B1641001

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)

STATISTICAL ANALYSIS PLAN

Compounds:	PF-05082566
Compound Name:	Utomilumab
Version:	Amendment 2
Date:	2-Mar-2017

[redacted]

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B1641001 is based on the protocol amendment 9 dated 6 Jan 2016.

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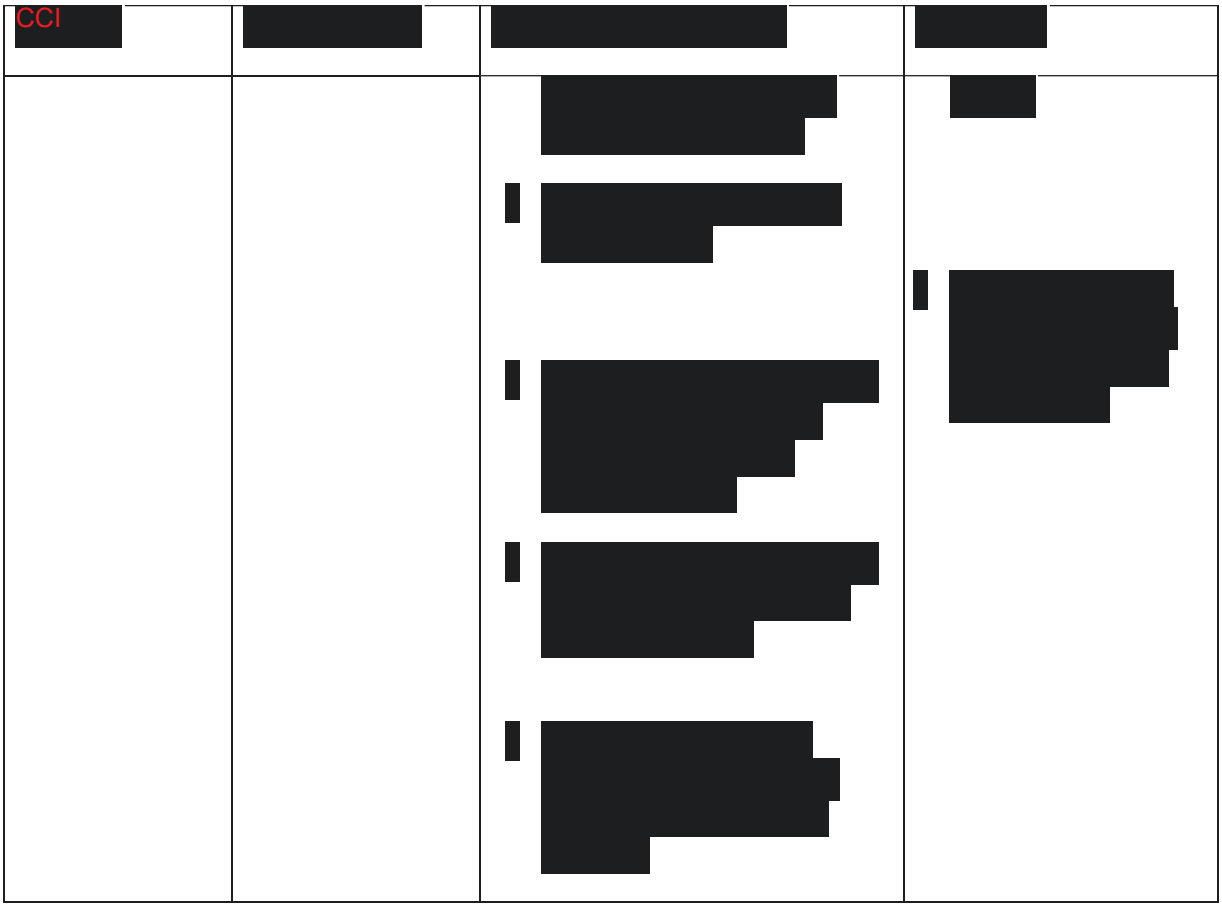

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B1641001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (ie, CCI data, PK data). The primary analysis will include all data up to a clinical cut-off date corresponding to 24 months (104 weeks) after the last patient is randomized (for randomized cohorts) or treated (for non-randomized cohorts). The final analysis of the data will be performed after last patient last visit (LPLV).

