signs (blood pressure, pulse rate, and body temperature);

- PK: PF-05082566 (C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ AUC_{tau}, CL, and V_{ss}, as data permits) and rituximab (C_{max} and C_{trough});
- Anti-Drug Antibody levels for PF-05082566 and rituximab;
- QTc interval;
- Duration of response;
- Time to tumor response;
- Progression-free survival;
- Overall survival.

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STUDY DESIGN

This is a Phase 1, open label, multi-center, multiple-dose study of single-agent PF-05082566 in patients with advanced solid tumors or B-cell lymphoma, and of PF-05082566 in combination with rituximab in patients with relapsed or refractory CD20-positive NHL. Approximately 270 patients are expected to be enrolled in the overall study.

There are 2 portions in this clinical study. Portion A is designed to assess the safety and tolerability, PK CCI and to estimate the MTD/pharmacologically active dose and determine the RP2D of PF-05082566 administered as a single agent in patients with advanced solid tumors or B-cell lymphoma. Two cohort(s) will be enrolled at clinical sites in Japan to evaluate safety, tolerability, and PK profile of PF-05082566 as a single agent in Japanese patients. Portion B is designed to assess the safety and tolerability, PK CCI and to estimate the MTD and determine the RP2D of PF-05082566 in combination with rituximab in patients with relapsed or refractory CD20-positive NHL. Acceptable safety of the single agent within the first 3 cohorts of Portion A will trigger the initiation of Portion B. Portions A and B will then escalate simultaneously and independently of each other.

Dose Escalation: Portion A

The criteria for dose escalation in Portion A will be based on the standard 3+3 design for dose escalation up to 0.3 mg/kg. For dose escalation above 0.3 mg/kg, doses of PF-05082566 will be assigned to each enrolled patient using a Time-to-Event Continual Reassessment Method (TITE-CRM) as this method has been found to be practical based on experience in Portion B.

PF-05082566 will be administered in escalating doses with available dose levels including the following: 0.006, 0.03, 0.06, 0.12, 0.18, 0.24, 0.30 (using the 3+3 design), and 0.6, 1.2, 2.4, 5.0, and 10 mg/kg (using the TITE-CRM design) by intravenous (IV) infusion of 1 hour (-5/+15 min) every 4 weeks. As of June 2016, the highest planned single-agent dose of 10 mg/kg was tested with no DLTs reported. Patients tolerated PF-05082566 well at the highest planned dose of 10 mg/kg. If a dose reduction is needed for patients being treated with 0.6 to 10 mg/kg, a dose reduction may be made from the next highest planned dose level to one of the following specific dose levels: 0.45, 0.9, 1.8, 3.6, and 7.5 mg/kg. In addition, these intermediate dose levels may be used for dose escalation if more than 1 DLT is observed at the preceding regular dose level.

Each patient will initially receive the first dose on Cycle 1 Day 1 with a 28-day observation period. Cycle 2 Day 1 will start on Day 29. Patients may continue treatment up to a maximum of 2 years from the first dose of study drug, or until one of the patient withdrawal criteria under Section 6.4 becomes a reason to permanently discontinue study treatment.

Initially, 3 patients will be treated at each dose level. For the first 3 cohorts (PF-05082566 given as a single agent at 0.006, 0.03, or 0.06 mg/kg), there will be a minimum 7-day time window between the first dose of a patient and the first dose of the next patient in the same cohort. For all subsequent patients enrolled up to the 0.6 mg/kg dose

level, a minimum 72 hour window will apply between first doses. Current study safety data indicates that PF-05082566 infusion does not result in clinically significant infusion reactions. Therefore, after completion of the 0.6 mg/kg dose level, there will no longer be a waiting period between patients in the same dose cohort and in dose expansion cohorts.

The dosing interval may be reconsidered and amended during the study based on the emerging safety and PK/CC data.

Japan Cohort(s) in Portion A:

The Japan cohort(s) will be conducted at Japanese sites following completion of enrollment of the dose escalation cohorts in Portion A of this study. Patients enrolled into the Japan cohort(s) will receive PF-05082566 administered as a single agent once every four weeks as an IV infusion. Patients enrolled in Japan will follow the same eligibility criteria, study procedures (unless otherwise specified), and discontinuation criteria as those patients in the dose escalation cohort of Portion A. The Japan cohort(s) will enroll approximately 9 patients in 2 cohorts. These cohorts will consist of 3 patients at 1 dose level below the MTD and 6 patients at the MTD based on non-Japanese population in Portion A.

Dose escalation in the Japan cohort(s) will be based on the standard 3+3 dose escalation design at 2 dose levels, 5.0 mg/kg and 10 mg/kg. Patients recruited in Japan will be enrolled and analysed to confirm safety, tolerability, and PK profile of PF-05082566 in Japanese patients. These patients will complete the first 2 cycles of PF-05082566 as a single-agent at a dose previously tested in non-Japan cohorts to evaluate potential DLTs.

The 5 mg/kg dose (every 4 weeks) has been chosen as the starting dosage for the Japan cohort. 5 mg/kg is well tolerated in a non-Japanese population, and there were no observed DLTs in Portion A at 5 mg/kg. PF-05082566 will be administered to 3 Japan cohort patients with advanced solid tumors or B cell lymphoma. After enrollment is complete, safety data from at least 2 cycles will be obtained and analyzed. If the 5 mg/kg dose level is found to be safe, escalation to 10 mg/kg dose level will occur. Lower dose levels may be explored at any time during the study if this is clinically and scientifically warranted. Study centers will receive a notification if additional dose levels are explored.

Each patient will initially receive the first dose on Cycle 1 Day 1 with a 28-day observation period. Cycle 2 Day 1 will start on Day 29. After completion of Cycle 2, patients will be asked to sign an additional consent document for confirmation of the patient's willingness to continue participation in this study before starting Cycle 3. Patients clinically benefiting from study treatment will be given the opportunity to continue treatment up to a maximum of 2 years from the first dose of study drug, or until one of the patient withdrawal criteria under Section 6.4 becomes a reason to discontinue study treatment.

Expansion Cohorts: Portion A

As of June 2016, the highest planned single-agent dose of 10 mg/kg PF-05082566 was tested with no DLTs reported in Portion A, and as of September 2016, 34 patients with advanced solid tumor, including 20 patients with melanoma, who had documented disease progression per RECIST v1.1 on a previous immune checkpoint inhibitor therapy (see Section 4.1 for the definition of disease that progressed from previous immune checkpoint inhibitor therapy)

have been enrolled in the expansion cohorts of Portion A and treated at the 0.24 or 1.2 mg/kg dose levels of PF-05082566. Because the RP2D of PF-05082566 has not yet been determined in Portion A, approximately 40 additional patients with melanoma who had documented disease progression per RECIST v1.1 on a previous immune checkpoint inhibitor therapy will be randomized 2:1:1 to treatment with single agent PF-05082566 at the 0.6, 0.24, or 1.2 mg/kg dose levels. The objective of the expansion cohorts is to provide additional safety, tolerability, PK/CCI and preliminary efficacy data for PF-05082566 in order to provide support for the selection of the RP2D. CCI

Dose Escalation: Portion B

The doses of PF-05082566 will be assigned to each enrolled patient using a TITE-CRM.

Safety of the single agent within the first 3 cohorts of Portion A will trigger the initiation of Portion B. The initiation of Portion B may occur after all patients in the single-agent 0.06 mg/kg cohort have completed Cycle 1 and received their second dose. Enrollment will then begin with PF-05082566 at a dose of 0.03 mg/kg and escalating at the same dose intervals as listed for Portion A. PF-05082566 will be given to patients IV (every 4 weeks) in combination with rituximab (375 mg/m^2, every week x 4 weeks). Patients clinically benefiting from study treatment without unacceptable toxicity, objective disease progression, or withdrawal of consent will be given the opportunity to continue treatment up to a maximum of 2 years from the first dose of study drug.

The first dose of PF-05082566 will be given approximately 24 hours after the second weekly full dose of rituximab (defined as either the planned dose or in the case of infusion reactions, at least 50% of planned rituximab dose; see Section 5 for details). For the first cohort (PF-05082566 given at 0.03 mg/kg) there will be a minimum 7 day window between the first dose of PF-05082566 for a patient and the first dose of rituximab for the next patient. For all subsequent dose escalation/de-escalation cohorts, up to 0.6 mg/kg, a minimum 72 hour window will apply between the first dose of PF-05082566 for a patient and the first dose of rituximab for the next patient in the same cohort. Updated study safety data indicate that PF-05082566 infusion does not result in clinically significant infusion reactions. Therefore, after completion of the 0.6 mg/kg dose level, there will no longer be a waiting period between the first dose of PF-05082566 for a patient and the first dose of rituximab for the next patient in the same dose cohort.

Japan will not participate in Portion B until determination of the MTD of PF-05082566 as a single agent in Japan cohort. Following the completion of Japan cohorts in Portion A, the combination of PF-05082566 with rituximab may also be tested in order to evaluate the safety of the combination therapy in patients enrolled in Japan. Enrollment of Japan cohort in Portion B is permitted and is dependent on the progress and status of the ongoing Portion B, as well as further development strategy.

Expansion Cohorts: Portion B

As of June 2016, the highest planned dose of 10 mg/kg PF-05082566 in combination with rituximab was tested with no DLTs reported in Portion B, and as of September 2016, 10 patients with rituximab-refractory FL (see Section 4.1 for definition of FL disease refractory to rituximab) and 4 patients with relapsed or refractory DLBCL have been enrolled in the expansion cohort of Portion B and treated at the 1.2 mg/kg dose level of PF-05082566. Because the RP2D of PF-05082566 administered in combination with rituximab has not yet been determined in Portion B, the expansion cohort of Portion B will enroll up to 100 patients with rituximab-refractory FL who will be treated with rituximab in combination with PF-05082566 at the 1.2 mg/kg and, following an assessment of the tolerability, efficacy, CCI and PK data collected for the combination of PF-05082566 at 1.2 mg/kg plus rituximab, at the 0.24 mg/kg dose level. In the first cohort (FL-1), up to 20 patients will be treated with rituximab in combination with PF-05082566 at 1.2 mg/kg and in the second cohort (FL-2) up to 20 patients may receive rituximab in combination with PF-05082566 at 0.24 mg/kg. The PF-05082566 dose level to be administered in the third cohort (FL-3) will be selected based on the overall evaluation of tolerability, efficacy, CCI and PK data collected for the combination of PF-05082566 plus rituximab in FL-1 and FL-2 (if this cohort is enrolled). In FL-3, approximately 60 patients will receive rituximab in combination with PF-05082566 either at the 0.24 or 1.2 mg/kg dose level. The objective of this expansion cohort is to provide additional safety, tolerability, PK/CCI and preliminary efficacy data for PF-05082566 given in combination with rituximab in order to provide support for the selection of the RP2D. CCI [redacted]

[redacted]

SCHEDULE OF ACTIVITIES:

Table 1. Schedule of Activities: Portion A (PF-05082566 Alone: Dose Escalation Only)

	Screen[1]	CYCLE 1				CYCLE 2-8				>Cycle 8[22,24,31]	End of Treatment[29]	Follow up[30]
Protocol Activity	**Within 28 days prior to enrollment**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1 (±) 2**	**Day 8 (±) 2**	**Day 15 (±) 2**	**Day 22 (±) 2**	**Day 1 (±) 2**		
Visit Window												
Informed Consent[2]	X											
Tumor History[3]	X											
Medical History[4]	X											
Physical Examination[5]	X	X				X				X	X	
ECOG Performance Status[6]	X	X				X					X	
Baseline Signs and Symptoms[7]	X											
Vital Signs (BP and pulse)[8]	X	X	X	X	X	X				X	X	
Safety Labs/Measurements												
12-Lead ECG[9]	X	X	X	X		X				X	X	
Hematology[10]	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[12]	X	X	X	X	X	X				X	X	
Urinalysis[13]	X	X									X	
Pregnancy test[14]	X	X				X				X	X	
Hepatitis B and C testing [hepatitis B surface antigen and core antibody; anti-hepatitis C antibody]	X											
Endocrine function assessment[15]	X	As clinically indicated										
LVEF assessment[16]	X	As clinically indicated										

Table 1. Schedule of Activities: Portion A (PF-05082566 Alone: Dose Escalation Only)

	Screen[1]	CYCLE 1				CYCLE 2-8				>Cycle 8[22,24,31]	End of Treatment[29]	Follow up[30]
Protocol Activity	**Within 28 days prior to enrollment**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1 (±) 2**	**Day 8 (±) 2**	**Day 15 (±) 2**	**Day 22 (±) 2**	**Day 1 (±) 2**		
Registration and Treatment												
Registration[17]		X										
Administration of PF-05082566[18]		X				X				X		
Tumor assessments												
CT or MRI scan or equivalent[19]	X	To be assessed every 8 weeks (±1 week) for the first 10 months on study treatment, then subsequently every 16 weeks (±1 week)									X	X
Other clinical assessments												
AEs[20]		Monitored and Recorded Continuously									X	
Review Prior/Concomitant Medication[21]	X	Monitored and Recorded Continuously									X	X

[redacted]

Table 2. Schedule of Activities: Portion A (PF-05082566 Alone: Dose Escalation Only): Pharmacokinetic, CCI Assessments

	Cycle 1 and Cycle 2					Cycle 3				Cycle 4			Cycle >4	End of Treatment[29]	Follow up[30]
Assessments [(±) 2 days for cycles >1]	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 3**	**Day 28**	**Day 1**		
Blood for PF-05082566 PK[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CCI															
CCI															
CCI															
CCI															
Blood for Immunogenicity (ADA) testing[27]	X		X	X		X		X		X			X	X	X
CCI															
CCI		←	←	←	←	←	←	←	←	←	←	←	→		

Footnotes for Schedule of Activities – Portion A (PF-05082566 Alone) Table 1 and Table 2.

*Patients enrolled into the Japan cohort(s) should follow the same schedule of assessments as non-Japanese patients in Portion A dose escalation cohort.

1. Screening: To be performed within 28 days prior to enrollment (Pfizer signature of the enrollment form).

2. Informed Consent: Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period. In Japan, after completion of cycle 2, patients will be asked to sign an additional consent document for confirmation of the patient's willingness to continue participation in this study before starting cycle 3.

3. Tumor History: To be collected within 28 days prior to enrollment. Includes oncology history; information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure based on Disease Specific Guidelines.

4. Medical History: To be collected within 28 days prior to enrollment. Includes history of other diseases (active or resolved) and concomitant illnesses.

5. Physical Examination: Includes major body systems. Weight for the purposes of dose calculation must be recorded at Screening and within 7 days pre-dose Day 1 of each cycle. Height will be measured at baseline only.

6. ECOG Performance Status: ECOG performance scale is available in Appendix 4.
7. Baseline signs and symptoms: Patients will be asked about any signs and symptoms experienced within the past 14 days prior to enrollment. During trial treatment any new or worsened conditions since baseline should be reported on the Adverse Event (AE) CRF.
8. Vital Signs: Blood pressure and pulse rate will be recorded.
9. Triplicate 12-Lead electrocardiogram (ECG): At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. ECGs will be collected as follows: a) at Screening; b) On Cycle 1 Day 1 (C1D1), at pre-dose, 1.5 hr post start of infusion and 24 hrs post-dose; c) On Cycle 1/ Days 8 and 15; d) On Cycles ≥2 Day 1, at 1.5 hr post start of infusion f) at End of Treatment. If the mean QTc interval is prolonged (>500 msec corrected by Fridericia's formula), then the ECGs should be re-evaluated by a qualified person at the center for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
10. Hematology: No need to repeat on C1D1 if the screening assessment is performed within 7 days prior to that date. To be performed weekly. If during the first 2 cycles of treatment a grade 4 hematologic event is evident, the hematology assessment should be repeated at least every other day to assess for events qualifying as DLT. See Table 8 for Laboratory Tests list.
11. Blood Chemistry: No need to repeat on C1D1 if the screening assessment is performed within 7 days prior to that date. To be performed weekly. See Table 8 for Laboratory Tests list.
12. Coagulation: No need to repeat on C1D1 if the screening assessment is performed within 7 days prior to that date. To be performed weekly for Cycle 1 and on Day 1 for all remaining cycles. See Table 8 for Laboratory Tests list.
13. Urinalysis: Dipstick is acceptable. Microscopic analyses if dipstick is abnormal. No need to repeat on C1D1 if the screening assessment is performed within 7 days prior to that date. To be performed at baseline and end of treatment. See Table 8 for Laboratory Tests list.
14. Serum/Urine Pregnancy Test: For female patients of childbearing potential, who do not fit for the definition of "female patients who are not of childbearing potential" in inclusion criterion 11, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting administration of study treatment: once at the start of screening and once at the baseline visit, immediately before administration of the first dose of study treatment. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
15. Endocrine function assessment during treatment to be performed in cases of suspected hypoadrenalism or hypopituitarism. See Table 8 for Laboratory Tests list.
16. LVEF assessment: measurement of ejection fraction by echocardiogram (ECHO), multigated acquisition (MUGA) scan, or an equivalent methodology.
17. Registration: Patient number and dose level allocation operated by Pfizer.
18. PF-05082566 administration: PF-05082566 will be administered once in 4 weeks as a 1-hour (-5/+15 min) IV infusion (each cycle =28 days). Refer to Section 5.4.
19. Tumor Assessments: Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans. Brain scans and bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out CNS metastases. CT or MRI scans to be done once every 8 weeks (±1 week) for the first 10 months on study treatment, then subsequently every 16 weeks (±1 week) until objective disease progression. Confirmation of response (CR/PR) should be done at least 4 weeks after the initial response for patient with advanced solid tumors. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. Patients whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 16 weeks (±1 week).

20. AE Assessment: AEs should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAE)s, 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 60 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

21. Concomitant Medications: All concomitant medications including supportive care drugs (eg, Anti-emetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases should be recorded in the CRF.

22. Blood for PF-05082566 Pharmacokinetics: Blood samples will be collected during Cycle 1 and Cycle 2 on (a) Day 1 at pre-dose, end of infusion, and at 1.5, 2, 6 and 24 hrs post start of infusion; (b) on Days 3, 8, 15, and 22. During Cycle 3 on (c) Day 1 at pre-dose, end of infusion, 1.5 and 24 hrs post start of infusion; (d) on Days 8, 15, and 22. During Cycle 4 on (e) Day 1 at pre-dose, end of infusion, and at 1.5 hr post start of infusion; (f) on Days 3 and 28 after the last dose administration. The PK sample for Day28 following the Cycle 4 dose of PF-05082566 need not be collected if a patient undergoes PF-05082566 dosing for additional cycles or if the patient starts another cancer therapy. If a patient continues with additional cycles of therapy (up to 2 years), PK samples will be collected pre-dose, end of infusion, and at 1.5 hours post start of infusion in each cycle. Timing of sampling may be modified based on emerging PK data. For patients ending from the study, a PK sample should be collected at the End of Treatment assessment. In Japan, patients will be hospitalized for PK sampling for at least the first 2 days of the first cycle of dosing of PF-05082566.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

27. Blood for Immunogenicity (ADA) testing: Blood for immunogenicity testing will be collected at a) in Cycle 1 and Cycle 2 Day 1 at pre-dose and Days 8 and 15; b) in Cycle 3 at Day 1 pre-dose and Day 15; c) in Cycle 4 at Day 1 pre-dose. If a patient continues with additional treatment cycles (Cycle >4), ADA samples will be collected at pre-dose in the higher cycles. For patients ending from the study therapy, immunogenicity samples should be collected at the End of Treatment assessment day. If ADAs are detected, additional samples may be collected every 3 months until ADA levels return to baseline. For patients who remain positive for ADA during the follow-up phase, Immunogenicity (ADA) samples should be collected at the same time as disease assessments are being performed until ADA levels return to baseline or until the patient enters the survival follow phase.

CCI [redacted]

29. End of Treatment: To be performed approximately 28 days after the last dose of study treatment. Obtain these assessments if not completed during the previous week (during the previous 6 weeks for tumor assessments).

[redacted]

30. Follow up period: Patients should be evaluated for serious adverse events up to 60 days after last dose of study treatment. Patients continuing to experience toxicity at this point 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. Immunogenicity (ADA) samples should be collected beyond 28 days for patients who are positive for ADA (Refer to Footnote 27). During the follow-up phase, Immunogenicity (ADA) samples should be collected at the same time as disease assessments are being performed until ADA levels return to baseline or until the patient enters the survival follow phase. Thereafter, patients whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 16 weeks (±1 week). Once patients have exhibited disease progression, they will enter into survival follow-up for assessment of survival only. A new anti-cancer therapy will be reported on the CRF. Follow-up for survival will be conducted every 12 weeks (+/- 4 weeks) for up to 2 years from first dose of study treatment for the last enrolled patient (telephone calls acceptable).
31. For patients continuing on study beyond 8 cycles of therapy, continued treatment will be on a reduced visit schedule (Day 1 of each cycle), or as clinically indicated, until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent up to a maximum of 2 years from the first dose of study drug.