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

Throughout this document 'start date' refers to date of randomization for randomized cohorts and first dose of study treatment for non-randomized cohorts.

2.1. Study 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 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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2.2. 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.

There are 2 portions in this clinical study.

Portion A is designed to assess the safety and tolerability, PK and PD, 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 and PD, 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.

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 becomes a reason to permanently discontinue study treatment.

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).

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.

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.

Japan Cohort(s) in Portion A:

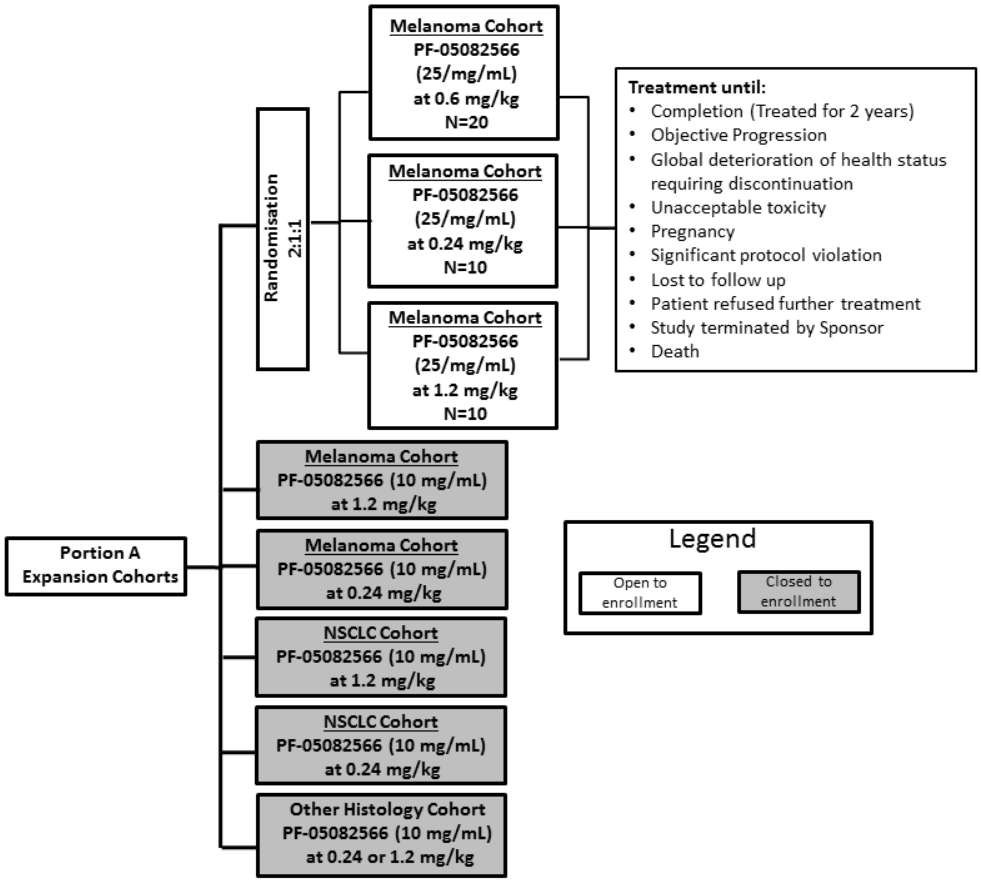
The Japan cohort(s) will be conducted at Japanese sites following completion of enrollment of the dose escalation cohorts in Portion A of this study. Patients enrolled into the Japan cohort(s) will receive PF-05082566 administered as a single agent once every four weeks as an IV infusion. Patients enrolled 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. 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.

Expansion Cohorts: Portion A

Figure 1. Study Design of the Expansion Cohort of 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 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.