CCI [redacted]

[redacted]

Table 3. Schedule of Activities: Portion B (PF-05082566 + Rituximab) Assessments (Dose Escalation Only)

	Screen[1]	CYCLE 1						CYCLE ≥2-8[35]				>Cycle 8 [23,26,35]	End of Treatment[32]	Follow up[33]
Protocol Activity (Cycle Day relative to PF-05082566 dosing)	**Within 28 days prior to enrollment**	**Day (-7)[34]**	**Day (0)**	**Day 1**	**Day 7**	**Day 14**	**Day 22**	**Day 1 (±) 2**	**Day 8 (±) 2**	**Day 15 (±) 2**	**Day 22 (±) 2**	**Day 1 (±) 2**		
Visit Window														
Informed Consent[2]	X													
Tumor History[3]	X													
Medical History[4]	X													
Physical Examination[5]	X	X		X				X				X	X	
ECOG Performance Status[6]	X	X		X				X					X	
Baseline Signs and Symptoms[7]	X													
Vital Signs (BP, pulse, and body temperature)[8]	X	X	X	X	X	X	X	X				X	X	
Safety Labs/Measurements														
12-Lead ECG[9]	X	X		X		X		X				X	X	
Hematology[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[12]	X	X	X	X	X	X	X	X				X	X	
Urinalysis[13]	X			X									X	
Pregnancy test[14]	X	X	X	X				X				X	X	
Hepatitis B and C testing [hepatitis B surface antigen and core antibody; anti-hepatitis C antibody]	X													
Endocrine function assessment[15]	X		As clinically indicated											

Table 3. Schedule of Activities: Portion B (PF-05082566 + Rituximab) Assessments (Dose Escalation Only)

	Screen[1]	CYCLE 1						CYCLE ≥2-8[35]				>Cycle 8 [23,26,35]	End of Treatment[32]	Follow up[33]
Protocol Activity (Cycle Day relative to PF-05082566 dosing)	**Within 28 days prior to enrollment**	**Day (-7)[34]**	**Day (0)**	**Day 1**	**Day 7**	**Day 14**	**Day 22**	**Day 1 (±) 2**	**Day 8 (±) 2**	**Day 15 (±) 2**	**Day 22 (±) 2**	**Day 1 (±) 2**		
LVEF assessment[16]	X		As clinically indicated											
Registration and Treatment														
Registration[17]		X												
Administration of PF-05082566[18]				X				X				X		
Administration of Rituximab[19]		X	X		X	X								
Tumor assessments				X										
CT or MRI scan or equivalent[20]	X							To be assessed approximately every 8 weeks (±1 week) for the first 10 months on study treatment, then subsequently every 16 weeks (±1 week)					X	X
Other clinical assessments														
AEs[21]		Monitored and Recorded Continuously											X	
Review Prior/Concomitant Medication[22]	X	Monitored and Recorded Continuously											X	X

Table 4. Schedule of Activities: Portion B (PF-05082566 + Rituximab: Dose Escalation Only): Pharmacokinetic, CCI CCI CCI Assessments

	Cycle 1							Cycle 2				Cycle 3		Cycle 4		Cycle >4	End of Treat-ment[32]	Follow up[33]
Assessments (Cycle Day relative to PF-05082566 dosing)	**Day (-7)**	**Day (0)**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 22**	**Day 1 (±)2**	**Day 8 (±)2**	**Day 15 (±)2**	**Day 22 (±)2**	**Day 1 (±)2**	**Day 22 (±)2**	**Day 1 (±)2**	**Day 28 (±)2**	**Day 1 (±)2**		
Blood for PF-05082566 PK[23]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for Rituximab PK[24]	X	X	X	X	X	X	X	X		X							X	
CCI			■	■	■	■	■	■	■	■	■	■	■	■			■	
CCI	■		■	■	■	■		■	■	■		■	■	■	■		■	
Blood for PF-05082566 Immunogenicity (ADA) testing[27]			X					X				X		X		X	X	X
Blood for Rituximab immunogenicity (ADA) testing[28]	X	X			X	X				X							X	
CCI			■							■								
CCI			■					■										
CCI			■															
CCI			■					■										

Footnotes for Schedule of Activities – Portion B (PF-05082566 + Rituximab) Table 3 and Table 4.

1. Screening: To be performed within 28 days prior to enrollment (Pfizer signature of the enrollment form).
2. Informed Consent: Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
3. Tumor History: To be collected within 28 days prior to enrollment. Includes oncology history, information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure based on Disease Specific Guidelines.
4. Medical History: To be collected within 28 days prior to enrollment. Includes history of other diseases (active or resolved) and concomitant illnesses.

5. Physical Examination: Includes major body systems. Weight for the purposes of dose calculation must be recorded at Screening and within 7 days at pre-dose on Day 1 of each cycle to ensure the patient did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the PF-05082566 dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the PF-05082566 dose must be recalculated using the actual weight at that visit. Height will be measured at baseline only.
6. ECOG Performance Status: ECOG performance scale is available in Appendix 4.
7. Baseline signs and symptoms: Patients will be asked about any signs and symptoms experienced within the past 14 days prior to enrollment. During trial treatment any new or worsened conditions since baseline should be reported on the AE CRF page.
8. Vital Signs: Blood pressure, pulse rate, and body temperature will be recorded.
9. Triplicate 12-Lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. ECGs will be collected as follows: a) at Screening; b) On Day (-7) prior to the dose of Rituximab and at end of infusion; c) On Cycle 1 Day 1 (C1D1), prior to the dose of PF-05082566 and 1.5 hours post start of infusion; d) On Cycle 1 Day 14; e) On Cycles ≥2 Day 1 at 1.5 hours post start of infusion and f) at End of Treatment. If the mean QTc interval is prolonged (>500 msec using any correction method), then the ECGs should be re-evaluated by a qualified person at the center for confirmation. Additional ECGs may be performed as clinically indicated.
10. Hematology: No need to repeat on Cycle 1 Day -7 [C1D(-7)] if the screening assessment is performed within 7 days prior to that date. To be performed weekly. If during the first 2 cycles of treatment a Grade 4 hematologic event is evident, the hematology assessment should be repeated at least every other day to assess for events qualifying as DLT. See Table 8 for Laboratory Tests list.
11. Blood Chemistry: No need to repeat on C1D(-7) if the screening assessment is performed within 7 days prior to that date. To be performed weekly. See Table 8 for Laboratory Tests list.
12. Coagulation: No need to repeat on C1D(-7) if the screening assessment is performed within 7 days prior to that date. To be performed weekly for Cycle 1 and on Day 1 for all remaining cycles. See Table 8 for Laboratory Tests list.
13. Urinalysis: Dipstick is acceptable. Microscopic analyses if dipstick abnormal. To be performed at screening, Cycle 1 Day 1, and at the end of treatment. See Table 8 for Laboratory Tests list.
14. Serum/Urine Pregnancy Test: For female patients of childbearing potential, who do not fit for the definition of "female patients who are not of childbearing potential" in inclusion criterion 11, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting administration of study treatment: once at the start of screening and once at the baseline visit, immediately before administration of the first dose of study treatment. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
15. Endocrine function assessment during treatment to be performed in cases of suspected hypoadrenalism or hypopituitarism. See Table 8 for Laboratory Tests list.
16. LVEF assessment: measurement of ejection fraction by echocardiogram (ECHO), multigated acquisition (MUGA) scan, or an equivalent methodology.
17. Registration: Patient number and dose level allocation operated by Pfizer.
18. PF-05082566 administration: PF-05082566 will be administered once in 4 weeks as a 1-hour (-5/+15 min) IV infusion (each cycle =28 days).
19. Rituximab administration: rituximab (375 mg/m^2) will be administered as an IV infusion once weekly for 4 doses during Cycle 1 starting on Cycle 1 Day -7. Refer to Section 5.4 on administration and management of infusion related AEs and to the rituximab package insert. Also refer to Footnote 1.
20. Tumor Assessments: Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans. Brain scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out CNS metastases. CT or MRI scans to be done once every 8 weeks (±1 week) for the first 10 months on study treatment, then subsequently every

16 weeks (±1 week) until objective disease progression. Confirmation of response (CR/PR) is not required per Cheson 2007 response criteria. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. Patients whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 16 weeks (±1 week).

21. AE Assessment: AEs should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 60 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 study drug are to be reported to the Sponsor.
22. Concomitant Medications: All concomitant medications including supportive care drugs (eg, Anti-emetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases should be recorded in the CRF.
23. Blood for PF-05082566 Pharmacokinetics: Blood samples will be collected during Cycle 1 on (a) Day 1 at pre-dose, the end of infusion, and at 1.5, 2, 6 and 24 hrs post start of infusion; (b) on Days 3, 7 (matched with rituximab pre-dose PK sample), 14 (matched with rituximab pre-dose PK sample) and 22. During Cycle 2 on (c) Day 1 at pre-dose, end of infusion, and at 1.5 and 24 hrs post start of infusion; (d) on Days 8, 15, and 22. During Cycle 3 on (e) Day 1 at pre-dose, end of infusion, and at 1.5 hr post start of infusion; (f) on Days 22. During Cycle 4 on (g) Day 1 at pre-dose, end of infusion, and at 1.5 hr post start of infusion; (h) on Day 28 post the Cycle 4 dose. The PK sample for Day 28 following the Cycle 4 dose of PF-05082566 need not be collected if a patient undergoes PF-05082566 dosing for additional cycles or if the patient starts another cancer therapy. If a patient continues with additional cycles of therapy (up to 2 years), PK samples will be collected pre-dose, end of infusion, and at 1.5 hours post start of infusion in each cycle. Timing of sampling may be modified based on emerging PK data. For patients ending/withdrawing from the study, PK samples should be collected at the End of Treatment/Withdrawal assessment day.
24. Blood for Rituximab Pharmacokinetics (NOTE: All days are numbered relative to PF-05082566 dosing): Blood samples will be collected on (a) Day (-7) at pre-dose and at 15 min post end of infusion, 6 and 24 hrs post start of infusion; (b) on Day (0) at pre-dose and 15 min post end of infusion; (c) on Cycle 1 Day 1 at 2 and 24 hrs post start of infusion of PF-05082566; (d) Cycle 1 Day 3; (e) on Cycle 1 Day 7 at pre-dose and 15 min post end of infusion; (f) on Cycle 1 Day 14 at pre-dose and 15 min post end of infusion; (g) on Cycle 1 Day 22; (h) on Cycle 2 Day 1 before the dose of PF-05082566; (i) on Cycle 2 Day 15. Timing of sampling may be modified based on emerging PK data. For patients ending/withdrawing from the study, PK samples should be collected at the End of treatment/Withdrawal assessment day. Note that whenever rituximab PK samples are collected on days when PF-05082566 PK samples are collected, they should be time matched to avoid multiple sticks.

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27. Blood for PF-05082566 Immunogenicity (ADA) testing: Blood for immunogenicity testing will be collected at a) All Cycles on Day 1 prior to the dosing of PF-05082566. If a patient undergoes additional treatment cycles (Cycle >4), ADA samples will be collected at pre-dose in the higher cycles. For patients ending from the study, immunogenicity samples should be collected at the End of Treatment assessment day. For patients who are remaining positive for ADA during the follow-up phase, Immunogenicity (ADA) samples should be collected at the same time as disease assessments are being performed until ADA levels return to baseline or until the patient enters the survival follow phase.

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28. Blood for Rituxim[redacted] Immunogenicity (ADA) testing (NOTE: All days are numbered relative to PF-05082566 dosing): Blood for immunogenicity testing will be collected at a) Cycle 1 On Day -7, Day 0, Day 7 and Day 14 prior to the dosing of Rituximab; (b) On Cycle 2 Day 15.

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32. End of Treatment: To be performed approximately 28 days after the last dose of study treatment. Obtain these assessments if not completed during the previous week (during the previous 6 weeks for tumor assessments).
33. Follow up period: Patients should be evaluated for adverse events up to 60 days after last dose of study treatment. Patients continuing to experience toxicity at this point 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. Immunogenicity (ADA) samples should be collected beyond 28 days for patients who are positive for ADA (Refer to Footnote 27). During the follow-up phase, Immunogenicity (ADA) samples should be collected at the same time as disease assessments are being performed until ADA levels return to baseline or until the patient enters the survival follow phase. Thereafter, patients whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 16 weeks (±1 week). Once patients have exhibited disease progression, they will enter into survival follow-up for assessment of survival only. A new anti-cancer therapy will be reported on the CRF. Survival follow-up will be conducted within 12 weeks (+/- 4 weeks) from the last survival follow-up for up to 2 years from first dose of study treatment for the last enrolled patient (telephone calls acceptable).
34. For infusion reactions to rituximab where a partial dose (<50% of the full dose) is administered, either the Day -7 dose OR the Day 0 administration of Cycle 1 and the associated procedures may be repeated one time based on the rituximab label guidelines, local practice, and eligibility for retreatment as detailed in Section 5.4.
35. For patients continuing on study beyond 8 cycles of therapy, continued treatment will be on a reduced visit schedule (Day 1 of each cycle), or as clinically indicated, until disease progression, unacceptable toxicity, or withdrawal of consent up to a maximum of 2 years from the first dose of study drug.

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[redacted]

Table 5. Schedule of Activities for Expansion Cohorts (Portions A and B)

	Screen[1]	CYCLE 1					CYCLE ≥2	End of Treatment[2]	Follow up[3]
Protocol Activity (Cycle Day relative to PF-05082566 dosing)	**Within 28 days prior to randomization OR enrollment**	**Day -7[4] (Portion B Only)**	**Day 0[4] (Portion B Only)**	**Day 1**	**Day 7 (Portion B Only)**	**Day 14 (Portion B Only)**	**Day 1 (±) 2**		
Informed Consent	X								
Tumor History[5]	X								
Medical History[6]	X								
Physical Examination[7]	X	X		X			X	X	
ECOG Performance Status[8]	X	X		X			X	X	
Baseline Signs and Symptoms[9]	X								
Vital Signs (BP, pulse, body temperature for Portion B)[10]	X	X	X	X	X	X	X	X	
Neurological Examination (Portion B)[29]	As clinically indicated								
Central histopathology review of FL diagnosis (Portion B)[30]	X								
Safety Labs /Measurements									
12-Lead ECG[11]	X	X		X			X (C2, C3, C4)	X	
Hematology and Blood Chemistry[12]	X	X	X	X	X	X	X	X	
Coagulation[13]	X	X	X	X	X	X	X	X	
Urinalysis[14]	X			X				X	
Pregnancy test[14]	X			X			X	X	
Hepatitis B and C testing [hepatitis B surface antigen and core antibody; anti-hepatitis C antibody]	X								
Endocrine function assessment[16]	X						X	X	
LVEF assessment[17]	X		As clinically indicated						
Registration and Treatment									
Registration[18]		X		X					
Administration of PF-05082566[19]				X			X		

Table 5. Schedule of Activities for Expansion Cohorts (Portions A and B)

	Screen[1]	CYCLE 1					CYCLE ≥2	End of Treatment[2]	Follow up[3]
Protocol Activity (Cycle Day relative to PF-05082566 dosing)	**Within 28 days prior to randomization OR enrollment**	**Day -7[4] (Portion B Only)**	**Day 0[4] (Portion B Only)**	**Day 1**	**Day 7 (Portion B Only)**	**Day 14 (Portion B Only)**	**Day 1 (±) 2**		
Administration of Rituximab (Portion B)[20]		X	X		X	X	X[21]		
Tumor assessments									
CT or MRI scan or equivalent[22]	X	To be assessed every 8 weeks (±1 week) for the first 10 months on study treatment, then subsequently every 16 weeks (±1 week)						X	X
Bone marrow (BM) biopsy or aspirate[32]	X	To be assessed in patients with potential CR by radiological assessments to determine the response category							
Other clinical assessments									
AEs[23]		Monitored and Recorded Continuously						X	
Review Prior/Concomitant Medication[24]	X	Monitored and Recorded Continuously						X	X
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Footnotes for Schedule of Activities – Expansion Cohorts (Portions A and B) Table 5.

1. Screening: To be performed within 28 days prior to randomization for the randomized cohorts and to enrollment (Pfizer signature of the enrollment form) for the non-randomized cohorts.

2. End of Treatment: To be performed approximately 28 days after the last dose of study treatment. Obtain these assessments if not completed during the previous week (during the previous 6 weeks for tumor assessments).
3. Follow-up period: Patients should be evaluated for adverse events up to 60 days after last dose of study treatment. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 16 weeks (±1 week). Once patients have exhibited disease progression, they will enter into survival follow-up for assessment of survival only. Any new anti-cancer therapy will be reported on the CRF. Survival follow-up will be conducted every 12 weeks (+/- 4 weeks) for survival status and subsequent anti-cancer treatment, up to 2 years from the first dose of study treatment for the last treated patient (for the non-randomized cohorts) or from the randomization date for the last randomized patient (for the randomized cohorts). Telephone calls are acceptable.
4. Portion B only. For infusion reactions to rituximab where a partial dose (<50% of the full dose) is administered, either the Day -7 dose OR the Day 0 administration of Cycle 1 and the associated procedures may be repeated one time based on the rituximab label guidelines, local practice, and eligibility for retreatment as detailed in Section 5.4.
5. Tumor History: To be collected within 28 days prior to randomization for the randomized cohorts and to enrollment for the non-randomized cohorts. Includes oncology history, information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure based on Disease Specific Guidelines. For patients enrolled in Portion B includes current Ann Arbor staging (Lister et al. 1989)[32], and for patients with FL, current FL grade and current Follicular Lymphoma International Prognostic Index (FLIPI) score (Solal-Celigny et al. 2004)[31].
6. Medical History: To be collected within 28 days prior to randomization for the randomized cohorts and to enrollment for the non-randomized cohorts. Includes history of other diseases (active or resolved) and concomitant illnesses.
7. Physical Examination: Includes major body systems. Weight for the purposes of dose calculation must be recorded at Screening and within 7 days at pre-dose on Day 1 of each cycle to ensure the patient did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the PF-05082566 dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the PF-05082566 dose must be recalculated using the actual weight at that visit. Height will be measured at baseline only.
8. ECOG Performance Status: ECOG performance scale is available in Appendix 4.
9. Baseline signs and symptoms: Patients will be asked about any signs and symptoms experienced within the past 14 days prior to randomization for the randomized cohorts and to enrollment for the non-randomized cohorts. During trial treatment, any new or worsened conditions since baseline should be reported on the AE CRF page.
10. Vital Signs: Blood pressure, body temperature (only for patients in Portion B), and pulse rate will be recorded.
11. Triplicate 12 Lead ECG: At each time point, 3 consecutive 12 lead ECGs will be performed approximately 2 minutes apart to determine mean QTc. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. ECGs will be collected as follows: a) at Screening; b) On Day -7, prior to the dose of Rituximab and at end of infusion (Portion B only); c) On Cycle 1 Day 1 (C1D1), prior to the dose of PF-05082566 and 1.5 hours post start of infusion; d) On Cycle 2-4 Day 1 at 1.5 hours post start of infusion; and e) at End of Treatment. Additional triplicate ECGs may be performed as clinically indicated. If the QTc interval is prolonged (>500 msec by any correction method), then the ECGs should be re-evaluated by a qualified person at the center for confirmation. A subset of approximately 30 FL patients enrolled at selected sites in the FL-3 expansion cohort of Portion B will be assessed using an ECG machine provided by central vendor to allow central review of ECG.
12. Hematology and Chemistry: No need to repeat on C1D1 for Portion A or Cycle 1 Day -7 [C1D(-7)] for Portion B if the screening assessment is performed within 7 days prior to that date. To be performed weekly only for portion B patients during Cycle 1, and on Day 1 for all subsequent cycles. See Table 8 for Laboratory Tests list.
13. Coagulation: No need to repeat on C1D1 (Portion A) or C1D(-7) (Portion B) if the screening assessment is performed within 7 days prior to that date. To be performed weekly only for portion B patients during Cycle 1, and on Day 1 of all subsequent cycles. See Table 8 for Laboratory Tests list.

14. Urinalysis: Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 (Portion A) if the screening assessment is performed within 7 days prior to that date. To be performed at screening, Cycle 1 Day 1, and at the end of treatment. See Table 8 for Laboratory Tests list.
15. Serum/Urine Pregnancy Test: For female patients of childbearing potential, who do not fit for the definition of "female patients of nonchildbearing potential" in inclusion criterion 11, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting administration of study treatment: once at the start of screening and once at the baseline visit, immediately before administration of the first dose of study treatment. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
16. Endocrine function assessment: thyroid function testing should be performed at screening, on Cycle 3 Day 1, every 12 week thereafter, and at the end of treatment; ACTH and cortisol levels should be assessed in cases of suspected hypoadrenalism or hypopituitarism. See Table 8 for Laboratory Tests list.
17. LVEF assessment: measurement of ejection fraction by echocardiogram (ECHO), multigated acquisition (MUGA) scan, or an equivalent methodology.
18. Registration: In the randomized cohorts of Portion A for patients with advanced melanoma, patient enrollment and assignment of PF-05082566 dose level is managed through the use of an interactive response technology (IRT) system. In the non-randomized cohorts of Portion A and Portion B patient number and dose level allocation is operated by Pfizer.
19. PF-05082566 administration: PF-05082566 will be administered once every 4 weeks as a 1 hour (-5/+15 min) IV infusion (each cycle =28 days). For the randomized cohorts in Portion A patients will be randomized 2:1:1 to the 0.6 mg/kg, 1.2 mg/kg and 0.24 mg/kg dose levels of PF-05082566, respectively. Patients enrolled in the non-randomized cohorts of Portion A and Portion B will receive either the 1.2 mg/kg or 0.24 mg/kg dose level of PF-05082566.
20. Rituximab administration (Portion B only): rituximab (375 mg/m^2) will be administered as an IV infusion once weekly for 4 doses during Cycle 1 starting on Cycle 1 Day -7. Refer to Section 5.4 of the protocol on administration and management of infusion related AEs and to the rituximab package insert.
21. In Portion B only, patients may have received additional doses of rituximab (375 mg/m^2) starting at Cycle 4, in accord with the local and institutional Standard of Care, and at the discretion of the investigator. A single dose of rituximab will be administered on Day 0 starting on Cycle 4 and will be repeated every 2 cycles up to a maximum of 4 additional doses (up to Cycle 10 Day 0).
22. Tumor Assessments: Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans. Brain scans and will be performed at baseline for patients with CNS disease or if disease is suspected, and on study as appropriate to follow disease. Baseline CNS imaging is not required unless to confirm stability of existing CNS metastases or for symptomatic patients to rule out CNS metastases. Bone scans will be performed at baseline if disease is suspected only for patients enrolled in Portion A, and on study (every 16 weeks ±1 week) as appropriate to follow disease. CT or MRI scans to be done once every 8 weeks (±1 week) for the first 10 months on study treatment, then subsequently every 16 weeks (±1 week) until objective disease progression. Confirmation of response (CR/PR) should be done at least 4 weeks after the initial response, per RECIST v1.1 [redacted] Confirmation of response (CR/PR) is not required for patients with NHL per Cheson 2007 response criteria. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. Patients whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 16 weeks (±1 week). All radiographic images from patients with rituximab refractory FL enrolled in the expansion cohorts Portion B must be collected and sent to a central radiology laboratory for potential future independent review. See the study manual for more details
23. AE Assessment: AEs should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study related procedure and/or receiving investigational product, through and including 60 calendar days after the last administration of the investigational product. SAEs experienced by 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 study drug are to be reported to the Sponsor.