Dose Escalation: Portion B

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

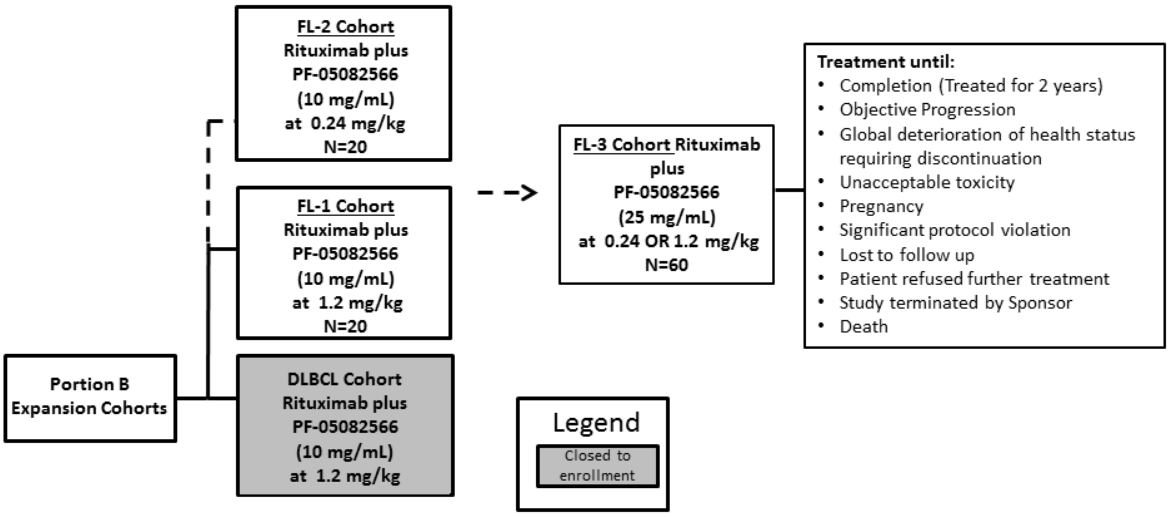
The initiation of Portion B may occur after all patients in the single-agent 0.06 mg/kg cohort have completed Cycle 1 and received their second dose. Enrollment will then begin with PF-05082566 at a dose of 0.03 mg/kg and escalating at the same dose intervals as listed for Portion A. PF-05082566 will be given to patients IV (every 4 weeks) in combination with rituximab (375 mg/m^2, every week x 4 weeks).

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). 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

Figure 2. Study Design of the Expansion Cohort of 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 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, PD 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, PD 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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint – Dose Escalation Cohorts

- First 2 cycles Dose-Limiting Toxicities (DLTs).

3.2. Secondary Endpoints – Dose Escalation Cohorts

3.2.1. Safety Endpoints

- Adverse events as characterized by type, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566 for Portion A and in combination with rituximab for Portion B;

- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing;

- Vital signs (blood pressure, and pulse rate);

- QTc interval.

3.2.2. Efficacy Endpoints

- Best Overall Response (BOR), Duration of Response (DR), Time to Tumor Response (TTR), Progression-free survival (PFS), per RECIST v1.1 for solid tumors and Cheson 2007 criteria for NHL based on Investigator assessment;

  BOR is defined as the best response recorded from 'start date' until documented disease progression. Only tumor assessments performed before the start of any further anti-cancer therapies will be considered in the assessment of BOR.

  DR is defined, for patients with an objective response (BOR of complete response [CR] or partial response [PR]), as the time from first documentation of objective response (CR or PR) to the date of first documentation of objective progression of disease (PD) or death due to any cause. For solid tumors, both CR and PR per RECIST v1.1 must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

  TTR is defined, for patients with an objective response, as the time from the 'start date' to the first documentation of objective response (CR or PR). For solid tumors, confirmation of response per RECIST v1.1 is required.

  PFS is defined as the time from 'start date' to the date of the first documentation of PD or death due to any cause, whichever occurs first.

- Overall Survival (OS);

  OS is defined as the time from 'start date' to the date of death due to any cause.

3.2.3. Pharmacokinetic Endpoints

- Pharmacokinetic parameters: 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}, C_{trough}).