24. Concomitant Medications: All concomitant medications including supportive care drugs (eg, Anti emetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases should be recorded in the CRF.

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30. Central Histopathology Review of FL Diagnosis (Portion B only): Slides from the archival (tissue collected within the last 6 months) OR a baseline (tissue collected *de novo* during the screening period prior to the first dose of PF-05082566) tumor biopsy must be sent to a central pathology laboratory for independent review. Confirmation of the FL diagnosis is not required for patient enrollment. See the study manual for more details.

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32. Bone marrow (BM) biopsy or aspirate: Required for patients with potential CR by radiological assessments to determine the response category.

[redacted]

Table 6. Schedule of Activities: Portion A (PF-05082566 Alone: Dose Expansion Cohorts): Pharmacokinetic assessments

	Cycle 1			Cycle 2 and 3	Cycle 4			Cycle ≥5	End of Treatment	
Assessments [(±) 2 days for cycles >1]	**Day 1**	**Day 7**	**Day 14**	**Day 1**	**Day 1**	**Day 7**	**Day 14**	**Day 1**		
Blood for PF-05082566 PK[1]	X	X	X	X	X	X	X	X (every 4 cycles)	X	
Blood for Immunogenicity (ADA) testing[2]	X			X	X			X (every 4 cycles)	X	

1. Blood for PF-05082566 Pharmacokinetics: Blood samples will be collected for at least 5 patients in each dose expansion cohort with the following schedule: during Cycle 1 on (a) Day 1 at pre-dose, end of infusion, and at 2, 6, and 24 hrs post start of infusion; (b) 1 sample on Days 7 and 14, respectively. During Cycle 2 and Cycle 3 on (c) Day 1 at pre-dose, and end of infusion. During Cycle 4 on (d) Day 1 at pre-dose, end of infusion, and at 2, 6, and 24 hrs post start of infusion; (e) 1 sample on Days 7 and 14, respectively. After Cycle 4, PK samples will be collected on Day 1 at pre dose every 4 cycles. For the remaining patients, PK samples will be collected on Day 1 of Cycles 1 to 4 at pre-dose and end of infusion. After Cycle 4, PK samples will be collected on Day 1 at pre-dose every 4 cycles. A PK sample should be collected at the End of Treatment assessment. In Japan, patients will be hospitalized for PK sampling for at least the first two days of the first cycle of dosing of PF-05082566.
2. Blood for Immunogenicity (ADA) testing: Blood for immunogenicity testing will be collected at a) Day 1 at pre-dose from Cycle 1 to Cycle 4; b) after Cycle 4, ADA samples will be collected on Day 1 at pre-dose every 4 cycles. Immunogenicity samples should be collected at the End of Treatment assessment day.

Table 7. Schedule of Activities: Portion B (PF-05082566 + Rituximab: Dose Expansion): Pharmacokinetic Assessments

	Cycle 1					Cycle 2 and 3	Cycle 4				Cycle ≥5		End of Treatment	
Assessments (Cycle Day relative to PF-05082566 dosing)	**Day (-7)**	**Day (0)**	**Day 1**	**Day 7**	**Day 14**	**Day 1**		**Day 1**	**Day 7**	**Day 14**		**Day 1**		
Blood for PF-05082566 PK[1]			X	X	X	X		X	X	X		X (every 4 cycles)	X	
Blood for Rituximab PK[2]	X	X	X	X	X	X (C2 only)							X	
Blood for PF-05082566 Immunogenicity (ADA) testing[3]			X			X		X				X (every 4 cycles)	X	
Blood for Rituximab immunogenicity (ADA) testing[4]	X	X		X	X	X (C2 only)							X	

1. Blood for PF-05082566 Pharmacokinetics: Blood samples will be collected for at least 5 patients in each dose expansion cohort (dosed with PF-05082566 at 1.2 mg/kg OR 0.24 mg/kg) with the following schedule: during Cycle 1 on (a) Day 1 at pre-dose, end of infusion, and at 2, 6 and 24 hr post start of infusion; (b) 1 sample on Days 7 and 14, respectively. During Cycle 2 and Cycle 3 on (c) Day 1 at pre-dose, end of infusion. During Cycle 4 on (d) Day 1 at pre-dose, end of infusion, and at 2, 6 and 24 hr post start of infusion; (e) 1 sample on Days 7 and 14, respectively. After Cycle 4, PK samples will be collected on Day 1 at pre-dose every four cycles. For the remaining patients, PK samples will be collected on Day 1 of Cycles 1 to 4 at pre-dose and end of infusion. After Cycle 4, PK samples will be collected on Day 1 at pre-dose every 4 cycles. A PK sample should be collected at the End of Treatment assessment.
2. Blood for Rituximab Pharmacokinetics (NOTE: All days are numbered relative to PF-05082566 dosing): Blood samples will be collected for at least 5 patients enrolled in the dose expansion cohort dosed with PF-05082566 at 1.2 mg/kg on (a) Day -7) and Day (0) at pre- dose and end of infusion of rituximab (b) on Cycle 1 Day 1 at 2 and 24 post start of infusion of PF-05082566; (c) on Cycle 1 Day 7 and Day 14 at pre-dose and end of infusion of rituximab; (f) 1 sample on Cycle 2 Day 1 before the dose of PF-05082566; PK samples should be collected at the End of treatment/Withdrawal assessment day. For the remaining patients, PK samples for rituximab will NOT be collected. Note that whenever rituximab PK samples are collected on days when PF-05082566 PK samples are collected, they should be time matched to avoid multiple sticks.
3. Blood for PF-05082566 Immunogenicity (ADA) testing: Blood for immunogenicity testing will be collected at a) Day 1 at pre-dose from Cycle 1 to Cycle 4 b) after Cycle 4, ADA samples will be collected on Day 1 at pre-dose every four cycles (Cycle 8, Cycle 12, etc.). Immunogenicity samples should be collected at the End of Treatment assessment day.
4. Blood for Rituximab Immunogenicity (ADA) testing (NOTE: All days are numbered relative to PF-05082566 dosing): Blood for immunogenicity testing will be collected at a) Cycle 1 On Day (-7), Day 0, Day 7 and Day 14 prior to the dosing of rituximab; (b) On Cycle 2 Day 1 prior to the dosing of PF-05082566; (d) end of treatment.

Table 8 Safety Laboratory Tests

SAFETY LABORATORY REQUIREMENTS **- May be performed up to 48 hours prior to scheduled cycle Day 1 visits to facilitate availability of results to the investigator at the time of the clinic visit.**	
Assessments	
Hematology Panel:	**Chemistry Panel:**
Absolute Neutrophil Count	Sodium
Hemoglobin	Potassium
	Calcium
Platelet Count	Creatinine
WBC with differential (5-part if available)	Albumin
	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
	Glucose
	Phosphorus
	Magnesium
	Bilirubin: total
	Blood urea nitrogen (BUN)
	Alkaline phosphatase
	Lactate dehydrogenase (LDH)
	Total protein
	Uric acid (or urate)
Coagulation Panel: international normalized ratio (INR) or prothrombin time (PT), Partial thromboplastin time (PTT)	**Hepatitis Screening:** hepatitis B surface antigen and core antibody; anti-hepatitis C antibody.

Table 8 Safety Laboratory Tests

SAFETY LABORATORY REQUIREMENTS **- May be performed up to 48 hours prior to scheduled cycle Day 1 visits to facilitate availability of results to the investigator at the time of the clinic visit.**	
Assessments	
Urinalysis: measurement of pH, specific gravity, protein/albumin, glucose, blood/hemoglobin, ketones/acetone, Urine dipstick for urine protein: if positive collect 24-hr and microscopic (Reflex Testing), Urine dipstick for urine blood: if positive collect a microscopic (Reflex Testing). No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. **Pregnancy Test (serum or urine):** Conducted for women of childbearing potential only.	**Endocrine Function Assessments:** baseline assessments including but not limited to: TSH, Free T4. In the presence of clinical suspicion of hypopituitarism or hypoadrenalism, laboratory testing should include one or more of the following: TSH, ACTH, and cortisol levels before and 30-60 minutes after corticotropin stimulation.

TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

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APPENDICES

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1. INTRODUCTION

This is the first-in-patient study of PF-05082566, also known as utomilumab, designed to evaluate the safety, pharmacokinetics (PK) CCI [redacted] of PF-05082566 administered IV as a single-agent or in combination with rituximab.

1.1. Mechanism of Action/Indication

PF-05082566 is a novel fully human IgG2 monoclonal antibody (mAb) agonist of 4-1BB (CD137, TNFRSF9), an inducible costimulatory receptor expressed on activated lymphocyte cells, being developed for cancer therapy. Stimulation of the immune response by a 4-1BB agonist has the potential to enhance anti-tumor responses, as a single-agent or in combination with therapeutic mAbs that have the potential to induce ADCC. In this study, PF-05082566 as a single-agent is under investigation for the treatment of patients with advanced solid tumor malignancies or B-cell lymphoma (Portion A) and PF-05082566 in combination with rituximab is under investigation for the treatment of patients with relapsed or refractory CD20-positive non-Hodgkin's lymphoma (NHL; Portion B).

1.2. Background and Rationale

1.2.1. Scientific Rationale: Target Biology and Mechanism of Action

4-1BB (CD137, TNFRSF9), first identified as an inducible costimulatory receptor expressed on activated T cells, is a membrane spanning glycoprotein of the Tumor Necrosis Factor (TNF) receptor superfamily. Current understanding of 4-1BB indicates that expression is generally activation dependent and encompasses a broad subset of immune cells including activated NK and Natural killer T (NKT) cells, regulatory T cells, dendritic cells (DC) including follicular DC, stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils (Wang et al. 2009),[27] and activated B cells (Zhang et al. 2009).[26] 4-1BB expression has also been demonstrated on tumor vasculature (Broll et al. 2001, Seaman et al. 2007)[2,25] and atherosclerotic endothelium (Olofsson et al. 2008).[21] The ligand that stimulates 4-1BB (4-1BBL) is expressed on activated antigen-presenting cells (APCs), myeloid progenitor cells, and hematopoietic stem cells.

Interaction of 4-1BB on activated normal human B cells with its ligand at the time of B-cell receptor engagement stimulates proliferation and enhances survival (Zhang et al. 2009).[29] The potential impact of 4-1BB engagement in B-cell lymphoma has been investigated in 2 published studies. Evaluation of several types of human primary NHL samples indicated that 4-1BB was expressed predominantly on infiltrating T cells rather than the lymphoma cells (Houot et al. 2011).[8] The addition of 4-1BB agonists to in vitro cultures of B lymphoma cells with rituximab and NK cells resulted in increased lymphoma killing (Kohrt et al. 2010).[11] Also, combination of an agonistic mAb against CD137 with a mAb with the potential to induce ADCC should result in enhanced ADCC as suggested in NHL[11] and breast cancer models[30]. In addition, B-cell immunophenotyping was performed in 2 experiments using PF-05082566 in cynomolgus monkeys with doses from 0.001-100 mg/kg; in these experiments, peripheral blood B-cell numbers were either unchanged or decreased.

4-1BB is undetectable on the surface of naive T cells but expression increases upon activation. Based on homology to other members of the tumor necrosis factor receptor super family (TNFRSF), ligand binding is expected to induce receptor trimerization resulting in activation (Chan et al. 2007).[3] Some members of the TNFRSF can cleave the extracellular domain from the cell surface and exist in a soluble form. Soluble 4-1BB and soluble 4-1BBL have been demonstrated in the serum of some patients with autoimmune diseases and cancers (Michel et al. 1998; Furtner et al. 2005; Hentschel et al. 2006).[6,7,14]

Upon 4-1BB activation, tumor necrosis factor receptor (TNFR) associated factor (TRAF) 1 and TRAF 2, pro-survival members of the TRAF family are recruited to the 4-1BB cytoplasmic tail resulting in downstream activation of Nuclear Factor kappa B (NFkB) and the Mitogen Activated Protein (MAP) Kinase cascade including Erk, Jnk, and p38 MAP kinases. NFkB activation leads to upregulation of Bfl-1 and Bcl-XL, pro-survival members of the Bcl-2 family. The pro-apoptotic protein Bim is downregulated in a TRAF1 and extracellular signal regulated kinase (Erk) dependent manner (Sabbagh et al. 2008).[24]

Numerous studies of murine and human T cells indicated that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production (Croft 2009).[5] Reports have shown that 4-1BB agonist mAbs increase costimulatory molecule expression and markedly enhance cytolytic T lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings and both monotherapy and combination therapy tumor models and have established durable anti-tumor protective T cell memory responses (Lynch 2008).[13] 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models (Vinay et al. 2006).[26] This dual activity of 4-1BB offers the potential to provide anti-tumor activity while dampening autoimmune side effects that can be associated with immunotherapy approaches that break immune tolerance.

1.2.2. Pre-Clinical Development of PF-05082566

PF-05082566, an intravenous (IV) fully human IgG2 monoclonal antibody (mAb), binds to the extracellular domain of human 4-1BB with high affinity and specificity and is capable of 4-1BB agonism. Injection with PF-05082566 has been shown to correlate with tumor cell line growth inhibition in xenogenic tumor models as a single agent. In addition, 4-1BB agonist mAbs demonstrate significant combinatorial efficacy with ADCC antibodies in lymphoma models. Preclinical studies support the use of this 4-1BB agonist mAb as a promising candidate for treatment of cancer, alone or in combination with ADCC-inducing mAbs.

1.2.2.1. In Vitro Data

PF-05082566 has shown immunomodulatory activity in various in vitro assays. In concert with a signal through the T-cell receptor, PF-05082566 has been shown to mediate ligation of 4-1BB, which results in activation of NFkB culminating in T cell cytokine release and proliferation. The in vitro properties of PF-05082566 are summarized in Table 9.

Table 9. In Vitro Properties of PF-05082566

In vitro Assay	Activity (nM)
Affinity for 4-1BB	
Biacore Affinity (KD) On rate (Ka) Off rate (Kd)	 8.7±1.0 1.4±0.06 x10^6 M^{-1} s^{-1} 0.012±0.001s^{-1}
Saturation Binding	
4-1BB ECD binding ELISA (EC50; n=3) Human Cyno	 0.124±0.041 0.198±0.024
4-1BB expressing 300.19 cells (FACS EC50; n=2) Human Cyno	 1.8 4.2
PHA stimulated primary cells Human PBMC (FACS EC50; n=12) Cyno PBMC (FACS EC50; n=7) Dog, rat, mouse (FACS; n=2)	 48.9±24 149±68 No binding up to 100 nM
Inhibition of ligand binding	
Ligand competition ELISA (IC50; n=2)	0.200±0.003
In vitro stimulation	
4-1BB transfected cells (NF-kB luciferase reporter) (EC50) Human (n=3) Cyno (n=3)	 0.15±0.04 0.4±0.039
Augmentation of primary human T cell activity CD3 induced IL-2 production (EC50{range max fold induction}; n=12)	 22.6±7.63 {2-20}
Selectivity (FACS) CD40, CD134	 No binding up to 1000 nM
ECD = Extracellular Domain	
ELISA = Enzyme Linked Immunosorbent Assay	
FACS = Fluorescence Activated Cell Sorting	
PHA = Phytohemagglutinin	
PBMC = Peripheral Blood Mononuclear Cell	
NF-kB = Nuclear Factor kappa B	
IL-2 = Interleukin-2	

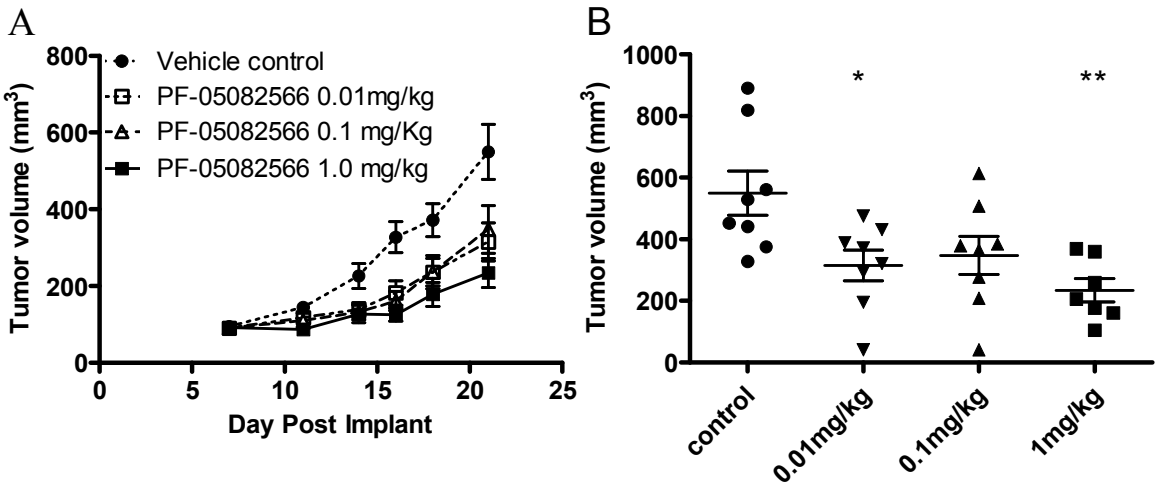
1.2.2.2. In Vivo Data: Functional Activity of PF-05082566

In pre-clinical studies, PF-05082566 has exhibited the ability to increase lymphocyte proliferation. In small animal models developed to test the *in vivo* function of PF-05082566, PF-05082566 was able to enhance expansion of human leukocytes in a dose dependent manner as evidenced by an increase in the proportion of human CD45+ cells in the peripheral blood of engrafted mice. Similarly, a dose-dependent increase in the proportion of human leukocytes expressing the proliferation marker Ki-67 was noted. In addition, PF-05082566 treatment of cynomolgus monkeys in single or multiple dose studies increased proliferation among cytotoxic central memory T cells (CD8 T_{CM}) in PBMC samples. Taken together, these data demonstrated evidence of PF-05082566's ability to enhance lymphocyte response *in vivo*.

1.2.2.3. Anti-Tumor Activity of PF-05082566

PF-05082566 has demonstrated anti-tumor activity in pre-clinical studies. Tumor cell lines representing melanoma, colon, and prostate tumor types were tested in a xenogenic tumor model. None of the tumor lines expressed 4-1BB; therefore, tumor cells were mixed with primary human PBMC from a healthy volunteer donor prior to injection in all cases. Once tumors were established, animals were treated with PF-05082566. PF-05082566 was found to be efficacious against all 3 tumor types. An example growth curve demonstrating the response to a prostate carcinoma is shown in Figure 1.

Figure 1. Effect of PF-05082566 on the Growth of PC3 Prostate Carcinoma in a huPBL SCID Model



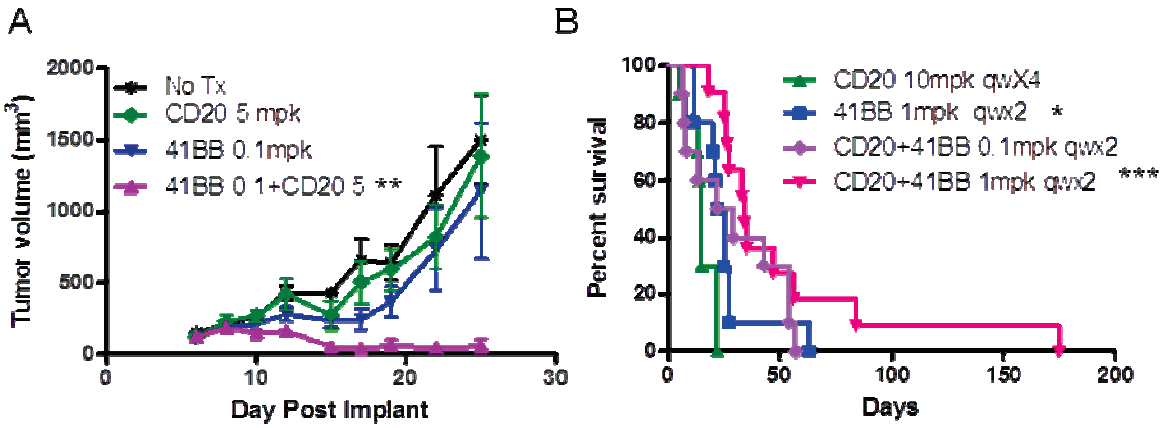
PF-05082566 inhibits the growth of the PC3 prostate carcinoma *in vivo* Panel A: mean tumor volume at each time point measured. Panel B: volume of each tumor on the final study day (Day 21). The mean and standard error of the mean (SEM) are indicated by bars. *p<0.05, ** p<0.005.

1.2.2.4. Combination Studies

Antibody-dependent cellular cytotoxicity (ADCC) has been hypothesized as a mechanism of tumor destruction resulting in direct antigen presentation and in the induction of tumor antigen-specific T-cell responses ('cross-priming") (Weiner et al. 2009).[28] This was supported by preclinical experiments demonstrating that the therapeutic efficacy of an anti-HER2/neu antibody depends on both innate and adaptive immunity (Park et al. 2010).[23]

The combinatorial anti-tumor activity of ADCC inducing mAb with 4-1BB agonist mAbs was assessed. A mouse anti-mouse CD20 antibody with ADCC inducing activity was selected as a surrogate mAb for rituximab (Ahuja et al. 2007).[1] MAB9371 was selected as a surrogate for PF-05082566, as PF-05082566 does not cross react with murine 4-1BB. MAB9371 is a commercially available rat anti-mouse 4-1BB agonist mAb (R & D Systems, Minneapolis MN). The binding affinity of MAB9371 for murine 4-1BB is similar to the affinity of PF-05082566 for human 4-1BB. In both models, treatment with a combination of surrogate mAbs at concentrations with limited single-agent efficacy, showed significant tumor growth inhibition (A20 model) and/or enhanced survival (Eμ-myc model) (Figure 2).

Figure 2. Combinatorial Efficacy of 4 1BB and CD20 Surrogate mAbs in Lymphoma Models



4-1BB agonist antibodies demonstrate significant combinatorial efficacy with ADCC antibodies in transplantable and spontaneous lymphoma models. A) A20 murine lymphoma cells were implanted on the flank of Balb/C mice. Group mean tumor volume measurements at the indicated times are shown above. Error bars represent SEM. Untreated vs. single agent p= not significant, untreated vs. combination p<0.01. B) Survival days post treatment. Median survival was: CD20=15 days, 1mpk 4-1BB =23.5 days, CD20+0.1mpk 4-1BB=25.5 days, CD20+1mpk 4-1BB= 34 days. Statistical significance of the 4-1BB treatment or combination treatment versus CD20 group was determined using a Log Rank (Mantel-Cox) test: CD20 vs. 4-1BB p<0.02, CD20 vs. CD20 + 0.1mpk 4-1BB p= not significant, CD20 vs. CD20 + 1mpk 4-1BB p<0.001.

CCI [redacted]

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1.4. Study Rationale

PF-05082566 is a promising new molecular entity that binds to human 4-1BB with high affinity and specificity. In vitro and in vivo data demonstrated significant immuno-modulatory activity and anti-tumor activity of PF-05082566 when dosed as a single agent and in combination with ADCC inducing antibodies. Preclinical studies have shown favorable PK and metabolic properties which suggest that it may be well tolerated when administered IV. Based upon the above considerations, this first-in-human Phase 1 study will assess the safety and establish the maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) of single-agent PF-05082566 in patients with advanced solid tumor or B-cell lymphoma, and the MTD and the RP2D of PF-05082566 in combination with rituximab in patients with CD20-positive NHL.

As of June 2016, 133 patients with advanced solid tumors and hematological malignancies received PF-05082566 in a dose range between 0.006 and 10 mg/kg in this study. Eight-six (86) patients (Portion A), mainly with advanced solid tumors, received single-agent PF-05082566 and 47 patients (Portion B) with NHL received PF-05082566 in combination with rituximab. No DLTs were reported either in Portion A or Portion B, and treatment-related adverse event (AE)s were generally mild or moderate in severity. In Portion A, 2 Grade 3 AEs (hyponatremia and fatigue) and 3 serious adverse events (SAE)s (enterocolitis, decreased appetite and pneumonitis reported in 2 patients) were assessed as related to treatment with single-agent PF-05082566. In Portion B no Grade ≥3 AEs and no SAEs were reported as related to PF-05082566. In Portion A 1 confirmed complete response (CR) and 1 confirmed partial response (PR) in Merkel cell carcinoma patients who were treated at 0.24 mg/kg and 0.6 mg/kg respectively were reported. In addition, 1 patient with anti-PD-1 refractory melanoma treated at 0.24 mg/kg had a PR that was not yet confirmed, and 1 patient with anti-PD-1 refractory melanoma treated at 0.24 mg/kg had a greater than 30% reduction in the diameters of multiple target tumors and achieved prolonged disease stabilizatio CCI [redacted] In Portion B, 8 patients with FL (7 patients were refractory to prior rituximab-containing regimen) achieved an objective response: 4 patients achieved a CR (2 treated at 1.2 mg/kg, 1 treated at 0.12 mg/kg, and 1 treated at 0.03 mg/kg) and 4 patients achieved a PR (2 treated at 0.18 mg/kg, 1 treated at 1.2 mg/kg, and 1 treated at 5.0 mg/kg). One (1) patient with CD20-positive nodular lymphocyte-predominant Hodgkin's lymphoma treated at 1.2 mg/kg achieved a PR and 1 patient with mantle cell lymphoma treated at 2.4 mg/kg achieved a PR.

Additional information for PF-05082566 may be found in the single reference safety document (SRSD), which for this study is the Investigator Brochure.

The SRSD for rituximab is the United States Prescribing Information for Rituxan®.

The Sponsor considers that the above reported nonclinical toxicity and safety pharmacology studies and clinical data support the development of PF-05082566 for the treatment of advanced cancers and the conduct of this Phase 1 clinical study B1641001.

Because the RP2D of PF-05082566 has not yet been optimized, enrollment into expansion cohorts for both Portion A and Portion B will be continued. The objectives of the dose expansion cohorts are to provide additional safety, tolerability, PK/CCI and preliminary

efficacy data for PF-05082566 in order to support the selection of the RP2D. CCI [redacted]

Portion A expansion cohort will focus on patients with advanced solid tumors who have had documented disease progression on a previous immune checkpoint inhibitor therapy (anti-CTLA-4, anti-PD1/PD-L1 antibodies) per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 criteria. Targeted blockade of CTLA-4 or PD-1 with antagonist monoclonal antibodies (mAbs) releases the "brakes" on T cells to boost anti-tumor immunity. Generating optimal T cell responses also requires T cell co-stimulation, which can be provided through ligation of tumor necrosis factor receptor family members, including 4-1BB (CD137) (Linch et al., 2015).[14] Upregulation of 4-1BB has been observed in an in vitro model of T-cell exhaustion caused by tonic signaling of chimeric antigen receptors (CARs), and inclusion of a 4-1BB endodomain in the CAR prevented exhaustion (Long et al., 2015).[12] This finding suggests that 4-1BB agonists such as PF-05082566 may reverse exhaustion mediated by tonic T-cell receptor signaling in the tumor. The exhausted phenotype has been reported in mouse models of PD-1 deficiency and may be expected in at least some patients treated with PD-1 and/or PD-L1 inhibitors (Odorizzi et al., 2015).[20] The preliminary evidence of clinical activity observed in 2 patients with melanoma that progressed on previous anti-PD-1 therapy enrolled in this study who achieved a PR that was not yet confirmed at the time of the June 2016 data cut, CCI [redacted] CCI [redacted] Thus, Portion A expansion cohorts will include patients with advanced solid tumors who have had documented disease progression on a previous immune checkpoint inhibitor therapy per RECIST v1.1 criteria.

Portion B expansion cohorts include patients with follicular lymphoma (FL) that are refractory to previous rituximab therapy or DLBCL with relapsed or refractory disease. Patients with FL disease that is refractory to rituximab represent an unmet medical need with very limited therapeutic options, and the preliminary evidence of clinical activity observed in this study support further evaluation of PF-05082566 in combination with rituximab in this patient population.

1.5. Summary of Benefit/Risk Assessment

The benefit/risk relationship has been carefully considered in the planning of this clinical trial. PF-05082566 has demonstrated clinical activity as monotherapy in patients with advanced solid tumors and in combination with rituximab in patients with CD20-positive NHL. The clinical safety profile of PF-05082566 is tolerable and supports its use as both a single agent and in combination with rituximab.

Based on the above reported nonclinical and clinical data for PF-05082566, the conduct of this clinical trial is considered justifiable using the dose and frequency of administration of PF-05082566 (1.2, 0.6, and 0.24 mg/kg IV every 4 weeks) as specified in this clinical trial protocol. Of note, the highest PF-05082566 dose to be administered in the dose expansion cohorts of this study is considerably lower than the highest dose tested (10 mg/kg).

Thus, the projected benefit/risk of PF-05082566 as a single agent or in combination with rituximab is anticipated to be favorable for investigation in this population of patients with advanced solid tumor malignancies who had documented disease progression on a previous immune checkpoint inhibitor therapy or relapsed or refractory CD20-positive NHL, respectively.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective – Dose Escalation Cohorts

Portion A:

- To assess safety and tolerability at increasing dose levels of single agent PF-05082566 in patients with advanced solid tumors or B cell lymphoma in order to estimate the MTD and select the RP2D.

Portion B:

- To assess safety and tolerability at increasing dose levels of PF-05082566 given in combination with rituximab in patients with relapsed or refractory CD20-positive NHL in order to estimate the MTD and select the RP2D.

2.1.2. Secondary Objectives – Dose Escalation Cohorts

Portion A:

All secondary objectives listed below are to be evaluated for PF-05082566 as a single agent in patients with advanced solid tumors or B cell lymphoma.

- To evaluate the overall safety profile;
- To characterize the pharmacokinetics of PF-05082566;
- To evaluate the immunogenicity of PF-05082566;
- To characterize the effects of PF-05082566 on QTc;
- To evaluate the anti-tumor effect of PF-05082566.

Portion B:

All secondary objectives listed below are to be evaluated for PF-05082566 in combination with rituximab in patients with relapsed or refractory CD20-positive NHL.

- To evaluate the overall safety profile;
- To characterize the pharmacokinetics of PF-05082566 and rituximab given in combination;

- To evaluate the immunogenicity of PF-05082566 and rituximab;
- To characterize the effects of PF-05082566 in combination with rituximab on QTc;
- To evaluate the anti-tumor effect of PF-05082566 in combination with rituximab.

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2.1.4. Primary Objective – Expansion Cohorts

Portion A:

- To estimate the objective response rate of PF-05082566.

Portion B:

- To estimate the objective response rate of PF-05082566 in combination with rituximab.

2.1.5. Secondary Objectives – Expansion Cohorts

Portion A:

All secondary objectives listed below are to be evaluated for PF-05082566 as a single agent in patients with advanced solid tumors or B cell lymphoma.

- To evaluate the overall safety profile;
- To characterize the pharmacokinetics of PF-05082566;
- To evaluate the immunogenicity of PF-05082566;
- To characterize the effects of PF-05082566 on QTc;
- To evaluate the anti-tumor effect of PF-05082566.

Portion B:

All secondary objectives listed below are to be evaluated for PF-05082566 in combination with rituximab in patients with relapsed or refractory CD20-positive NHL.

- To evaluate the overall safety profile;

[redacted]

- To characterize the pharmacokinetics of PF-05082566 and rituximab given in combination;
- To evaluate the immunogenicity of PF-05082566 and rituximab;
- To characterize the effects of PF-05082566 in combination with rituximab on QTc;
- To evaluate the anti-tumor effect of PF-05082566 in combination with rituximab.

CCI

[redacted]

2.2. Endpoints

2.2.1. Primary Endpoint – Dose Escalation Cohorts

- First 2 cycles DLTs.

2.2.2. Secondary Endpoints – Dose Escalation Cohorts

Portion A:

- Safety: Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; Vital signs (blood pressure and pulse rate);
- PK: PF-05082566 (C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ AUC_{tau},CL, and V_{ss}, as data permits);
- Anti-Drug Antibody levels for PF-05082566;
- QTc interval;
- Objective response as assessed by using the RECIST v1.1;

- Duration of response;
- Time to tumor response;
- Progression-free survival;
- Overall survival.

Portion B:

- Safety: Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566 in combination with rituximab; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; Vital signs (blood pressure, pulse rate, and body temperature);
- PK: PF-05082566 (C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ AUC_{tau}, CL, and V_{ss}, as data permits) and rituximab (C_{max} and C_{trough});
- Anti-Drug Antibody levels for PF-05082566 and rituximab;
- QTc interval;
- Objective response as assessed by using the Cheson 2007 criteria;
- Duration of response;
- Time to tumor response;
- Progression-free survival;
- Overall survival.

CCI [redacted]

CCI

[redacted]

2.2.4. Primary Endpoint – Expansion Cohorts

- For Portion A: Objective response as assessed by using the RECIST v1.1.
- For Portion B: Objective response as assessed by using the Cheson 2007 criteria.

2.2.5. Secondary Endpoints – Expansion Cohorts

Portion A:

- First 2 cycles DLTs;
- Safety: Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; Vital signs (blood pressure and pulse rate);
- PK: PF-05082566 (C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ AUC_{tau},CL, and V_{ss}, as data permits);
- Anti-Drug Antibody levels for PF-05082566;
- QTc interval;
- Duration of response;
- Time to tumor response;
- Progression-free survival;
- Overall survival.

Portion B:

- First 2 cycles DLTs;

[redacted]

- Safety: Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566 in combination with rituximab; Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; Vital signs (blood pressure, pulse rate, and body temperature);
- PK: PF-05082566 (C_{max}, C_{trough}, T_{max}, $AUC_{0\text{-}last,}$, $AUC_{0\text{-}\infty,}$ AUC_{tau}, CL, and V_{ss}, as data permits) and rituximab (C_{max} and C_{trough});
- Anti-Drug Antibody levels for PF-05082566 and rituximab;
- QTc interval;
- Duration of response;
- Time to tumor response;
- Progression-free survival;
- Overall survival.

CCI

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open label, multi-center, multiple-dose study of single agent PF-05082566 in patients with advanced solid tumors or B cell lymphoma, and of PF-05082566 in combination with rituximab in patients with refractory or relapsed CD20-positive NHL. Approximately 270 patients are expected to be enrolled in the overall study.

There are 2 portions in this clinical study. Portion A is designed to assess the safety and tolerability, PK [redacted] and to estimate the MTD/pharmacologically active dose and determine the RP2D of PF-05082566 administered as a single agent in patients with advanced solid tumors or B-cell lymphoma. Two cohort(s) will be enrolled at clinical sites in Japan to evaluate safety, tolerability and PK profile of PF-05082566 as a single agent in Japanese patients.

Portion B is designed to assess the safety and tolerability, PK [redacted] and to estimate the MTD and determine the RP2D of PF-05082566 in combination with rituximab in patients with relapsed or refractory CD20-positive NHL. Acceptable safety of the single agent within the first 3 cohorts of Portion A will trigger the initiation of Portion B. Portions A and B will then escalate simultaneously and independently of each other.

As of June 2016, the dose escalation components of Portion A and Portion B have been completed with no DLTs reported for PF-05082566 administered either as single agent or in combination with rituximab. Patients tolerated well PF-05082566 administration at the highest planned dose of 10 mg/kg in both Portions of the study and no further dose escalation was performed (see Section 1.4, 1.5, and the PF-05082566 Investigator Brochure for additional details).

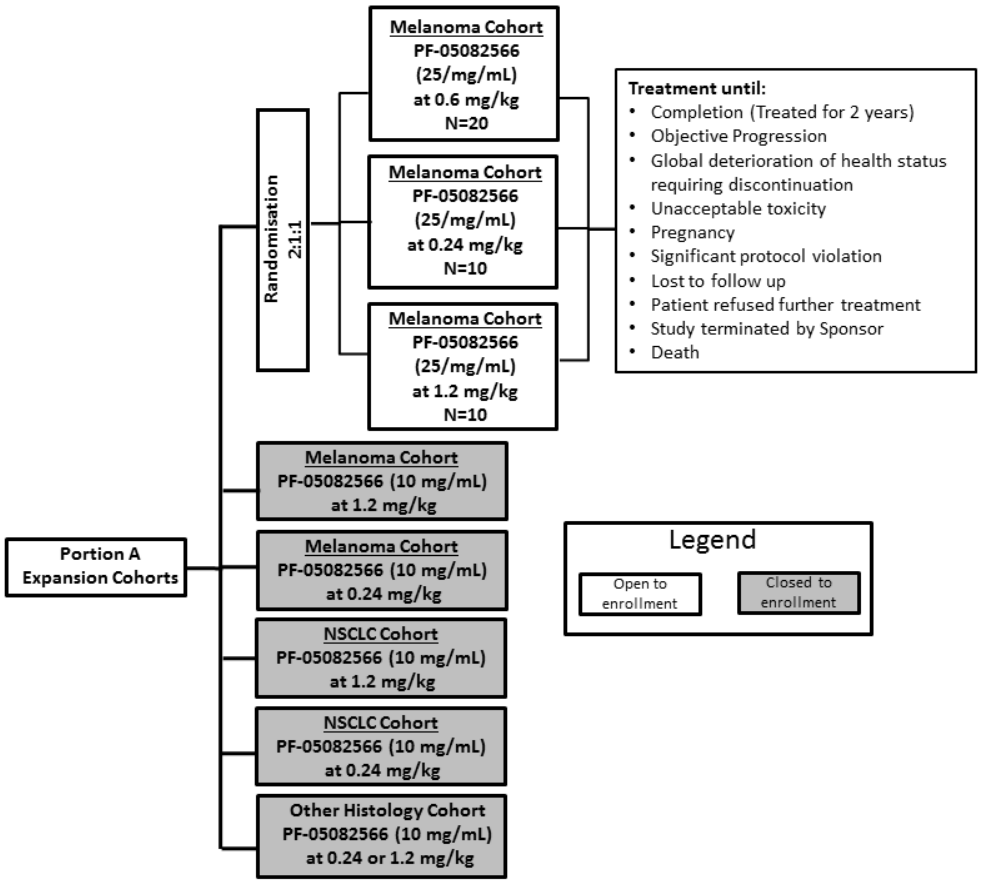
Because the RP2D of PF-05082566 administered as a single-agent or in combination with rituximab has not yet been determined, enrollment at several dose levels of PF-05082566 will be continued in expansion cohorts for both Portion A and Portion B. [redacted] In addition, early signs of clinical activity were reported with single-agent PF-05082566 dose levels between 0.24 mg/kg to 0.6 mg/kg in patients with MCC and melanoma and responses were also observed with the combination of PF-05082566 and rituximab in NHL at dose levels as low as 0.03 mg/kg with the majority of responses observed at dose levels ≤1.2 mg/kg. Finally, exploratory exposure (dose) response analyses indicated that better efficacy is expected at PF-05082566 dose levels ≤1.2 mg/kg. Taken these data together, 3 PF-05082566 dose levels will be further evaluated in Portion A expansion cohorts: 0.24 mg/kg, 0.6 mg/kg and 1.2 mg/kg, and 2 dose levels may be further evaluated in Portion B expansion cohorts: 1.2 mg/kg and 0.24 mg/kg based on emerging data.

Because no significant toxicities were observed during dose escalation, patients enrolled into the expansion cohorts will have a modified visit schedule (see Table 5).

3.1.1. Portion A Expansion Cohorts

As of September 2016, 34 patients with advanced solid tumor, including 20 patients with melanoma, who had documented disease progression per RECIST v1.1 on a previous immune checkpoint inhibitor therapy (see Section 4.1 for the definition of disease that progressed from previous immune checkpoint inhibitor therapy) have been enrolled in the expansion cohorts of Portion A and treated at the 0.24 or 1.2 mg/kg dose levels of PF-05082566. These two dose levels will be further expanded and an intermediate dose level (0.6 mg/kg) will also be evaluated. Approximately 40 additional patients with melanoma who had documented disease progression per RECIST v1.1 on a previous immune checkpoint inhibitor therapy will be randomized 2:1:1 to treatment with single agent PF-05082566 at the 0.6, 0.24, or 1.2 mg/kg dose levels. The study design of the Portion A expansion cohorts is illustrated in Figure 3.

Figure 3. Study Design of the Expansion Cohort of Portion A

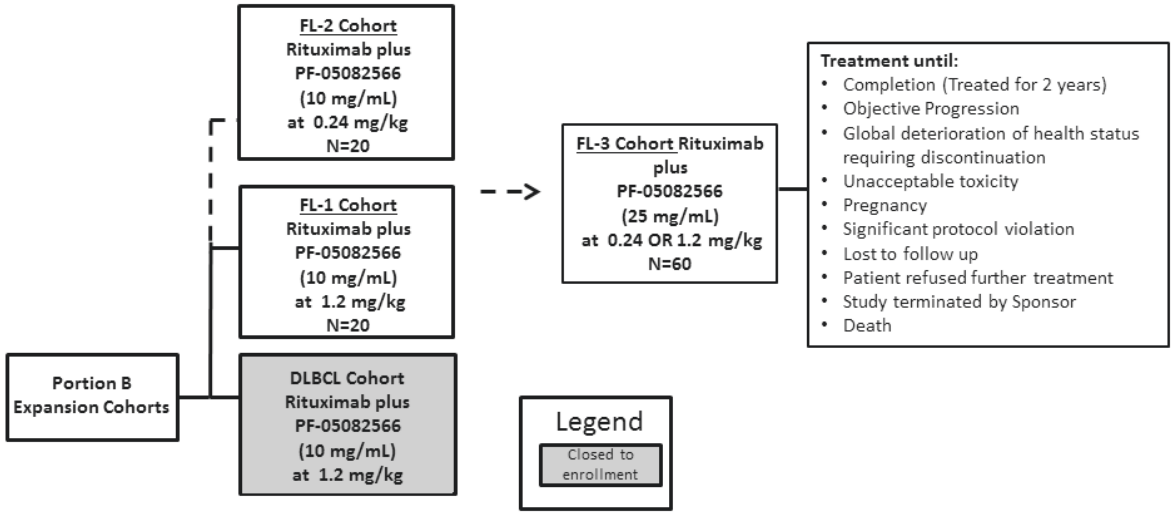


For each cohort the primary diagnosis, the PF-05082566 dose levels (0.24, 0.6, or 1.2 mg/kg), the PF-05082566 drug preparation to be used (10 mg/mL or 25 mg/mL) and the enrollment status are illustrated. No switch between the 2 different preparations is allowed during study treatment.

3.1.2. Portion B Expansion Cohorts

As of September 2016, 10 patients with rituximab-refractory FL (see Section 4.1 for the definition of FL disease refractory to rituximab) and 4 patients with relapsed or refractory DLBCL have been enrolled in the expansion cohort of Portion B and treated at the 1.2 mg/kg dose level of PF-05082566. The expansion cohort of Portion B will enroll up to 100 patients with rituximab-refractory FL who will be treated with rituximab in combination with PF-05082566 at the 1.2 mg/kg and, following an assessment of the tolerability, efficacy, CC and PK data collected for the combination of PF-05082566 at 1.2 mg/kg plus rituximab, at the 0.24 mg/kg dose level. In the first cohort (FL-1), up to 20 patients will be treated with rituximab in combination with PF-05082566 at 1.2 mg/kg and in the second cohort (FL-2) up to 20 patients may receive rituximab in combination with PF-05082566 at 0.24 mg/kg. The PF-05082566 dose level to be administered in the third cohort (FL-3) will be selected based on the overall evaluation of tolerability, efficacy, CCI PK data collected for the combination of PF-05082566 plus rituximab in FL-1 and FL-2 (if this cohort is enrolled). In FL-3, approximately 60 patients will receive rituximab in combination with PF-05082566 either at the 0.24 or 1.2 mg/kg dose level. The study design of the Portion B expansion cohort is illustrated in Figure 4.