Table 2. PK Parameters to be Determined for PF-05082566 and Rituximab

Parameter	Definition	Method of Determination
$AUC_{0\text{-last}}$	Area under the serum concentration-time curve from time zero to the time of the last measurable concentration (C_{last})	Log-Linear trapezoidal method
AUC_{tau}[a]	Area under the serum concentration-time curve over dosing interval τ	Log-Linear trapezoidal method
$AUC_{0\text{-}\infty}$[a]	Area under the serum concentration-time curve from time 0 to infinity	Log-Linear trapezoidal method
C_{max}	Maximum observed serum concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression during the terminal phase of the natural log-transformed concentration-time profile
C_{trough}	Predose concentration during multiple dosing	Observed directly from data
CL[a]	Clearance	Dose / $AUC_{0\text{-}\infty}$ after single dose Dose / AUC_{tau} after multiple doses
V_{ss}[a]	Steady state volume of distribution	CL•MRT_{iv}, where MRT_{iv} is mean residence time after intravenous administration
$AUC_{0\text{-last}}(dn)$	Dose normalized $AUC_{0\text{-last}}$	$AUC_{0\text{-last}}$ / Dose
$AUC_{0\text{-}\infty}(dn)$[a]	Dose normalized $AUC_{0\text{-}\infty}$	$AUC_{0\text{-}\infty}$ / Dose
$C_{max}(dn)$	Dose normalized C_{max}	C_{max} / Dose
Rac	Accumulation ratio	AUC_{tau} after multiple dosing/AUC_{tau} after single dose

[a] If data permit

3.2.4. Immunogenicity Endpoints

- Anti-drug Antibody (ADA)/neutralizing antibody (Nab) titers for PF-05082566 and rituximab.

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3.4. Primary Endpoint – Expansion Cohorts

- For Portion A: Objective response (confirmed CR or PR) as assessed by using the RECIST v1.1.

- For Portion B: Objective response (CR or PR) as assessed by using the Cheson 2007 criteria.

3.5. Secondary Endpoints – Expansion Cohorts

3.5.1. Safety Endpoints

- First 2 cycles of DLTs;

- Adverse events as characterized by type, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy PF-05082566 for Portion A and in combination with rituximab for Portion B;

- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing;

- Vital signs (blood pressure, and pulse rate);

- QTc interval.

3.5.2. Efficacy Endpoints

- DR, TTR, PFS, per RECIST v1.1 for solid tumors and Cheson 2007 criteria for NHL based on Investigator assessment;
- OS.

3.5.3. Pharmacokinetic Endpoints

- Pharmacokinetic parameters: 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}). Refer to Table 2 for definitions and methods of PK parameters.

3.5.4. Immunogenicity Endpoints

- Anti-Drug Antibody levels for PF-05082566 and rituximab.

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3.7. Baseline Variables

3.7.1. Study Drug, Study Treatment and Baseline Definitions

In this study, '**study drug**' refers to PF-05082566 or rituximab and '**study treatment**' (or '**treatment group**') refers to one of the following:

- PF-05082566 0.006 mg/kg q4wks;
- PF-05082566 0.03 mg/kg q4wks;
- PF-05082566 0.06 mg/kg q4wks;
- PF-05082566 0.12 mg/kg q4wks;
- PF-05082566 0.18 mg/kg q4wks;
- PF-05082566 0.24 mg/kg q4wks;
- PF-05082566 0.3 mg/kg q4wks;
- PF-05082566 0.6 mg/kg q4wks;
- PF-05082566 1.2 mg/kg q4wks;
- PF-05082566 2.4 mg/kg q4wks;
- PF-05082566 5 mg/kg q4wks;
- PF-05082566 10 mg/kg q4wks;
- PF-05082566 0.03 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.06 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.12 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.18 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.24 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.3 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.6 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 1.2 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;

- PF-05082566 2.4 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 5 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 10 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4.

Start and end dates of study treatment:

For single agent PF-05082566:

The date/time of first dose of study treatment is the earliest date/time of non-zero dosing of the study drug.

The date/time of last dose of study treatment is the latest date/time of non-zero dosing of the study drug.

For PF-05082566 + rituximab:

The date/time of first dose of study treatment in a combination arm is the earliest date/time of the first non-zero dose date/time for each of the study drugs.

The date/time of last dose of study treatment in a combination arm is the latest date/time of the last non-zero dose date/time for each of the study drugs.

Definition of baseline:

Definition of baseline for efficacy analyses in randomized cohorts

The last measurement prior to randomization will serve as the baseline measurement for efficacy analyses. If such a value is missing, the last measurement prior to the first dose of study treatment will be used as the baseline measurement except for analyses of tumor assessment data where the baseline assessment would be considered as missing.