Figure 4. Study Design of the Expansion Cohort of Portion B



For each cohort the primary diagnosis, the PF-05082566 dose levels (0.24, or 1.2 mg/kg), and the PF-05082566 drug preparation to be used (10 mg/mL or 25 mg/mL) are illustrated. No switch between the 2 different preparations is allowed during study treatment. FL-2 opens to enrollment following an assessment of the tolerability, efficacy, CCI PK data collected in FL-1. The PF-05082566 dose level to be administered in the FL-3 will be selected based on the overall evaluation of tolerability, efficacy, CCI PK data collected in FL-1 and FL-2 (if this cohort is enrolled).

3.1.3. Study Treatment Duration

Patients clinically benefiting from study treatment will be given the opportunity to continue treatment for up to 2 years from the first dose of study drug, or until one of the patient withdrawal criteria under Section 6.4 becomes a reason to discontinue study treatment. Evidence of benefit includes objective responses, mixed responses, immune-related

responses, or stable disease. See Tumor Response Assessment Section 7.7 for description and cases of mixed response [redacted]

Patients whose disease has not progressed at the end of study treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 16 weeks (±1week). Once patients have exhibited disease progression, they will enter into survival follow-up for assessment of survival only.

3.2. Starting Dose

3.2.1. Portion A

The starting dose for PF-05082566 in Portion A was 0.006 mg/kg. This dose is based on the MABEL approach. This starting dose is 50 times lower than the observed LOAEL (0.3 mg/kg) in the cynomolgus monkey multiple dose toxicity study.

3.2.1.1. Japan cohort(s) in Portion A

The starting dose for PF-05082566 in Japan cohort was 5 mg/kg. This doses has been well tolerated in a non-Japanese population and no non-Japanese patients have experienced DLTs at 5 mg/kg in Portion A.

3.2.2. Portion B

Initiation of Portion B dose cohort 1 commenced after the third dose level of Portion A (0.06 mg/kg) was determined to be safe. The starting dose for PF-05082566 in Portion B was 0.03 mg/kg, equal to one half of the single-agent, multiple dose (SAMD) cohort 3 (ie, 0.06 mg/kg) in Portion A.

3.3. Criteria for Dose Escalation

3.3.1. Portion A (Single Agent PF-05082566)

The criteria for dose escalation in Portion A will be based on the standard 3+3 design for dose escalation up to 0.3 mg/kg. For dose escalation above 0.3 mg/kg, doses of PF-05082566 will be assigned to each enrolled patient using a Time-to-Event Continual Reassessment Method (TITE-CRM), as this method has been found to be practical based on experience in Portion B.

PF-05082566 will be administered in escalating doses with available dose levels including the following: 0.006, 0.03, 0.06, 0.12, 0.18, 0.24, 0.30 using the 3+3 design, and 0.6, 1.2, 2.4, 5.0 and 10 mg/kg using the Time-to-Event Continual Reassessment Method (TITE-CRM design)[4] by IV infusion of 1 hour (-5/+15 min) every 4 weeks. As of June 2016, the highest planned single agent dose of 10 mg/kg was tested with no DLTs reported in Portion A and no further dose escalation was performed. Patients tolerated PF-05082566 well at the highest planned dose of 10 mg/kg.

If a dose reduction is needed for patients being treated with 0.6 to 10 mg/kg, a dose reduction may be made from the next highest planned dose level to one of the following specific dose levels: 0.45, 0.9, 1.8, 3.6, and 7.5 mg/kg. In addition, these intermediate dose levels may be

used for dose escalation if more than one dose limiting toxicity is observed at the preceding regular dose level

Each patient will initially receive the first dose on Cycle 1 Day 1 with a 28-day observation period. Cycle 2 Day 1 will start on Day 29. Patients clinically benefiting from study treatment without unacceptable toxicity, objective disease progression, or withdrawal of consent will be given the opportunity to continue treatment up to a maximum of 2 years from the first dose of study drug.

For the 3+3 method, the following algorithm is followed:

If a DLT is observed in 1 of the initial 3 treated patients, 3 additional patients will be enrolled and treated at the same dose level.

If no further DLT is observed, the next dose level will be opened.

Subsequent dose levels will not be opened until all patients entered at the current dose level have been treated and observed for at least 28 days after the second dose is given (ie, through the end of Cycle 2), and the number of DLTs among those patients in their first 2 cycles has been determined. If a patient in a cohort drops out of study during the DLT observation period due to reasons other than a dose limiting toxicity (eg, progression of disease, no longer willing to participate, etc.), another patient will be enrolled.

Dose escalation will continue until DLTs are observed in at least 2 of the 3-6 patients treated at a dose level, leading to the conclusion that the MTD has been exceeded and ending dose escalation. When a dose exceeding the MTD has been identified, the next lower dose is declared the MTD, provided that 6 patients have already been treated at that dose with 0 or 1 DLTs experienced in total. (3 additional patients may need to be enrolled at this dose level for a total of 6). If 2 or more patients are deemed to have DLTs, the dose will be further de-escalated and the dosing interval will be adjusted based on the observed DLTs.

Initially, 3 patients will be treated at each dose level. For the first 3 cohorts (PF-05082566 given as a single agent at 0.006, 0.03, or 0.06 mg/kg), there will be a minimum 7 day time window between the first dose of a patient and the first dose of the next patient in the same cohort. For all subsequent patients enrolled up to the 0.6 mg/kg dose level, a minimum 72 hour window will apply between first doses. Updated safety information in patients indicates that PF-05082566 infusion has thus far not resulted in clinically significant infusion reactions. Therefore, there will be no longer be a waiting period between patients in the same dose cohort and in dose expansion cohorts.

The dosing interval may be reconsidered and amended during the study based on the emerging safety and PK/CC data.

For dose escalation above 0.3 mg/kg, the doses of PF-05082566 will be assigned to each enrolled patient using the modified TITE-CRM (Cheung et al., 2000),[4] as described in detail for Portion B in Sections 3.3.2 and Section 9.2.

As of June 2016, the highest planned single-agent dose of 10 mg/kg PF-05082566 was tested with no DLTs reported in the dose escalation cohorts of Portion A and, as of September 2016, 34 patients with advanced solid tumor, including 20 patients with melanoma, who had documented disease progression per RECIST v1.1 on a previous immune checkpoint inhibitor therapy (see Section 4.1 for the definition of disease that progressed from previous immune checkpoint inhibitor therapy) have been enrolled in the expansion cohorts of Portion A and treated at the 0.24 or 1.2 mg/kg dose levels of PF-05082566. Because the RP2D of PF-05082566 has not yet been determined in Portion A, approximately 40 additional patients with melanoma who had documented disease progression per RECIST v1.1 on a previous immune checkpoint inhibitor therapy will be randomized 2:1:1 to treatment with single agent PF-05082566 at the 0.6, 0.24, or 1.2 mg/kg dose levels.

The expansion cohorts will provide additional safety, tolerability, PK/CCI and preliminary efficacy data for PF-05082566 in order to support the selection of the RP2D. CCI [redacted] Cumulative safety data will continue to be evaluated using the Bayesian statistical model. Should emerging data in the expansion cohort indicate that any of the dose levels tested in the expansion cohort is more toxic than previously estimated (>25% DLT rate), or in the case of a clear exposure plateau or CCI [redacted] the next lower dose level may be explored, and may be declared as the RP2D for PF-05082566 as a single agent.

3.3.1.1. Japan cohort(s) in Portion A (PF-05082566 as a Single Agent)

The Japan cohort(s) will be conducted at Japanese sites following the completion of enrollment of the dose escalation cohorts in Portion A of this study. Patients enrolled into the Japan cohort(s) will receive PF-05082566 administered as a single agent once every four weeks as an IV infusion. Patients enrolled in Japan will follow the same eligibility criteria, study procedures (unless otherwise specified) and discontinuation criteria as those patients in the dose escalation cohorts of Portion A. The Japan cohort(s) will enroll approximately 9 patients in 2 cohorts. These cohorts will consist of 3 patients at one dose level below the MTD and 6 patients at the MTD based on non-Japanese population in Portion A.

Dose escalation in the Japan cohort(s) will be based on the standard 3+3 dose escalation design at 2 dose levels: 5.0 mg/kg and 10 mg/kg. Patients recruited in Japan will be enrolled and analysed to confirm safety, tolerability and PK profile of PF-05082566 in Japanese patients. These patients will complete the first 2 cycles of PF-05082566 as a single agent at a dose previously tested in non-Japan cohorts to evaluate potential dose-limiting toxicities (DLTs).

The 5 mg/kg dose (every 4 weeks) has been chosen as the starting dosage for the Japan cohort(s). 5 mg/kg is well tolerated in non-Japanese population and there were no observed DLT's in Portion A at 5 mg/kg. PF-05082566 will be administered to 3 Japan cohort patients with advanced solid tumors and B cell lymphoma. After enrollment is complete, safety data from at least 2 cycles will be obtained and analyzed. If the 5 mg/kg dose level is found to be safe, escalation to 10 mg/kg dose level will occur. Lower dose levels may be explored at any time during the study if this is clinically and scientifically warranted. Study centers will receive a notification if additional dose levels are explored.

Each patient will initially receive the first dose on Cycle 1 Day 1 with a 28-day observation period. Cycle 2 Day 1 will start on Day 29. After completion of Cycle 2, patients will be asked to sign an additional consent document for confirmation of the patient's willingness to continue participation in this study before starting Cycle 3. Patients clinically benefiting from study treatment without unacceptable toxicity, objective disease progression, or withdrawal of consent will be given the opportunity to continue treatment on a reduced visit schedule (Day 1 of each cycle), or as clinically indicated, until disease progression, unacceptable toxicity, or withdrawal of consent up to a maximum of 2 years from the first dose of study drug, or until one of the patient withdrawal criteria under Section 6.4 becomes a reason to discontinue study treatment. Dose escalation will follow the 3+3 algorithm described in Section 3.3.1.

Patients discontinuing from the study before the second dose is given (Cycle 2 Day 1) for reasons other than treatment-related toxicity will be replaced in order to complete the cohort and have an adequate assessment.

Patients that discontinue from the study after the completion of second dose of therapy for reasons other than treatment-related toxicity will be discussed on a per patient basis between the sponsor and the investigator in terms of whether the patient requires replacement or can continue to be observed off study for the duration of the DLT observation period (ie, total 8 week period).

If the above replacement occurs, the patients who are lost to follow-up due to reasons unrelated to treatment related adverse events (AEs) are not evaluable for DLT. See Section 9.1.

Updated safety information in non-Japanese patients indicate that PF-05082566 infusion has thus far not resulted in clinically significant infusion reactions. Therefore, there will not be a waiting period in the same dose cohort between adjacent patients.

The dosing interval may be reconsidered and amended during the study based on the emerging safety and PK[redacted] data.

Seven (7) patients have been enrolled in the 2 cohorts described above and the 2 tested dose levels of PF-05082566 (5.0 mg/kg and 10 mg/kg) were well tolerated in patients recruited in Japan with no DLTs reported. Japanese sites are currently participating in the expansion cohort of Portion A and Portion B.

3.3.2. Portion B (PF-05082566 + Rituximab)

Safety of the single agent within the first 3 cohorts of Portion A will trigger the initiation of Portion B. The initiation of Portion B may occur after all patients in the single agent 0.06 mg/kg cohort have completed Cycle 1 and received their second dose. Enrollment will then begin with PF-05082566 at a dose of 0.03 mg/kg and escalating at the same dose intervals as listed for Portion A. PF-05082566 will be given to patients IV (every 4 weeks) in combination with rituximab (375 mg/m^2, every week during Cycle 1). Patients clinically benefiting from study treatment without unacceptable toxicity, objective disease progression, or withdrawal of consent will be given the opportunity to continue treatment up to a

maximum of 2 years from the first dose of study drug. The first dose of PF-05082566 will be given approximately 24 hours after the second weekly, full dose of rituximab (defined as either the planned dose or in the case of infusion reactions, at least 50% of planned rituximab dose; see Section 5 for details). For the first cohort (PF-05082566 given at 0.03 mg/kg) there will be a minimum 7 day window between the first dose of PF-05082566 for a patient and the first dose of rituximab for the next patient.

For all subsequent dose escalation/de-escalation cohorts, up to 0.6 mg/kg, a minimum 72 hour window will apply between the first dose of PF-05082566 for a patient and the first dose of rituximab for the next patient in the same cohort. Updated safety information in patients indicates that PF-05082566 infusion has thus far not resulted in clinically significant infusion reactions. Therefore, there will be no longer be a waiting period between patients in the same dose cohort and in dose expansion cohorts.

The proposed doses and schedule may be reconsidered and amended during the study based on the emerging safety and PK[CCI] data.

See the additional rules below for more details regarding dose escalation. Patients in Portion B will be replaced only if they discontinue prior to receiving the first dose of PF-05082566.

The doses of PF-05082566 will be assigned to each enrolled patient using the modified TITE-CRM (Cheung et al., 2000).[4] The goal of the trial is to determine the dose of PF-05082566 associated with a 25% probability of a DLT (a target DLT rate of 0.25). In Portion B, the first 3 patients (first cohort) will be treated at 0.03 mg/kg. For each subsequent patient eligible for enrollment, the probability of DLT is estimated for each level based on all the collected data from all treated patients up to that time and the prior expectations of toxicity, and the patient is assigned to the currently estimated target level (with escalation restrictions as indicated below), defined as the dose having an estimated probability of DLT closest to but not greater than the target rate (25%). The probabilities of toxicity are estimated based on a Bayesian statistical model with prior distribution (projected from the Portion A single agent data and pre-clinical data) to learn about the overall dose-toxicity relationship. Patients' DLT data will be reported to the study statistician who will update the dose-toxicity model before the next enrolled patient is treated.

In the TITE-CRM paradigm, patients who have enrolled in the trial but have not experienced DLT will be included in the probability calculation with an initial weight equal to the proportion of the 8-week (2 cycles of PF-05082566) DLT observation period the patients have completed (however the weight function may be modified if the Portion A safety data suggest different weight (toxicity) patterns in Cycle 1 and Cycle 2+ of PF-05082566, and/or accumulating safety data in Portion B suggest a different pattern); patients who experience DLT or complete the observation period without DLT will be assigned full weight (=1). Details on the TITE-CRM method are provided in Section 9.2 and the Statistical Analysis Plan.

To avoid overly rapid escalation and to retain the efficiency of dose administration when enrollment is fast, the following restrictions and practical considerations will be followed.

- Dose skipping in escalation to untested doses is not allowed (k −> k+1). In particular, at least 3 patients should have been treated at dose level k before escalation to dose level k+1;

- At least 3 patients should have been on treatment (for a minimum of 3 weeks) and observed DLT rate <33% at dose level k before a patient is assigned to dose level k+1 (*Note that the waiting window depends on our knowledge in the time-to-event pattern of toxicity and accumulating safety data, and thereby the confidence in the associated weights. However, intentional delay in enrollment in the absence of DLT or serious AEs should be minimized and discouraged*);

- Dose escalation recommendation by the TITE-CRM algorithm may be overruled (but frequency should be minimized) by the sponsor if the nature of the existing data causes safety concern;

- If the most recent 3 patients have been treated at dose level k, the next enrolled patient will not be treated at the same dose until at least 2 of the most recent 3 patients have completed 3-week follow-up in order to collect timely safety information.

Dose finding (dose escalation and de-escalation) of the trial stops if: (1) the maximum sample size has been reached (45 in total, see Section 9.3 for details), (2) at least 9 patients have been treated at a dose that is predicted to be the MTD or (3) all doses appear to be overly toxic and the MTD cannot be determined in the current trial. The final posterior probability and 90% posterior probability interval estimates of DLT at each dose level will be calculated, with data from all patients.

As of June 2016, the highest planned dose of 10 mg/kg PF-05082566 in combination with rituximab was tested with no DLTs reported in Portion B and no further dose escalation was performed. As of September 2016, 10 patients with rituximab-refractory FL (see Section 4.1 for definition of FL disease refractory to rituximab) and 4 patients with relapsed or refractory DLBCL have been enrolled in the expansion cohort of Portion B and treated at the 1.2 mg/kg dose level of PF-05082566. Because the RP2D of PF-05082566 administered in combination with rituximab has not yet been determined in Portion B, enrollment will be expanded to enroll up to 100 patients with rituximab-refractory FL. Patients with rituximab-refractory FL will be treated with rituximab in combination with PF-05082566 at the 1.2 mg/kg and, following an assessment of the tolerability, efficacy[redacted] and PK data collected for the combination of PF-05082566 at 1.2 mg/kg plus rituximab, at the 0.24 mg/kg dose level. In the first cohort (FL-1), up to 20 patients will be treated with rituximab in combination with PF-05082566 at 1.2 mg/kg and in the second cohort (FL-2) up to 20 patients may receive rituximab in combination with PF-05082566 at 0.24 mg/kg. The PF-05082566 dose level to be administered in the third cohort (FL-3) will be selected based on the overall evaluation of tolerability, efficacy, [redacted] and PK data collected for the combination of PF-05082566 plus rituximab in FL-1 and FL-2 (if this cohort is enrolled). In FL-3, approximately 60 patients will receive rituximab in combination with PF-05082566 either at the 0.24 or 1.2 mg/kg dose level.

The objective of the expansion cohorts is to provide additional safety, tolerability, PK[redacted] and preliminary efficacy data for PF-05082566 in combination with rituximab, in order to support the selection of the RP2D. [redacted]

Cumulative safety data will continue to be evaluated using the Bayesian statistical model. Should emerging data indicate that any of the dose levels tested in the expansion cohort is more toxic than previously estimated (>25% DLT rate), [redacted] and may be declared as the RP2D for PF-05082566 in combination with rituximab.

Japanese sites are currently participating in Portion B following the evaluation of the PF-05082566 safety profile in Japanese patients enrolled in Portion A.

3.4. DLT Definition

Severity of AEs will be graded according to CTCAE v 4.03. AEs meeting the following definition occurring in the first two cycles of treatment (up to 28 days post second dose) which are not related to progressive disease and attributable to PF-05082566 alone (Portion A) or to PF-05082566 in combination with rituximab (Portion B) will be classified as DLTs:

Hematologic:

- Grade 4 neutropenia [absolute neutrophil count (ANC) <500/mm^3 or <0.5 x 10^9/L] lasting >7 days;
- Febrile neutropenia (defined as neutropenia ≥ Grade 3 [ANC <1000 cells/mm^3] and a body temperature ≥38.5°C);
- Neutropenic infection (ANC <1,000/mm^3 or <1.0 x 10^9/L, and Grade >3 infection);
- Grade ≥3 thrombocytopenia (<50,000 - 25,000/mm^3 or <50.0 – 25.0 x 10^9/L) with bleeding;
- Grade 4 thrombocytopenia (<25,000/mm^3 or <25.0 x 10^9/L) >3 days;
- Grade 4 anemia (hemoglobin <6.5 g/dL or 4.0 nmol/L);
- Grade ≥3 hemolysis (>2 gm decrease in hemoglobin requiring medical intervention [transfusion or steroids]).

Non-Hematologic:

- Grade ≥3 toxicities, except those grade 3 events that respond to treatment (eg, grade 3 nausea, vomiting, diarrhea that responds to standard medical supportive care within 48 hours would not be considered a DLT).

3.5. MTD Definition (Portion A and Portion B)

The MTD estimate is the dose level associated with ≤25% of patients experiencing a dose-limiting toxicity. Due to the discreteness of the dose levels and in the interest of safety of patients, the estimated MTD is the highest dose level with DLT rate closest to but no more than 0.25 per the TITE-CRM method (for Portion A in which the 3+3 design was used for PF-05082566 doses of up to 0.3 mg/kg and for Japan cohorts, the MTD estimate is the dose level at which 0/6 or 1/6 evaluable patients experience a DLT during the first two treatment cycles with the next higher dose having at least 2 of 3 to 6 patients experiencing DLTs).

3.6. RP2D (Portions A and B)

The RP2D will be chosen for further clinical development based on data for the primary and secondary endpoints of this study. Given the broad active dose range for many immunotherapies, significant clinical activity observed at lower doses will also be a factor in choosing the RP2D.

To be declared the RP2D, the MTD should also prove to be clinically feasible in a higher number of patients for long term administration. Once the MTD is identified, additional patients may be enrolled at this dosing level. In the expansion cohort, patients' DLT data will still be entered into the Bayesian statistical model of the TITE-CRM procedure. If the posterior distribution of the model incorporating the additional data from the expansion cohort suggests the estimated MTD is associated with a DLT rate, or in the case of a clear exposure plateau CCI [redacted] the next lower dose or an intermediate dose level will be explored, and may be declared as the RP2D.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

1. Portion A: Histological diagnosis of advanced solid tumor malignancy or B-cell lymphoma, for which no curative therapy is available. For patients to be enrolled in the expansion cohorts:

   - Diagnosis of melanoma, renal cell carcinoma (RCC), non-small cell lung carcinoma (NSCLC), or squamous cell carcinoma of the head and neck (SCCHN);

   - Documented disease progression per RECIST v1.1 on a previous systemic immune checkpoint inhibitor therapy (anti-CTLA-4, anti-PD-1/PD-L1) administered as a single agent OR in combination;

- Measurable disease with at least 1 target lesion by RECIST v1.1 that has not been previously irradiated.

2. Portion B: Histological diagnosis of relapsed or refractory CD20-positive NHL for which no curative therapy is available, including small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL) with nodal disease (not including SLL/CLL with >10,000 lymphocytes/μl, prolymphocytic leukemia, hairy cell leukemia, heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone, extraosseous plasmacytoma, lymphomatoid granulomatosis, and large B-cell lymphoma arising in Castleman disease). For patients to be enrolled in the expansion cohorts:

   - Diagnosis of FL or DLBCL;
   - Measurable disease with at least 1 extranodal tumor mass >1.0 cm in the greatest transverse diameter (GTD) or in the case of malignant lymph nodes >1.5cm in the GTD and the product of the diameters ≥2.25cm^2 as measured by Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI);
   - FL disease (Grade 1, 2, or 3a) refractory to rituximab defined as:
     - Lack of a CR or PR during a previous rituximab containing regimen comprising at least 2 doses of 375 mg/m^2, OR
     - Occurrence of PD within 6 months of completion of a previous rituximab containing regimen comprising at least 2 doses of 375 mg/m^2
   - Treatment with ≥2 prior regimens for FL.

3. Availability of an archival (tissue collected within the last 6 months) OR baseline tumor biopsy (tissue collected *de novo* during the screening period); this tissue sample must be available also for a central pathology laboratory for independent review.

4. Age 18 years or older (or ≥20 years of age if required by local regulation).

5. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1.

6. Adequate bone marrow function, for Portion A defined as absolute neutrophil count (ANC) ≥1.5 x 10^9/L (≥1,500/μL), platelet count ≥100 x 10^9/L (≥100,000/μL), and hemoglobin >9.0 g/dL (>5.6 mmol/L), and for Portion B as ANC ≥1.0 x 10^9/L (≥1,000/uL), platelet count ≥75 x 10^9/L (≥75000/μL), and hemoglobin ≥8.0 g/dL (≥5.0 mmol/L) or ≥8.5 mmol/L (≥5.3 mmol/L) for Japanese patients. In both cases, patients must be transfusion independent [ie, no blood product transfusions for a period of at least 14 days prior to enrollment (Portion B) or randomization (Portion A)].

7. Adequate Renal Function, including serum creatinine ≤2 x upper limit of normal (ULN) or estimated creatinine clearance ≥50 mL/min as calculated using the method standard for the institution.

8. Adequate Liver Function, including: a) Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome; b) Aspartate and Alanine Aminotransferase (AST and ALT) ≤2.5 x ULN.

9. Adequate Cardiac Function, as measured by left ventricular ejection fraction (LVEF) that is greater than 40%, or the presence of New York Heart Association (NYHA) classification of no greater than stage II congestive heart failure.

10. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTCAE v. 4.03 except for AEs not constituting a safety risk by investigator judgment.

11. Serum or urine pregnancy test (for females of childbearing potential) negative at screening. Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause;

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

    - Have medically confirmed ovarian failure.

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

12. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective method(s) of contraception throughout the study and for at least 90 days (180 days if required by local regulation) after the last dose of assigned treatment.

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

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

4.2. Exclusion Criteria

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

1. Patients with known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery

prior to enrollment (Portion B) or randomization (Portion A), have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

2. Prior allogeneic hematopoietic stem cell transplant.

3. Chemotherapy, growth factors, or investigational agents within 28 days before the first dose of study treatment (for the purposes of this protocol, study treatment includes rituximab in Portion B). Immunosuppressive regimens involving systemic corticosteroids within 14 days before the first dose of study treatment.

4. Therapeutic or experimental monoclonal antibodies in last 28 days prior to enrollment (Portion B) or randomization (Portion A).

5. Prior therapy with a compound of the same mechanism of action.

6. Vaccination within 4 weeks prior to enrollment (Portion B) or randomization (Portion A) except for administration of inactivated vaccines (for example, inactivated influenza vaccines).

7. Major surgery within 28 days prior to enrollment (Portion B) or randomization (Portion A).

8. Radiation therapy within 14 days prior to enrollment (Portion B) or randomization (Portion A).

9. Autoimmune disorders (eg, Crohn's Disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus) and other diseases that compromise or impair the immune system.

10. Active and clinically significant bacterial, fungal or viral infection including tuberculosis, hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness (HIV testing is not required).

11. Unstable or serious concurrent medical conditions in the previous 6 months, eg, pancreatitis, severe/unstable angina, prolonged QT interval corrected by Fridericia's formula (QTcF) >470 msec (calculated as average of triplicate readings, taken no greater than 2 minutes apart, and no history of Torsades de Pointes or symptomatic QTc abnormality), symptomatic congestive heart failure, myocardial infarction and/or pulmonary hypertension, ongoing maintenance therapy for life-threatening ventricular arrhythmia, stroke, and uncontrolled major seizure disorder.

12. Concurrent active malignancy other than non-melanoma skin cancer or carcinoma in situ of the cervix.

13. Patients who are pregnant or breastfeeding (including patients who wean).

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

15. 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.

16. Investigator 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, including their family members, directly involved in the conduct of the study.

4.3. Life Style Guidelines

Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 90 days (180 days if required by local regulation) after the last dose of PF-05082566. Women of childbearing potential who received rituximab during the study should use effective contraception for 12 months following the last dose of rituximab. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient and his or her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. The investigator or designee, at each study visit, will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or 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 hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected*, implanted*, transdermal), provided the patient or male patient's female partner 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 separate spermicide product* (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 postvasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

*Not commercially available in Japan.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the patient.

All sexually active male patients must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 90 days (180 days if required by local regulation) after the last dose of PF-05082566.

4.4. Sponsor Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a 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 center number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The contact center number is not intended for use by the patient directly and if a patient calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator 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).

For this study, the investigational products is PF-05082566. Rituximab is considered to be an investigational product in some countries and not others, according to local regulations.

Portion A:

During the dose escalation phase, PF-05082566 will be administered in escalating doses with available dose levels including the following: 0.006, 0.03, 0.06, 0.12, 0.18, 0.24, 0.30 (using the 3+3 design), and 0.6, 1.2, 2.4, 5.0 and 10 mg/kg (using the TITE-CRM design) by IV infusion of 1 hour (-5/+15 min) every 4 weeks. If a dose reduction is needed for patients being treated with 0.6 to 10 mg/kg, a dose reduction may be made from the next highest planned dose level to one of the following specific dose levels: 0.45, 0.9, 1.8, and 3.6 mg/kg. If the 10 mg/kg dose is not well tolerated, there is an option to de-escalate to 7.5 mg/kg. Each patient will initially receive the first dose on Cycle 1 Day 1 with a 28-day observation period. Cycle 2 will start on Day 29.

In the expansion cohort, PF-05082566 will be administered at either 0.24 mg/kg, 0.6 mg/kg, or 1.2 mg/kg by IV infusion of 1 hour (-5/+15 min) every 4 weeks. If a dose reduction is required due to the treatment-related toxicity, this may be allowed as an alternative to discontinuation of treatment. No dose reduction is allowed for patients treated at the 0.24 mg/kg dose level. See Section 5.4.4 for details.

Japan cohort(s) in Portion A:

PF-05082566 will be administered at 2 planned dose escalation levels (5.0 mg/kg and 10 mg/kg) by IV infusion of 1 hour (-5/+15 min) every 4 weeks. Each patient will initially receive the first dose on Cycle 1 Day 1 with a 28-day observation period. Cycle 2 Day 1 will start on Day 29. After completion of Cycle 2, patients will be asked to sign an additional consent document for confirmation of the patient's willingness to continue participation in this study before starting Cycle 3. Lower dose levels, as described above for Portion A, may be explored at any time during the study if this is clinically and scientifically warranted based on the emerging safety data in Japanese patients. Study centers will receive a notification if additional dose levels are explored.

Portion B:

PF-05082566 will be administered by IV infusion of 1 hour (-5/+15 min) every four weeks at dose levels as shown for Portion A, with the exception that the Portion B dose escalation starts at 0.03 mg/kg.

In the expansion cohort, patients enrolled in Portion B will receive a dose of PF-05082566 at 0.24 mg/kg or 1.2 mg/kg in combination with 375 mg/m^2 rituximab. If a PF-05082566 dose reduction is required due to the PF-05082566-related toxicity, this may be allowed as an alternative to discontinuation of treatment. No dose reduction is allowed for patients treated at the 0.24 mg/kg dose level. See Section 5.4.4 for details.

Rituximab will be administered in Cycle 1 at a fixed dose of 375 mg/m^2, once per week for a total of 4 weeks. The first dose of rituximab will be administered on Cycle 1 Day (-7) followed by the second dose a week later on Day (0).

The first dose of PF-05082566 will be given approximately 24 hours after the second weekly, full dose of rituximab (Cycle 1 Day 1). This allows for the observance of any potential reactions to rituximab treatment prior to the initiation of PF-05082566 dosing. In this study, full dose of rituximab is defined as either the planned dose, or for those patients who develop an infusion reaction, as at least 50% of the planned dose. Continuation with protocol activities as scheduled, following administration of less than the planned rituximab dose, requires confirmation of dose acceptability from the Sponsor.

The proposed schedule and duration of infusion may be reconsidered and amended during the study based on the emerging safety and PK[redacted] data.

Duration of Treatment

Patients clinically benefiting from study treatment will be given the opportunity to continue treatment for up to 2 years, unless one of the patient withdrawal criteria under Section 6.4 becomes a reason to permanently discontinue study treatment earlier. Evidence of benefit includes objective responses, mixed responses, immune-related responses, or stable disease. See Tumor Response Assessment Section 7.7 for descriptions and cases of mixed response[redacted]

Patients who have objective disease progression and are receiving clinical benefit from the study treatment will be given an opportunity to continue up to 2 years, after being reconsented and informed that the patient may be foregoing other therapies with possible clinical benefit(s) by continuing with study treatment.

5.1. Allocation to Treatment

5.1.1. Allocation to Treatment for Patients Enrolled in the Randomized Expansion Cohorts of Portion A

Allocation of patients with advanced melanoma to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web based response [IWR]). The site staff (study coordinator or specified designee) will be required to have an active or valid account and password with the IRT system, enter or select information including but not limited to the protocol number, specific protocol entrance criteria indicated in the system and the screening number. The site staff will then be provided with, at a minimum, a treatment assignment and a randomization number. The IRT system will provide a confirmation report containing the patient number and the randomization number. The confirmation report must be stored in the site's files. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

Eligible patients will be randomized in a 2:1:1 ratio to receive PF-05082566 at the 0.6, 0.24 or 1.2 mg/kg dose levels, respectively. Study treatment must start within 3 days after patient randomization.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.1.2. Allocation to Treatment for Patients Enrolled in the Non Randomized Expansion Cohorts of Portion A and Portion B

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 (fax or/and email) a complete Registration Form to the designated Sponsor study team member. The Sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that patient and (fax or/and email) to the site.

No patient shall receive the investigational products until the Investigator or designee has received the following information in writing from the Sponsor:

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

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

5.2. Patient Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigational site. The site will complete required dosage Preparation Record located in the Investigational Product manual (IP 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 sponsor and/or designee.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. PF-05082566

PF-05082566 drug product will be supplied by the sponsor or designee. PF-05082566 drug product is a solution and should be stored refrigerated at 2-8°C. PF-05082566 drug product will be supplied in glass vials at a 10 mg/mL (100 mg/vial) and 25 mg/mL (125 mg/vial) concentration and labeled as open supplies. Each vial is packed in an individual carton. For packaging and labeling information on rituximab, refer to the most recent version of the local product labeling. The administration of each preparation in the Portion A and Portion B expansion cohorts should follow Table 10 below; see Section 3.1 for additional details about the different expansion cohorts. **No switch between the 2 different preparations is allowed during study treatment**. See the IP manual for additional information.

Table 10. PF-05082566 Preparations to be Administered in the Expansion Cohorts

Portion	Cohort	PF-05082566 dose level	Preparation to Use	
			10 mg/mL (100 mg/vial	25 mg/mL (125 mg/vial)
A Non Randomized	CCI Other Histology	1.2 or 0.24 mg/kg	X	
A Randomized	Melanoma	1.2 mg/kg		X
	Melanoma	0.6 mg/kg		X
	Melanoma	0.24 mg/kg		X
B	FL-1	1.2 mg/kg	X	
	FL-2	0.24 mg/kg	X	
	FL-3	1.2 mg/kg or 0.24 mg/kg		X
	DLBCL	1.2 mg/kg	X	

Grey Shading: close to enrollment; No shading: Open to enrollment. No switch between the 2 different preparations is allowed during study treatment.

5.3.1.2. Rituximab

Rituximab is commercially available. Central supply or locally obtained commercial supplies of this drug will be used in accordance with local regulations and the package insert.

5.3.2. Preparation and Dispensing

See the PF-05082566 IP manual and the rituximab package insert for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

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

5.4. Administration

Patients will receive doses of PF-05082566 IV once every 4weeks (1 cycle). A cycle is defined as the time from the Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 4 weeks in duration.

Premedication is recommended for all patients, and may include an antihistamine, an anti-inflammatory agent, or a pain reliever.

The duration of infusion is 1 hour (-5/+15 minutes). The infusion rate should be reduced or interrupted in the case of symptoms of infusion reaction, and symptomatic treatment administered. The infusion may be continued at one-half the previous rate upon improvement of symptoms. If symptoms persist or worsen, the infusion should be discontinued permanently.

Patients on Portion B of the study will receive doses of rituximab IV once every week for the first cycle of treatment at a fixed dose of 375 mg/m^2. Initiation of PF-05082566 will commence approximately 24 hours after the second weekly on study full dose of rituximab has been administered. For additional details about the administration of rituximab, refer to rituximab package insert.

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 dose strength, or administration of a study drug at the wrong study visit day. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (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 adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE) CRF page.

Given the known side effects of rituximab and the pre-clinical and clinical safety data for PF-05082566 (see the PF-05082566 Investigator Brochure for additional details), it is not anticipated that overlapping side effects will occur. Patients will be treated with two doses of rituximab prior to the initiation of PF-05082566 to assess for rituximab specific side effects. Patients should be monitored carefully, however, for potential infusion reactions, particularly for the earlier doses of PF-05082566. Rituximab can cause severe, including fatal, infusion reactions. Severe reactions have typically occurred during the first infusion with time to onset of 30-120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. Refer to the rituximab package insert for additional details.

Guidance for prevention and management of infusion reactions to rituximab: Premedicate patients with an antihistamine and acetaminophen prior to dosing. For patients with rheumatoid arthritis or a previous history of rituximab-associated infusion reactions it is

suggested to administer a glucocorticoid (such as methylprednisolone) IV 30 minutes prior to each infusion. Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue rituximab. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells. Refer to the rituximab package insert for additional details.

Delay of rituximab dosing before Day 1 of Cycle 1: for patients who undergo interruption of dosing of rituximab such that dosing cannot be completed within 24 hours, repeat dosing may be acceptable in certain cases. A repeat of the rituximab dose is contingent upon communication with the Sponsor that, in the opinion of the investigator the patient is a candidate for retreatment, and only if a patient has already received less than 50% of the planned rituximab dose. Repeated dosing of rituximab will only be allowed for Day -7 or Day 0 of Cycle 1 for a maximum of one repeated rituximab infusion, and allowed only if the reasons for interruption do not include persistence of a Grade 3 or Grade 4 AE attributed to rituximab.

Delay of rituximab dosing after Day 1 of Cycle 1: Patients who have dose interruptions of rituximab that preclude completion of the infusion within 24 hours will permanently discontinue the study treatment, including treatment with PF-05082566.

Patients who develop progressive multifocal leukoencephalopathy (PML) should permanently discontinue study treatment (see Section 7.1.2.1 for more details).

5.4.1. Recommended Dose Modifications for PF-05082566

Every effort should be made to administer PF-05082566 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 2 ways:

- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

5.4.2. Dosing Interruptions for PF-05082566

Patients experiencing a DLT according to the definitions provided in Section 3.4 or intolerable Grade 2 toxicity should have their treatment interrupted (Note for Portion B: AEs attributed to rituximab only do not meet the DLT definition).

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 Section 5.4.3.

Doses may be held as needed until toxicity resolution. Depending on when the AE resolves, a treatment interruption may lead to delay the initiation of the subsequent cycle.

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 5.4.4, 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 >8 weeks, treatment resumption will be decided in consultation with the Sponsor.

5.4.3. Dose Delays for PF-05082566

A new cycle of treatment may begin only if:

- ANC ≥500/μL;
- Platelet count ≥50,000/μL;
- 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).

Note: withhold scheduled dose for liver function test related AEs (including asymptomatic) Grade ≥3 until return to baseline or Grade ≤1 severity. In cases of potential liver injury, see Section 8.5.2. In such cases, consultation with a hepatologist should be considered in the decision to initiate treatment with anti-inflammatory medications.

If the above conditions are not met, treatment must be delayed. If, within 8 weeks all toxicities have recovered within the limits described above, treatment with PF-05082566 can be resumed. If persisting toxicity does not allow for the resumption of treatment after 8 weeks of delay, the patient will be permanently discontinued from study treatment.

5.4.4. Dose Modifications for PF-05082566

Following dosing interruption or cycle delay due to toxicity (see Section 5.4.2 and 5.4.3), the PF-05082566 dose may need to be reduced when treatment is resumed.

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

Patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level, if possible, once recovery to Grade ≤1 or baseline is achieved.

Patients experiencing an AE meeting the DLT definition (see Section 3.4 for DLT definition) may resume dosing at the next lower dose level, if possible, once adequate recovery is achieved (see Section 5.4.3).

Dose reduction of PF-05082566 by 1 and, if needed, 2 dose levels (Table 11) will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be permanently discontinued from the study treatment and entered into the follow-up phase. Once a patient has a dose reduction of PF-05082566 for a PF-05082566 related toxicity, the dose will not be re-escalated. All dose modifications and adjustments must be clearly documented in the patient's source notes and CRF.

Patients treated with PF-05082566 at 0.24 mg/kg requiring a dose reduction should be permanently withdrawn from study treatment.

Table 11. Available Dose Levels for PF-05082566 (mg/kg)

1.2
0.6
0.24

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparator and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. See the IP manual, package insert, or equivalent for storage conditions of the product once reconstituted and/or diluted. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

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 evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

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

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

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

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

5.6. Investigational Product Accountability

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

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Medication(s)

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

All concomitant medications, blood products, as well as interventions (eg, paracentesis, etc.) received by patients from screening until the end of study visit will be recorded on the CRF.

5.7.1. Other Anticancer or Experimental Drugs

No additional anticancer therapy will be permitted while patients are receiving study therapy.

Additionally, the concurrent use of vitamins or herbal supplements should be considered with caution.

Palliative and supportive care for disease related symptoms may be administered at the Investigator's discretion.

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

The use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. Erythropoietin* may be used at the investigator's discretion for the supportive treatment of anemia.

*Use of erythropoietin for the treatment of anemia with cancer patients is not approved in Japan.

5.7.4. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed. Systemic anti-inflammatory therapies may be used to treat SAEs potentially related to the study drug. However, in such cases it is suggested that Investigators consult with a specialist based on the involved organ systems before instituting treatment.

5.7.5. Corticosteroids

Chronic, systemic corticosteroid use for palliative or supportive purpose, except for the use of systemic corticosteroids according to the rituximab prescribing information, is not permitted. Use of corticosteroids as symptomatic treatment may be allowed on individual basis and upon discussion with the Sponsor. Acute emergency administration, topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed. Physiologic use for replacement in cases of adrenal insufficiency at doses equivalent to ≤10 mg of prednisone daily is acceptable.

5.7.6. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-05082566 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-05082566 is recommended at least 14 days prior to surgery. Postoperatively, the decision to reinitiate PF-05082566 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.7.7. Radiation Therapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline, otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.

6. STUDY PROCEDURES

For screening, treatment period and follow-up procedures, see Schedule of Activities (Table 1-7).

For the treatment period discussed below, where multiple procedures are scheduled at the same nominal time point(s) relative to dosing, the following prioritization of events should be adhered to, where possible, in order of the most important to the least important:

- CCI [redacted]
- Pharmacokinetic blood specimens - obtain at the scheduled time.
- ECGs – obtain as close as possible to the scheduled time, but prior to PK blood specimen collection and within 30 minutes of the nominal time.
- Blood pressure/pulse rate – may be obtained prior to or after ECG collection but must be obtained prior to PK blood specimen collection and within 60 minutes of the nominal time.
- Clinical safety lab tests – obtain as close as possible to the scheduled time.
- Other procedures – All other procedures should be obtained as close as possible to the scheduled time, but may be obtained before or after blood specimen collection, unless sampling is determined by the study personnel to potentially impact the results.

6.1. Screening

For screening procedures see Schedule of Activities (Table 1-7).

6.2. Treatment Period

For treatment period procedures, see Schedule of Activities (Table 1-7).

6.3. Follow-up Visit

Patients whose disease has not progressed at the end of treatment will enter into disease follow-up. During this follow-up period, patients will have disease assessments performed every 16 weeks (±1 week). Once patients have exhibited disease progression, they will enter into survival follow-up for assessment of survival only. A new anti-cancer therapy will be reported on the CRF.

Patients will be followed for at least 2 years after first dose of the last patient unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor, whichever occurs first. Patients will be contacted every 12 weeks (+/- 4 weeks) for survival status and subsequent anti-cancer treatment.

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.

For follow-up procedures see Schedule of Activities (Table 1-7).

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, behavioral, or administrative reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigative site.

Reasons for discontinuation of study treatment may include:

- CCI [redacted]
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity (including PML, clinically significant opportunistic infections and tuberculosis);
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by Sponsor;
- Death.

CCI [redacted]

[redacted]

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

CCI [redacted]

[redacted]

[redacted]

7. ASSESSMENTS

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

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

7.1. Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, neurological examination, ECG (12-lead), laboratory assessments, including pregnancy tests and verification of concurrent medications. A neurological examination will be performed as clinically indicated because of the risk of progressive multifocal leukoencephalopathy with rituximab.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting administration of study treatment: once at the start of screening and once at the baseline visit, immediately before administration of the first dose of study treatment. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will be repeated at every treatment cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study.