Definition of baseline for efficacy CCI and for safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety, efficacy CCI If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Patients who start treatment and discontinue from the study treatment on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for heart rate and QT/QTc interval assessments will be derived from the visit where both heart rate and QT are not missing. Triplicate ECGs are collected in the study and the baseline for each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on heart rate and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

3.7.2. Baseline Characteristics

Baseline characteristics (including demographics, physical measurements, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.8. Safety Endpoints

3.8.1. Adverse Events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event is during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only patients who signed informed consent will be included in the analysis sets below.

4.1. 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 one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one treatment the patient will be classified according to the first treatment received.

4.2. Safety Analysis Set

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

4.3. Other Analysis Set

4.3.1. DLT-evaluable Set

The DLT-evaluable set is a subset of the safety analysis set, and it includes all patients who receive 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.

4.3.2. PK Analysis Set

The PK concentration population is defined as all treated patients (subset of the safety analysis set) who have at least 1 concentration.

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

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4.3.4. Immunogenicity Analysis Set

The immunogenicity analysis set is a subset of the safety analysis set and will include patients who have at least one ADA/Nab sample collected for either PF-05082566 or rituximab.

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5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size Determination

No formal statistical hypothesis testing is planned.

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 277 patients will need to be enrolled to achieve the objectives of the study.

Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the TITE-CRM approach cannot 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 (CI) of width <0.30. A sample size of 45 also enables detection of 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 will also be implemented if:

- Maximum sample size (N=45) is reached; or
- 9 DLT-evaluable patients have been treated at the estimated MTD; or
- all doses appear to be overly toxic and the MTD cannot be determined in the current trial.

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. With 20 patients with advanced melanoma, the maximum standard error of the ORR is 0.11.

Portion B expansion cohorts include approximately 80 patients with FL refractory to rituximab and to an alkylating agent at either 1.2 mg/kg or 0.24 mg/kg of PF-05082566. With 80 patients, the maximum standard error of the ORR is 0.06.

5.1.2. Decision Rules Using the TITE-CRM Method

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), and its variants.

Delayed-onset toxicities are a particular challenge for phase I trials of combination therapies (Muler et al., 2004). 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 Huang et al. (2014) 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:

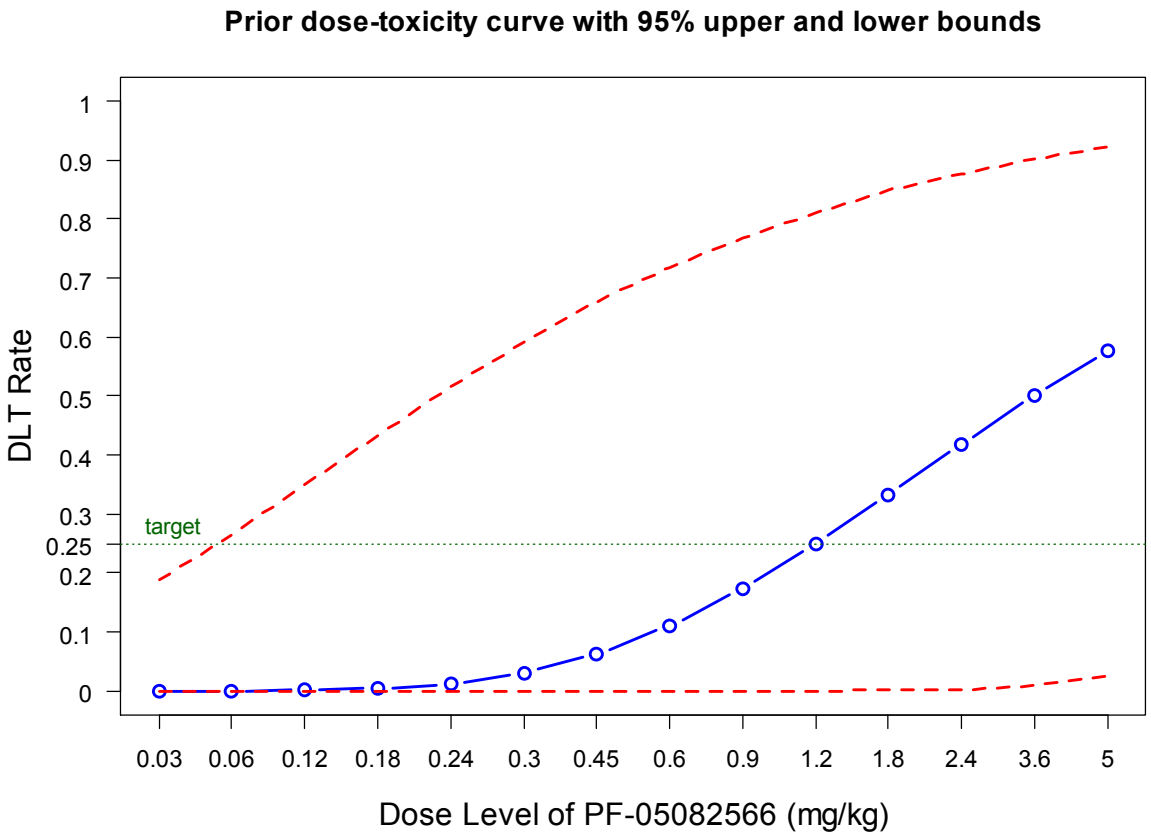
$$F_i(\beta) = p_i^{\exp(\beta)}$$

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 3 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 3. 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).

5.2. General Methods

As described in Section 3.7.1, in this study '**treatment group**' refers to one of the following:

- PF-05082566 0.006 mg/kg q4wks;
- PF-05082566 0.03 mg/kg q4wks;
- PF-05082566 0.06 mg/kg q4wks;
- PF-05082566 0.12 mg/kg q4wks;
- PF-05082566 0.18 mg/kg q4wks;
- PF-05082566 0.24 mg/kg q4wks;
- PF-05082566 0.3 mg/kg q4wks;
- PF-05082566 0.6 mg/kg q4wks;
- PF-05082566 1.2 mg/kg q4wks;
- PF-05082566 2.4 mg/kg q4wks;
- PF-05082566 5 mg/kg q4wks;
- PF-05082566 10 mg/kg q4wks;
- PF-05082566 0.03 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.06 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.12 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.18 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.24 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.3 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 0.6 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 1.2 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 2.4 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 5 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4;
- PF-05082566 10 mg/kg q4wks + rituximab 375 mg/m^2 q1wk x4.

Baseline characteristics, disposition and efficacy data will be summarized based on the FAS by treatment group.

DLTs will be summarized based on the DLT-evaluable set by treatment group.

Other safety data, exposure data, concomitant medications and non-drug treatments will be summarized based on the safety analysis set by treatment group.

CCI [redacted]

PK data will be summarized based on the PK analysis set by treatment group.

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

Immunogenicity data will be summarized based on the immunogenicity analysis set by treatment group.

5.2.1. Data Handling After the Cut-off Date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of Centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of patients randomized/treated at each center.

5.2.3. Presentation of Continuous and Qualitative Variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of Study Day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment +1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of Start of New Anti-cancer Drug Therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Follow-up Systemic Therapy' eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using only data from the 'Follow-up Systemic Therapy' eCRF pages.

5.2.6. Definition of Start of New Anti-cancer Therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 6.1.2 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the first dose of study treatment for non-randomized cohorts or after the date of randomization for randomized cohorts amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Follow-up Systemic Therapy' eCRF pages.
- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy' with 'Treatment Type' not equal to 'Palliative'.
- Surgery date recorded in 'Concomitant Surgery' when "Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Systemic Therapy', 'Concomitant Radiation Therapy' and 'Concomitant Surgery' eCRF pages.

5.2.7. Definition of On-treatment Period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard Derivations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth)
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

- BMI (kg/m^2) = weight (kg)/[height (m)]^2
- BSA (m^2) = ([height (cm) × weight (kg)] / 3600)$^{0.5}$

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. E.g., 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled Visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

5.2.10. Adequate Baseline Tumor Assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including ‘start date’.
- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions (for patients with solid tumor) or index lesions (for patients with NHL) and non-missing lesions status at baseline for non-target lesions (for patients with solid tumor) or non-index lesions (for patients with NHL)).

- Computerized tomography (CT) or magnetic resonance imaging (MRI) is required at baseline and may include chest, abdomen and pelvis. Brain scans 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 as appropriate to follow disease.