7.1.2. Adverse Events

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

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

7.1.2.1. Adverse Events of Special Interest

Due to pre-clinical results and human experience with compounds of a similar nature, patients should be carefully monitored for endocrine (including but not limited to hypopituitarism and hypoadrenalism) and hepatic events. Evaluation of hypopituitarism or hypoadrenalism should be considered in patients who develop signs and symptoms that may include unexplained loss of body and facial hair, decreased blood pressure, and hyponatremia with hyperkalemia; in the presence of clinical suspicion, laboratory testing should include one or more of the following: thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and cortisol levels before and 30-60 minutes after corticotropin stimulation. See Study Flowcharts, Table 3, Table 5, and Safety Lab table (Table 8) for guidance.

John Cunningham virus infection resulting in PML and death can occur in rituximab treated patients with hematologic malignancies. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab. Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

7.1.3. Laboratory Safety Assessments

Hematology and blood chemistry (Table 8) will be drawn at the time points described in the Schedule of Activities (Table 5) and analyzed at local laboratories.

Blood and/or urine for hematology, chemistry, coagulation, hepatitis B and C, endocrine function, urinalysis and pregnancy testing will be collected at the time points described in the Schedule of Activities, Table 3, and Table 5, and analyzed at local laboratories.

7.1.4. Vital Signs and Physical Examinations

Patients will have a physical exam to include weight, blood pressure, heart rate, body temperature (Portion B only), assessment of ECOG status and height; height will be measured at baseline only. Physical exams will be performed at the time points described in the Schedule of Activities, Table 3 and Table 5.

7.1.5. ECG Assessments

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing in the supine position 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, Table 3, and Table 5), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTc interval. If the mean QTc is prolonged (>500 msec by any correction method, 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 QTc interval) should be performed. In addition, repeat ECGs should be

immediately performed hourly for at least 3 hours until the QTc interval resolves to Grade 1 or less. If QTc interval reverts to less than 500 msec, and in the judgment of Investigator(s) and Sponsor is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 500 msec the study drug will be held until the QTc interval decreases to Grade 1 or less. Patients will then re-start the study drug at the next lowest dose level. If the QTc interval has still not decreased to <500 msec after 2 weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

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

If 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.

If an ECG assessment is 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 overrides the timing of the ECG collections).

7.2. Pharmacokinetics Assessments

7.2.1. Portion A: Single Agent PF-05082566 (Dose Escalation, and Japan Cohort(s))

Blood samples will be collected for PK of PF-05082566 at the following times:

- During Cycle 1 and Cycle 2 on (a) Day 1 at pre-dose, end of infusion, and at 1.5, 2, 6 and 24 hrs post start of infusion; (b) on Days 3, 8, 15 and 22;
- During Cycle 3 on (c) Day 1 at pre-dose, end of infusion, and at 1.5 and 24 hrs post start of infusion; (d) on Days 8, 15 and 22;
- During Cycle 4 on (e) Day 1 at pre-dose, end of infusion, and at 1.5 hr post start of infusion; (f) on Day 3 and Day 28 after administration of the last dose.

For patients ending the study, PK samples should be collected at the End of Treatment assessment day.

The PK sample for Day 28 following the Cycle 4 dose of PF-05082566 need not be collected if a patient undergoes PF-05082566 dosing for additional cycles or if the patient starts another cancer therapy. If a patient continues with additional cycles of therapy (up to 2 years), PK samples will be collected pre-dose, end of infusion and at 1.5 hours post start of infusion in each cycle.

In Japan, patients will be hospitalized for PK sampling for at least the first 2 days of the first cycle of dosing of PF-05082566 (Note: this is a planned hospitalization and thus is not considered a serious adverse event (SAE) unless prolonged due to study drugs. See section on SAEs for more information).

7.2.2. Portion B: PF-05082566 + Rituximab (Dose Escalation)

7.2.2.1. PF-05082566

Blood samples will be collected for PK of PF-05082566 at the following times:

- During Cycle 1 on (a) Day 1 at pre-dose, end of infusion, and at 1.5, 2, 6, and 24 hrs post start of infusion; (b) on Days 3, 7, 14 and 22;
- During Cycle 2 on (c) Day 1 at pre-dose, end of infusion, and at 1.5 and 24 hrs post start of infusion; (d) on Days 8, 15 and 22;
- During Cycle 3 on (e) Day 1 at pre-dose, end of infusion and at 1.5 hrs post start of infusion; (f) on Day 22;
- During Cycle 4 on (g) Day 1 at pre-dose, end of infusion and at 1.5 hrs post start of infusion; (h) and on Day 28 post Cycle 4 dose.

For patients ending from the study, PK samples should be collected at the End of Treatment assessment day.

The PK sample for Day 28 following the Cycle 4 dose of PF-05082566 need not be collected if a patient undergoes PF-05082566 dosing for additional cycles or if the patient starts another cancer therapy. If a patient continues with additional cycles of therapy up to 2 years, PK samples will be collected pre-dose, end of infusion and at 1.5 hours post start of infusion in each cycle.

7.2.2.2. Rituximab

Blood samples will be collected for PK of rituximab at the following times (NOTE: All days are numbered relative to the start of PF-05082566 dosing):

- On Day (-7) at pre-dose and at 15 min post end of infusion, 6 and 24 hrs post start of infusion;
- On Day (0) at pre-dose and 15 min post end of infusion;
- During Cycle 1 on: Day 1 at 2 and 24 hrs post start of infusion of PF-05082566*;* Day 3; Day 7 at pre-dose and 15 min post end of infusion; Day 14 at pre-dose and 15 min post end of infusion; and Day 22;
- During Cycle 2 on: Day 1 prior to the dose of PF-05082566 and Day 15.

For patients ending from the study, PK samples should be collected at the End of treatment assessment day.

Note that whenever rituximab PK samples are collected on days where PF-05082566 PK samples are being collected, these collections should be time matched to avoid multiple needle sticks. The time matched collections are shown in the above list in italics.

For both Portion A and Portion B, PK sampling schedule may be modified based on emerging PK data.

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

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

PK samples will be assayed for PF-05082566 and rituximab using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

7.2.3. Dose Expansion Cohorts – Portion A and Portion B

7.2.3.1. PF-05082566 PK Sampling for Dose Expansion Cohorts (Portions A and B)

For patients enrolled into each of the expansion cohorts for Portions A and B, blood samples will be collected for PK of PF-05082566 for at least 5 patients in each dose cohort at the following times:

- During Cycle 1 on (a) Day 1 at pre-dose, end of infusion, and at 2, 6, and 24 hrs post start of infusion; (b) one sample on Days 7 and 14, respectively;
- During Cycles 2 and 3 on (c) Day 1 at pre-dose, and end of infusion;
- During Cycle 4 on (d) Day 1 at pre-dose, and end of infusion, and 2, 6, and 24 hrs post start of infusion; (e) one sample on Days 7 and 14, respectively;
- Subsequently, every 4 cycles on Day 1 at pre-dose (Cycles 8, 12, 16, etc.);
- At the End of Treatment visit.

For the remaining patients in Portions A and B expansion cohorts, PK samples will be collected on Day 1 of Cycles 1 to 4 at pre-dose and end of infusion. After Cycle 4, PK samples will be collected on Day 1 at pre-dose every 4 cycles (Cycles 8, 12, 16, etc.). A final PK sample should be collected at the End of Treatment visit.

7.2.3.2. Rituximab PK Sampling for Dose Expansion Cohort (Portion B Only)

Blood samples will be collected for PK of rituximab for at least 5 patients enrolled in the expansion cohort for FL at the following times (NOTE: All days are numbered relative to the start of PF-05082566 dosing):

- On Day (-7) and Day (0) at pre-dose and end of infusion of rituximab;
- During Cycle 1 on: (a) Day 1 at 2 and 24 hrs post start of infusion of PF-05082566; (b) Day 7 and Day 14 at pre-dose and end of infusion of rituximab;
- During Cycle 2 on: Day 1 prior to the dose of PF-05082566;
- A final PK sample should be collected at the End of treatment visit.

For the remaining patients in Portion B expansion cohorts, PK samples for rituximab will not be collected.

Note that whenever rituximab PK samples are collected on days where PF-05082566 PK samples are being collected, these collections should be time matched to avoid multiple needle sticks.

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All efforts should be made to time match the PK samples with the biomarker samples whenever these samples are collected together.

CCI [redacted]

Flow cytometry of peripheral blood mononuclear cells (PBMCs) will also be conducted to determine the absolute counts of key cell types, including T cells B cells, and NK cells. These measurements will be used to detect changes in PBMC composition after treatment and will be conducted in parallel with the PK assessment as in Section 7.2.1 and 7.2.2.

CCI [redacted]

7.3.3.3. Immunogenicity Assessments for Expansion Cohorts (Portion A and Portion B)

7.3.3.3.1. Immunogenicity to PF-05082566

Blood for PF-05082566 immunogenicity testing will be collected at

- Day 1 prior to the dosing of PF-05082566 for Cycles 1-4;
- After Cycle 4, ADA samples will be collected on Day 1 at pre-dose every 4 cycles (Cycles 8, 12, 16, etc.);
- End of Treatment visit.

Samples will be analyzed by a laboratory to be identified by Pfizer. See the Laboratory Manual for additional details.

7.3.3.3.2. Immunogenicity to Rituximab (Portion B Only)

Blood for rituximab immunogenicity testing (NOTE: All days are numbered relative to PF-05082566 dosing) will be collected at:

- Cycle 1 Day -7, Day 0, Day 7 and Day 14 prior to the dosing of rituximab;
- Cycle 2 Day 1 prior to the dosing of PF-05082566;
- End of treatment.

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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 a serious adverse event (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 60 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 case report form (CRF) from the time the patient has taken at least one dose of investigational product through the patient's last visit.

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

8.3. Definition of an Adverse Event

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

- Abnormal test findings;

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

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational Exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Abnormal Test Findings

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

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

- Test result is considered to be an adverse event by the investigator or sponsor.

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

8.5. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a 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 a 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 adverse event and as a SAE with common terminology criteria for adverse events (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.

8.5.1. Protocol-Specified Serious Adverse Events

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

8.5.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and for oncology studies, 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 (GGT), 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 serious AEs.

8.6. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation 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 a serious adverse event. Examples include:

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

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

8.7. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.03 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 a 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.

8.8. Causality Assessment

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

8.9. Exposure During Pregnancy

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

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

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

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

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

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

If the outcome of the pregnancy meets the criteria for a serious adverse event (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 serious adverse events.

Additional information about pregnancy outcomes that are reported as serious adverse events 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 serious adverse events. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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

8.10. Occupational Exposure

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

An occupational exposure is reported to 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 subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE report form is maintained in the investigator site file.

8.11. 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 adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

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

8.12. Eliciting Adverse Event Information

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

8.13. Reporting Requirements

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

8.13.1. Serious Adverse Event Reporting Requirements

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

In the rare event that the investigator does not become aware of the occurrence of a 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 timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible

causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of serious AE 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 serious AE information.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

Japan cohort(s) data will be summarized separately from the patients enrolled outside of Japan in Portion A of the study.

9.1. Analysis Sets

According to ICH E9 only analysis sets needed for main analysis are indicated here. Other analysis sets are indicated in the SAP.

1. Safety analysis set.

   For the randomized cohorts: The safety analysis set will include all patients who receive at least 1 dose of study drug. Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period, in which case patients will be classified according to the first study treatment received.

   For non-randomized cohorts: The safety analysis set will include all patients who receive at least 1 dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than 1 study treatment, the patient will be classified according to the first treatment received.

2. Full analysis set.

   For the randomized cohorts: The full analysis set (FAS) will include all randomized patients. Patients will be classified according to the treatment assigned at randomization.

For non-randomized cohorts: The FAS will include all patients who receive at least 1 dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than 1 treatment, the patient will be classified according to the first treatment received. In the non-randomized cohorts of the study, the FAS and the safety analysis set are identical.

3. Per protocol analysis set (DLT-evaluable set).

The per protocol analysis set is a subset of the safety analysis set, and it includes all patients who received at least 1 dose of study treatment (for Portion A: at least 1 dose of PF-05082566; for Portion B: at least 1 dose of PF-05082566 and 1 dose of rituximab). Note that every patient will contribute to the determination of the MTD including patients who are lost to follow up prior to completion of the 2 cycles' DLT observation period.

4. PK analysis sets.

The PK concentration population is defined as all treated patients who have at least 1 concentration.

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

9.2. Statistical Methods for Dose Allocation: TITE-CRM

A number of alternative designs have been proposed to the standard 3+3 design for Phase I dose escalation trials that improve its accuracy, efficiency and statistical validity, including the continual reassessment method (CRM) (O'Quigley et al., 1990)[22], and its variants.

Delayed-onset toxicities are a particular challenge for phase I trials of combination therapies (Muler et al., 2004).[22] Most of the available dose-escalation designs, including the 3+3 design, the up-and-down designs and the CRM design, require all patients to have completed a fixed observation period for toxicity (eg, 1-2 cycles of the experiment regimen, or 6-8 weeks after start of treatment) before additional cohorts of patients can be enrolled. Thus, trial accrual is subject to opening and closing which may pose logistical risk on the success and completion of the study. In addition, patients who are either lost to follow-up or die of events unrelated to treatment are usually required to be replaced. Due to these reasons, the trial duration could be unacceptably long in case of prolonged observation window and unexpected high rate of patient drop-out.

The time-to-event continual reassessment method (TITE-CRM), a variant of the original CRM method, is open to accrual continually, and maintains other advantages of the CRM relative to the 3+3 design. Like CRM, TITE-CRM seeks to determine the target MTD dose, defined as the dose most closely identified with the target rate, which is the largest acceptable DLT rate determined by the investigators based on the relative costs and benefits of the treatment.

TITE-CRM is to be implemented as described by Cheung et al. (2000) and Normolle et al. (2006)[19] for the dose escalation of PF-05082566. PF-05082566 will be administered IV at escalating doses of 0.60, 1.2, 2.4, 5 mg/kg as a single agent in Portion A (the standard 3+3 method is used for doses up to 0.30 mg/kg), and at escalating doses of 0.03, 0.06, 0.12, 0.18, 0.24, 0.30, 0.60, 1.2, 2.4, 5 mg/kg given once every 4 weeks in Portion B in combination with rituximab, which will be administered at a fixed dose of 375 mg/m^2, once per week for 4 weeks total (Cycle 1). If 5 mg/kg of PF-05082566 is well tolerated, the sponsor may investigate the 10 mg/kg level for the estimation of the MTD. The following dose levels are available for the dose ranges bracketed between 0.6 and 5 mg/kg based on the TITE-CRM indicated dose reduction from the next highest planned dose level: 0.45, 0.9, 1.8, 3.6, and 7.5 mg/kg). However, they will not be tested if a dose reduction is not recommended by the statistical model. In addition, these intermediate dose levels may be used for dose escalation if one dose limiting toxicity is observed at the preceding regular dose level

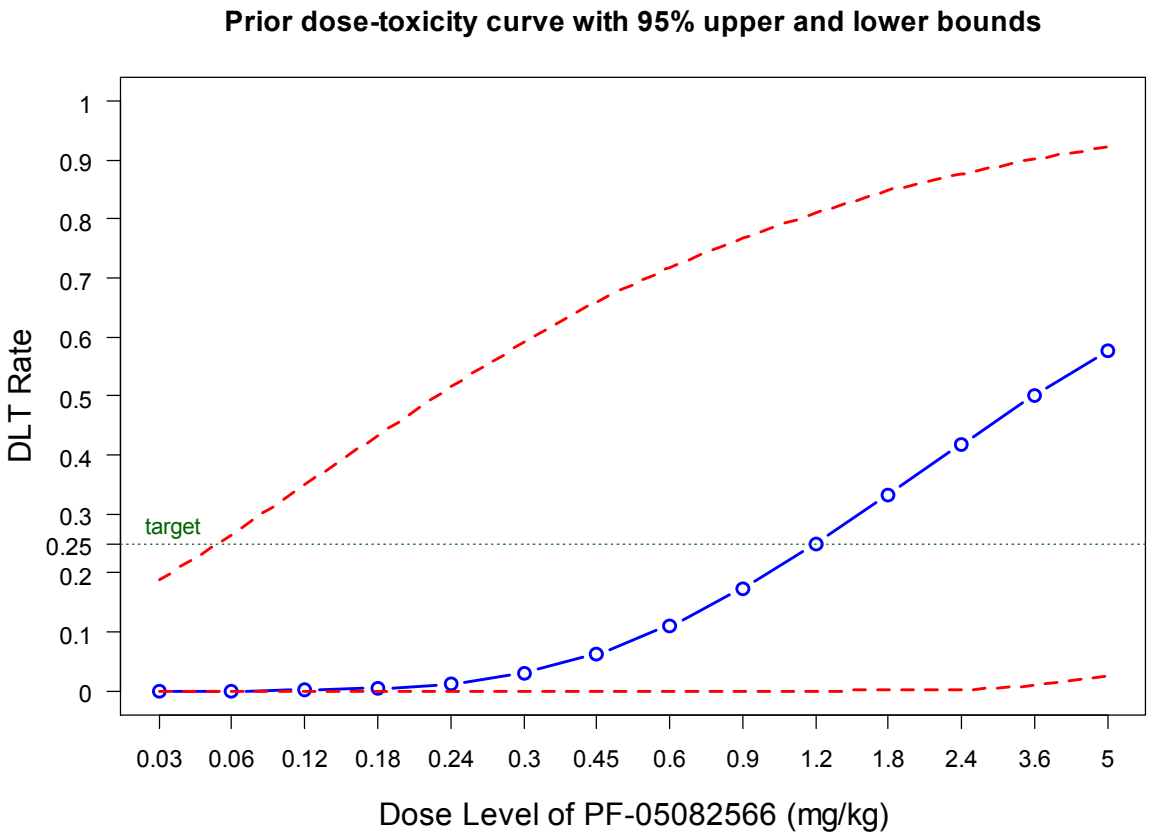
We define the MTD to be the highest dose that is associated with a DLT rate ≤25%. A power function modeling DLT rate at each dose d_i (i=1, …, 14) expressed as Pr (DLT | d_i) = F_i (β) will be used:

$$F_i(\beta) = p_i^{\exp(\beta)}$$

where p_i is the prior estimate of DLT rate at dose level d_i, and $p_1 \leq p_2 \leq \ldots \leq p_{14}$. These estimates will be projected based on the Portion A single-agent PF-05082566 safety profile in the first 3 dose levels, together with the pre-clinical animal data. β is an unknown single parameter modeling the dose-toxicity relationship, with prior distribution $N(0, \sigma_0^2)$, where σ_0 is the standard deviation of the normal prior distribution with mean=0. At the beginning of the trial, the initial prior value of β is set as 0, the prior mean, which gives a prior dose-toxicity model of $F_i(\beta) = p_i$ based on the power function.

In the Bayesian paradigm, the prior distribution $N(0, \sigma_0^2)$ expresses the researchers' belief in the quality of the initial estimates p_i. The smaller the standard deviation σ_0, the more confidence researchers have in the precision of p_i. and vice versa. As the trial progresses, this prior distribution is combined mathematically with the observed data to yield the posterior distribution of the parameter β (the posterior mean of β will be calculated to model the dose-toxicity relationship). The prior distribution determines how responsive TITE-CRM is to the accumulated data. With a small σ_0 upfront, the posterior toxicity probability estimates remain close to the prior estimates unless significantly discrepant data otherwise occur; with a large σ_0, the model will tend to be more immediately responsive to data. In our trial, we set σ_0=0.97, which provides a reasonably flat prior distribution of β, with 95% Bayesian credible interval of $\exp(\beta)$: [0.15, 6.67], sufficiently wide to cover a wide spectrum of dose-toxicity scenarios. Figure 5 illustrates the dose-toxicity curve with 95% upper and lower bounds when the initial prior estimates p_i are (1.4e-05, 1.4e-04, 9.0e-04, 3.8e-03, 0.01, 0.03, 0.06, 0.11, 0.17, 0.25, 0.33, 0.42, 0.50, 0.58).

Figure 5. Example Plot of Prior Dose-Toxicity Curve



In the trial conduct, the first 3 patients will be treated at the lowest dose level. For each subsequent patient eligible for enrollment, the probability of DLT is estimated for each level based on all the collected data from all treated patients up to that time and the prior expectations of toxicity, and the patient is assigned to the currently estimated MTD, defined as the dose having an estimated probability of DLT closest to but not greater than the target rate (25%). The probabilities of toxicity are estimated based on the Bayesian power model with prior distribution of the parameter to learn about the overall dose-toxicity relationship. Patients' DLT data will be reported in real time to the study statistician who will estimate the MTD before the next enrolled patient is treated.

In the TITE-CRM paradigm, patients who have enrolled in the trial but have not experienced DLT will be included in the probability calculation with a weight equal to the proportion of the 8-week (2 cycles of PF-05082566) DLT observation period the patients have completed (however the weight function may be modified if safety data suggest different weight (toxicity) patterns in Cycle 1 and Cycle 2 of PF-05082566, or an adaptive weight function if ongoing safety data suggest different toxicity patterns in Cycle 1 and Cycle 2 of PF-05082566); patients who experience DLT or complete the observation period without DLT will be assigned full weight (=1) (for details see the Statistical Analysis Plan).

Section 3.3.2 describes stopping rules and some restrictions and practical considerations on dose escalation.

9.3. Sample Size Determination

The sample sizes planned for the study arise from logistic feasibility and past experience with first in human (FIH) studies in oncology and are not driven by statistical considerations. It is expected that approximately 270 patients will be required (including dose escalation and expansion cohorts of Portion A and Portion B).

Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the TITE-CRM approach can not be determined in advance. The maximum sample size is set as 45 in order to have a reliable and accurate estimate of the MTD based on simulation results. Based on probability theory, a sample size of 45 will ensure the estimates of any binary variable (eg, objective response rate) have a 95% confidence interval of width <0.30. A sample size of 45 also enables us to detect any unexpected toxicity that occurs at 5% rate (in a non-dose-dependent fashion) with a probability of 0.90, and that occurs at 10% rate with a probability of 0.99.