5.2.11. Adequate Post-baseline Tumor Assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined (see Section 6.1.2.1). Time points where the response is NE or no assessment was performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all patient data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg, when they cannot be calculated, should be presented as 'ND' or 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1.1. Pharmacokinetic Concentrations

Concentrations Below the Limit of Quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample);

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.1.2. Pharmacokinetic Parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses. If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (ie, not calculated). NC values will not be generated beyond the day that a patient discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Handling of Incomplete Dates

5.3.2.1. Disease History

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 1st day of the month.
- If both day and month are missing, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse Events

Incomplete AE-related dates will be imputed as follows:

- If only the day part of the AE onset date is missing, then the AE onset date will be replaced by 1st of the month. For example, if the AE onset date is --/JAN/2015, then the imputed AE onset date will be 01/JAN/2015.
- If both the day and month of the AE onset date are missing, then the onset date will be replaced by January 1st of the year. For example, if AE onset date is --/---/2014, then the imputed AE onset date will be 01/JAN/2014. In all other cases the missing onset day or missing onset month will be replaced by 1

- If after above imputation, the imputed onset date with same month and year of the start of study treatment but less than the start of study treatment, and stop date is not less than the start of study treatment, then the imputed AE onset date will be re-assigned as the start of study treatment.

    - If the AE onset date is missing completely, then the onset date will be imputed as following:If not missing the visit date and visit date is less than the start of study treatment and less than or equal to the stop date, then the visit date will be used to impute the onset date.

    - Else if previous visit date is greater than or equal to the start of study treatment and less than or equal to the stop date, then the previous visit date will be used to impute the onset date.

    - Else if previous visit date is less than the start of study treatment and the start of study treatment is less than or equal to stop date, then the start of study treatment will be used to impute the onset date.

    - Else Stop date will be used to impute the onset date.

- Incomplete stop date will be replaced by the last day of the month (if day is missing only).

- Incomplete stop date will be replaced by the last month of the year (if month is missing).

- If the AE stop date is missing completely and still present, then the stop date will be imputed as following:

    - If not missing death date, then death date will be used to impute the stop date.

    - Else if not missing withdraw date or Date Decision to Discontinue Treatment, the stop date will be imputed as the maximum of Withdrawal date, Date Decision to Discontinue Treatment, Onset date or AE visit date.

    - Else if missing withdraw date and Date Decision to Discontinue Treatment, the stop date will be imputed as the maximum of subject summary visit date, Onset date or AE visit date.

    - Else the stop date will be imputed as the maximum of onset date or last dosing date.

- If the AE stop date is missing completely and event resolved, then the stop date will be imputed as following:

    - If visit date is greater than onset date, then the visit date will be used to impute the stop date.

    - Else the onset date will be used to impute the stop date.

- If after above imputation, the imputed stop date is less than the start of study treatment, then the imputed AE stop date will be re-assigned as the start of study treatment.

- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and Concomitant Medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, no imputation will be performed.

- If the day of medication date is missing, then the medication date will be replaced by 1st of the month. For example, if the medication start date is --/JAN/2015, then the imputed medication start date will be 01/JAN/2015.

- If both the day and month of medication start date are missing, then the medication date will be replaced by January 1st of the year. For example, if the medication start date is --/---/2014, then the imputed medication start date will be 01/JAN/2014.

- In all other cases the missing medication day or missing medication month will be replaced by 1.

- Incomplete stop date will be replaced by the last day of the month (if day is missing).

- Incomplete stop date will be replaced by the last month of the year (if month is missing).

- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date or last dose date.

5.3.3. Imputation Rules for Date of Last Contact and Efficacy Assessments

5.3.3.1. Date of Last Contact

The date of last contact will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments).

- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.

- AE start and end dates.

- Last date of contact collected on the 'Survival Follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive').

- Study drug start and end dates.
- Randomization date for the randomized cohorts and enrollment date for the non-randomized cohorts.
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.3.2. Death Date

Partial death dates will be imputed based on the last contact date:

- If the day or both the day and the month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death.
  - Missing day and month: January 1st of the year of death.

5.3.3.3. Tumor Assessments

All investigation dates (eg, X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, ie, radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (eg, X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.3.4. Date of Start of New Anti-cancer Therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period.