A stopping rule (Section 3.3.2) will also be implemented for possible early stopping if there is strong confidence in the estimated MTD.

Portion A expansion cohorts include patients with solid tumors of interest who progressed after treatment with an immune checkpoint inhibitor (anti-CTLA-4, anti-PD-1/PD-L1). The target sample size is approximately 20 patients with advanced melanoma at each tested dose (0.24 mg/kg, 0.6 mg/kg, 1.2 mg/kg) and approximately 20 patients, including other tumor types as described in Section 4.1, Inclusion Criteria (Criterion 1). With 20 patients with advanced melanoma, the maximum standard error of the objective response rate (ORR) is 0.11.

Number of Patients with Responses/Sample Size (Advanced Melanoma)	**Objective Response Rate (ORR) and Estimated 95% CI (%)***
2/20	10% (1.2, 31.7)
4/20	20% (5.7, 43.74)
6/20	33% (11.9, 54.3)
10/20	50% (27.2, 72.8)

*Clopper-Pearson CI

Portion B expansion cohorts include approximately 100 patients with FL refractory to rituximab (see Section 4.1 for definition of FL disease refractory to rituximab) with 80 patients treated at the selected RP2D (1.2 mg/kg or 0.24 mg/kg) dose level of PF-05082566. With 80 patients, the maximum standard error of the ORR is 0.06.

Responses/Sample size (FL Refractory to Rituximab)	Objective Response Rate (ORR) and Estimated 95% CI (%)*
40/80	50% (38.6, 61.4)
44/80	55% (43.5, 66.2)
48/80	60% (48.4, 70.8)
56/80	70% (58.7, 79.7)

*Clopper-Pearson CI

9.4. Efficacy Analysis

In this first-in-human study anti-tumor activity is a secondary objective in the dose escalation cohorts and a primary objective in the expansion cohorts and will be evaluated separately in Portion A and Portion B.

The detailed definitions of objective response (OR), best overall response (BOR), objective ORR, duration of response (DR), time to tumor response (TTR), progression-free survival (PFS), and overall survival (OS) will be provided in a Statistical Analysis Plan (SAP).

Tumor Response will be presented in the form of patient data listings that include, but are not limited to, tumor type, received (maximum) dose, overall tumor response at each visit, and best overall response. In addition, progression date, death date, date of first response and last tumor assessment date will be listed, together with Duration of Response, Progression Free Survival and Overall Survival. If any responses are observed for patients with measurable disease at baseline, tumor responses will be tabulated by dose level(s).

ORR by treatment group will be calculated along with the two-sided 95% CI using the Clopper-Pearson method.

DR, PFS, and OS will be analysed using Kaplan-Meier methods and descriptive statistics. Point estimates will be presented with their 95% confidence intervals.

TTR will be summarized using simple descriptive statistics (eg median and range).

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9.5. Analysis of Other Endpoints

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Single- and Multiple-Dose PF-05082566 and Rituximab PK Analysis

Standard serum PK parameters including the maximum serum concentration (C_{max}), time to maximum serum concentration (T_{max}), and area under the serum concentration versus time curve (AUC) for PF-05082566 will be estimated using non-compartmental analysis, as data permits. If data permit or if considered appropriate, minimum serum concentration (C_{min}), average serum concentration (C_{ave}), pre-dose serum concentration during multiple dosing (C_{trough}), area under the serum concentration versus time curve from 0 to infinity (AUC_{inf}), area under the serum concentration versus time curve over dosing interval (AUC_{tau}), terminal elimination half-life ($t_{1/2}$), total systemic clearance (CL), steady state volume of distribution (V_{ss}), accumulation ratio (Rac) will be estimated. For rituximab, C_{max} and C_{trough} will be summarized. Descriptive statistics will be provided for these PK parameters in tabular form (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle and day.

For PF-05082566 and rituximab concentrations, individual values and descriptive statistics (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) will be presented by dose, cycle, day of assessment, and nominal time in tabular form. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day. Median profiles will be presented on both linear-linear and log-linear scales. AUC_{inf} (AUC_{tau} at steady state), AUC_{last} and C_{max} for PF-05082566 may be plotted against dose (using a logarithmic scale). These plots will include individual patient values and the geometric means for each dose. These plots will be used to help understand the dose proportionality for PF-05082566.

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9.5.1.3. Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies (Nab) will be summarized by dose. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The effect of ADA/Nab on PF-05082566 PK and safety will be evaluated if data permit.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

CCI [redacted]

[redacted]

9.6. Safety Analysis

Summaries and analyses of the primary safety endpoint(2-cycle DLT) in the dose escalation cohorts will be based on the per protocol analysis set. DLT will continue to be monitored as a secondary endpoint in the expansion cohorts based on the per protocol analysis set. Summaries and analyses of all other safety parameters will include all patients in the safety analysis set.

9.6.1. Analysis of Primary Endpoint in the Dose Escalation Cohorts

First 2 cycles DLTs 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 MTDs of PF-05082566 with or without rituximab as described in Section 4.4. AEs constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints

Adverse Events

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

Laboratory Tests Abnormalities

The number and percentage of patients who experience 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, Cycle 2, and Cycles ≥2).

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

Electrocardiograms

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. ECG collected prior to the first day of dosing will be considered the baseline ECG.

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 as individual values obtained at unscheduled time points.

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

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

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

The effect of drug concentrations on QTc change from baseline will be explored graphically. Additional concentration-QTc analyses may be performed. Data may be pooled with other study results and/or explored further with PK[CCI] 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 consisting of physician, safety specialist, and statistician to review individual and summary data collected in the safety and clinical databases. Procedures include:

- Surveillance for SAEs according to regulatory guidelines;
- The Investigators and Sponsor will discuss results, AEs, clinical laboratory tests seen at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and benefit/risk ratio and decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP)s are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be patient to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry".

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

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

11.2. Record Retention

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

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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

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

12.2. Ethical Conduct of the Study

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

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

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

Patient names, address, birth date and other identifiable data will be replaced by an alpha-numerical code consisting of a numbering system provided by Pfizer and year of birth.

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

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

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

12.4. Patient Recruitment

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Study 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 Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-05082566 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 5 business days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, patient to the other requirements of this Section.

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

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled

Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. Abbreviations

4-1BB	TNFRSF9, CD137, ILA
4-1BBL	4-1BB Ligand, TNFSF9
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine amino transferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
APC	Antigen presenting cell
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the concentration vs time curve
AUC0-168	area-under-the-curve from time zero to 168 hours
AUC0-672	area-under-the-curve from time zero to 672 hours
AUC0-last	area-under-the-curve from time zero to last measurable concentration
BM	Bone marrow
BOR	Best overall response
BUN	Blood urea nitrogen
CARs	Chimeric antigen receptors
CCI	[redacted]
CD20	Cluster of differentiation 20
CCI	[redacted]
CD40	Cluster of differentiation 40, TNFRSF5
CCI	[redacted]
CD45RA	CD45 (PTPRC) RA isoform
CCI	[redacted]
CCI	[redacted]
CD134	Cluster of differentiation 134, TNFRSF4, OX-40
CCI	[redacted]
Cave	Estimated average serum concentration
CI	Confidence interval
CL	Clearance
CLL	Chronic lymphocytic leukemia
Cmax	Maximum observed serum concentration
CR	Complete response
CRF	Case report form
CRM	Continual reassessment method
CRP	C reactive protein
CT	Computerized Tomography
CTA	Clinical study application
CTCAE	Common Terminology Criteria for Adverse Events
CXCR6	Chemokine (C-X-C motif) receptor 6; CD186
CTLA-4	Cytotoxic T-Lymphocyte-Associated protein 4
DC	Dendritic cell
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose limiting toxicity
CCI	[redacted]

DR	Duration of response
EC	Ethics committee
EC10	Concentration required to achieve 10% of the maximal response
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ED50	Dose required to achieve 50% of the maximal response
EIU	Exposure in Utero
ELISA	Enzyme linked immunosorbent assay
ERK	Extracellular signal-regulated kinase
CCI	[redacted]
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
EQ-VAS	Visual analogue scale
FAS	Full analysis set
FACS	Fluorescent-activated cell sorting; flow cytometry
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FIH	First in human
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCPs	Good Clinical Practices
GGT	Gamma-glutamyl transferase
GTD	Greatest transverse diameter
Hb	Hemoglobin
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICH	International Code of Harmonization
CCI	[redacted]
IEC	Independent ethics committee
[redacted]	CCI [redacted]
IgG	Immunoglobulin G
IgG2	Immunoglobulin G subclass 2
IHC	Immunohistochemistry
[redacted]	CCI [redacted]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
IND	Investigational new drug
INN	International non-proprietary name
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
CCI [redacted]	[redacted]
IRT	Interactive response technology
ITGB7	Integrin beta 7
IUD	Intrauterine device
IV	Intravenous(ly)
CCI [redacted]	[redacted]
LFT	Liver function test
LDH	Lactate dehydrogenase

[redacted]

LOAEL	Lowest observed adverse effect level
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MABEL	Minimal anticipated biological effect level
MAP	Mitogen activated protein
MCL	Mantle cell lymphoma
MCC	Merkel cell carcinoma
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	UK Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MUGA	Multigated acquisition
MPK	Milligrams per kilogram, mg/kg
MTD	Maximum tolerated dose
Nab	Neutralizing antibodies
NCI	National Cancer Institute
NF-kB	Nuclear Factor kappa B
NHL	Non-Hodgkin's Lymphoma
NK	Natural killer cell
NKT	Natural killer T cell
NSCLC	Non-small cell lung carcinoma
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
OBD	Optimal biological dose
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBL	Peripheral blood leukocyte
CCI C	[redacted]
PD-1	Programmed cell Death-1
PD-L1	Programmed cell Death- Ligand 1
PET	Positron emission tomography
PR	Partial response
PFS	Progression-free survival
PK	Pharmacokinetics
PML	progressive multifocal leukoencephalopathy
POM	Proof of mechanism
PR	Partial response
CCI	[redacted]
PT	Prothrombin time
QTcF	QT interval corrected by Fridericia's formula
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
CCI	[redacted]
RP2D	Recommended Phase 2 Dose
SAMD	Single agent, multiple dose
SAP	Statistical analysis plan
SC	Subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
sCD25	Soluble CD25
CCI	[redacted]
SCID	Severe combined immunodeficiency
SAE	Serious Adverse Event
CCI	[redacted]
SEM	Standard error of the mean

[redacted]

sFasL	Soluble Fas Ligand
CCI	[redacted]
SLL	Small lymphocytic lymphoma
SOP	Standard Operating Procedures
SDP	Sum of the product diameters
SPR	Surface plasmon resonance
SRSD	Single reference safety document
t1/2	Half-life
TCR	T-Cell Receptor
TGI	Tumor growth inhibition
TITE-CRM	Time-to-Event Continual Reassessment Method
TNF	Tumor necrosis factor
[redacted]	CCI [redacted]
TNFR	Tumor necrosis factor receptor
TNFRSF	Tumor necrosis factor receptor super family
TRAF	TNFR associated factor
TSH	Thyroid-stimulating hormone
TTR	Time to tumor response
ULN	Upper limit of normal
US	United States
USA	United States of America
CCI	[redacted]
Vss	Volume of distribution at steady state
WHO	World Health Organization

[redacted]

Appendix 2. Determination of Efficacy – Solid Tumors

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

Non-measurable disease

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

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

Normal sites

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

RECORDING TUMOR ASSESSMENTS

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

Target lesions

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

- If 2 target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

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

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

Non-target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

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

Target disease

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

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

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

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented; and

  - One or more target measurable lesions have not been assessed;

    or

  - Assessment methods used were inconsistent with those used at baseline;

    or

  - One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

    or

  - One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

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

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

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

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

New Lesions

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

Supplemental Investigations

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

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

Subjective progression

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

Table 12. Objective Response Status at Each Evaluation

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

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

Table 13. 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

- Adapted from: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Appendix 3. Determination of Efficacy – Non-Hodgkin's Lymphoma

Efficacy will be assessed using the International Working Group response criteria (Cheson Criteria Version 2007). Tumor responses are determined using information from objective measurements from CT scans, as well as clinical information including B-symptom evaluation, physical examination, ECOG performance status, assessment of liver and spleen, laboratory assessments such as bone marrow biopsies and/or aspirates, biochemical markers of disease activity (ie, LDH) and hematology results.

Tumor and clinical assessments will be performed as described in the Tumor Assessment flowchart. Treatment delays should not alter the schedule of tumor and clinical assessment evaluations and should continue at the frequency outlined in the flowchart.

For patients to be considered evaluable for efficacy, they must have completed at least 1 follow-up radiological tumor assessment post randomization, they must have received sufficient investigational product (at least one cycle of PF-05082566) and they must not have had any major protocol violations as determined by the sponsor.

Measurable/Abnormal Lesions

A nodal site of disease is considered measurable/abnormal if:

- Any nodal lesion can have a single diameter of >15 mm in the GTD, and the perpendicular dimension to the GTD must have a diameter >10 mm in order to be considered abnormal and measurable.
- Any nodal lesion can have >10 mm through ≤15 mm in the GTD, and the perpendicular dimension to the GTD must have a diameter >10 mm to be considered abnormal.

A nonnodal site of disease is considered measurable/abnormal if it measures ≥10 mm in 2 perpendicular dimensions.

Nonmeasurable Lesions

All non nodal sites of disease that that measure <10 mm in a single GTD are considered non measurable. Other sites of disease that are considered evaluable, but not measurable include pleural effusions, ascites and bone lesions.

Index Lesions

Up to 6 measurable/abnormal lesions should be selected as index lesions. Lesions can be selected as index lesions if they are clearly measurable in 2 perpendicular dimensions. Lesions cannot be selected as index lesions if they have been in an area of prior radiotherapy without evidence of progression. These lesions should be selected from disparate regions of the body as possible and should include mediastinal and retroperitoneal sites if these sites are involved. The greatest transverse diameter and the greatest perpendicular transverse diameter will be recorded for each index lesion. The product of these 2 dimensions will be recorded and the sum of the product diameters (SPD) of the index lesions will be the baseline value used in determining response.

Non-Index Lesions

All other lesions, either measurable or non measurable, are considered non index lesions. Multiple lesions may be grouped together as a non-index lesion (ie, multiple bony lesions in scapula). The status of the non index lesion will be recorded on the CRF.

Method of Measurement

- At a minimum, conventional CT or MRI should be performed with contiguous slices of 10 mm or less in thickness. Spiral CT should be performed by use of 8 mm or less contiguous reconstruction interval. The same method of measurement should be used throughout.
- CT scans with contrast should be performed for radiographic assessments. If a chest CT is not feasible with contrast, a non contrast CT should be performed. If CT abdomen/pelvis with contrast is not feasible, then an MRI of the abdomen/pelvis should be performed.
- Positron emission tomography (PET) scans should not be used for the determination of response, however, may be obtained if clinically indicated. Additionally, ultrasounds should not be used for purposes of measuring or evaluating disease in this study.

Clinical Assessments

In addition to radiographic tumor measurements, other clinical assessments should be obtained when evaluating disease. These include:

- Physical examination findings, evaluation presence, absence or any new lymph nodes. Additionally, an assessment of ECOG performance status will be obtained.
- Evaluation of B-symptoms.
- Bone marrow biopsies and/or aspirates.
- Evaluation of the liver and spleen.
- Biochemical markers of disease, including LDH.

Response Criteria

Evaluation of Index Lesions

Term	Definition
Complete Response	Complete disappearance of all detectable clinical and radiographic evidence of disease. All lymph nodes must have returned to normal size. If a lymph node GTD was ≥15 mm, it must have returned to <15 mm. If the short axis was >10 mm and the GTD was >11 mm, it must have returned to ≤10 mm. The spleen and/or liver, if enlarges prior to therapy on PE or CT, should no longer be palpable on PE and normal by imaging.
Partial Response	≥50% decrease in the SPD of up to 6 index lesions. No increase in size of other nodes, liver or spleen.
Stable Disease	Failure to attain a CR/PR or PD.
Progressive Disease/Relapsed Disease	≥50% increase in SPD of previously involved sites from nadir.
Unable to Evaluate	Incomplete data (ie, missing scans or unreadable images). Not all index lesions evaluated. Index lesions not assessed.

Evaluation of Non-Index Lesions

Term	Definition
Complete Response	Complete disappearance of all non-index lesions.
Stable Disease/Incomplete Response	Persistence of one or more non-index lesion not qualifying for CR or PD.
Progressive Disease	Any new nonnodal lesion. Any new nodal lesion ≥15 mm in GTD. Unequivocal progression of existing non-index lesions. Bone marrow that was negative and is now positive. Any new circulating lymphoma cells in blood cell count and/or pleural fluid. Any new circulating blasts in the blood cell count.
Unable to Evaluate	Incomplete data (ie, missing scans or unreadable images). Not all non-index lesions evaluated. Non-index lesions not assessed.
Not Applicable	No non-index lesions at baseline.

Overall Response

Index Lesions	Non-Index lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	SD/IR	No	PR
CR	UE	No	CR
CR	NA	No	CR
PR	CR	No	PR
PR	SD/IR	No	PR
PR	UE	No	PR
PR	NA	No	PR
SD	CR	No	SD
SD	SD/IR	No	SD
SD	UE	No	SD
SD	NA	No	SD
RD/PD	Any	Yes/No	RD/PD
Any	RD/PD	Yes/No	RD/PD
Any	Any	Yes	RD/PD
UE	Non-PD	No	UE

- Adapted from: Cheson B, Pfistner B, Juweid M, et al. Revised Response for Malignant Lymphoma. Journ Clin Onc. 2007;25(5):579-586.

[redacted]

Appendix 4. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Grade	Description	*Karnofsky Score**
0	Fully active, able to carry on all predisease performance without restriction	*100*
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light house work, office work.	*80 or 90*
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	*60 or 70*
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	*40 or 50*
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	*20 or 30*

* Karnofsky Performance Score is provided for reference. Please record corresponding ECOG grade only.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

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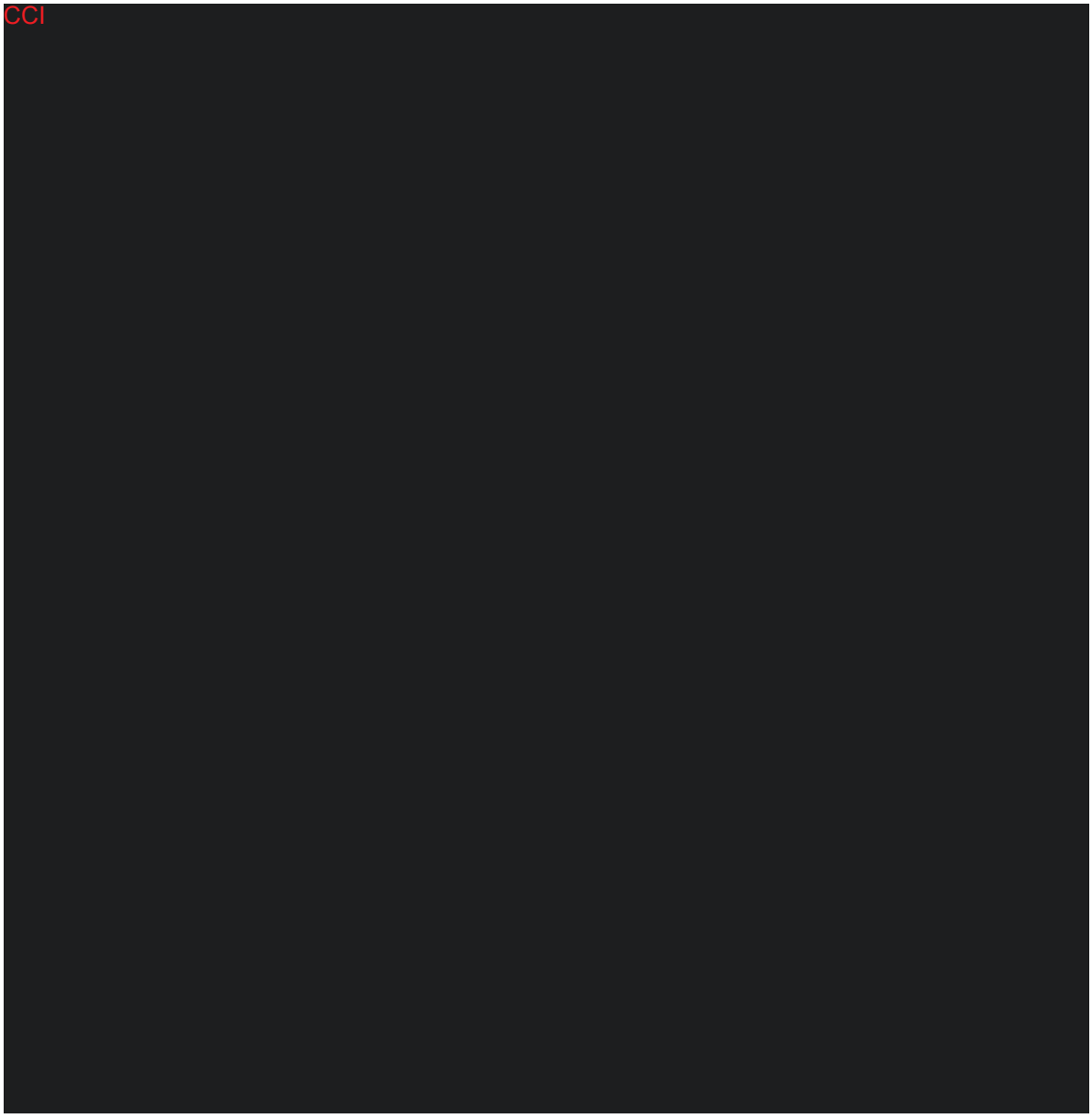
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