- If the end date of new anti-cancer therapy is:
  - completely missing then it will be ignored in the imputations below.
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy.
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy.
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is:
  - completely missing then it will be ignored in the imputations below.
  - partially missing with only year (YYYY) available then the imputations below will consider 01JANYYYY as the start date of the new anti-cancer therapy.
  - partially missing with only month and year available then the imputations below will consider the first day of the month for MMMYYYY as the start date of the new anti-cancer therapy.

6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.2 for general methodology.

6.1. Primary Endpoints

6.1.1. DLT (Dose-escalation Cohorts)

6.1.1.1. Primary Analysis

The primary analyses will be based on the DLT-evaluable set. DLTs will be listed and summarized by treatment group.

6.1.2. Objective Response as Assessed by the Investigator (Expansion Cohorts)

6.1.2.1. Primary Analysis

Refer to Section 6.2.2.1.

6.2. Secondary Endpoint(s)

6.2.1. Safety Endpoints

Refer to Section 6.6.

6.2.2. Efficacy Endpoints

The following analyses will be based on the FAS by treatment group. Assessment of response will be made using RECIST v1.1 for solid tumors and Cheson 2007 criteria for NHL.

6.2.2.1. Objective Response as Assessed by the Investigator

BOR will be assessed based on reported overall lesion responses at different evaluation time points from the 'start date' until documented disease progression, according to the following rules. Only tumor assessments performed before the start of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.

BOR Based on Confirmed Responses for Solid Tumors

- CR = at least two determinations of CR at least 4 weeks apart and before progression.
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before progression (and not qualifying for a CR).
- SD (applicable only to patients with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after 'start date' and before progression (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after 'start date' and before progression (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after 'start date' (and not qualifying for CR, PR, SD or non-CR/non-PD).
- Not Evaluable (NE): all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Patients who do not have an on-treatment radiographic tumor assessment due to early progression, who receive anti-tumor therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set.

ORR by treatment group will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of patients with confirmed BOR of CR, PR, SD, PD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), and NE will be tabulated. Patients with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment.
- No post-baseline assessments due to death.
- No post-baseline assessments due to other reasons.
- All post-baseline assessments have overall response NE.
- New anti-cancer therapy started before first post-baseline assessment.
- SD or non-CR/non-PD of insufficient duration (<6 weeks after 'start date').
- PD too late (>12 weeks after 'start date').

Special and rare cases where BOR is NE due to both early SD or non-CR/non-PD and late PD will be classified as 'SD too early'.

BOR Based on Unconfirmed Responses for NHL:

- CR = one objective status of CR documented before progression.
- PR = one objective status of PR documented before progression (and not qualifying for CR).
- SD = at least one SD assessment (or better) ≥6 weeks after 'start date' and before progression (and not qualifying for CR or PR).
- PD = progression ≤12 weeks after 'start date' (and not qualifying for CR, PR, or SD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 50% from the nadir, but enough that a previously documented 50% decrease from baseline no longer holds (see Section 6.2.2.2 on details of tumor change).

OR is defined as BOR of CR or PR according to Cheson 2007 criteria.

Patients who do not have an on-treatment radiographic tumor assessment due to early progression, who receive anti-tumor therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set.

ORR by treatment group will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of patients with a BOR of CR, PR, SD, PD, and NE will be tabulated. Patients with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessments.
- No post-baseline assessments due to death.
- No post-baseline assessments due to other reasons.
- All post-baseline assessments have overall response NE.
- New anti-cancer therapy started before first post-baseline assessment.
- SD of insufficient duration (<6 weeks after 'start date').
- PD too late (>12 weeks after 'start date').

Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD too early'.

6.2.2.2. Tumor Shrinkage

Tumor Shrinkage for Solid Tumors:

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100.

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anticancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100.

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created. This plot will display the best percentage change from baseline in the sum of the diameter of all target lesions for each patient with measurable disease at baseline and at least one adequate post-baseline assessment.

Tumor Shrinkage for NHL:

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 and tumor shrinkage.

Tumor shrinkage will be summarized as the percent change from baseline in index lesions (SPD) per time point. It will be derived as:

- ((SPD at week XX – SPD at baseline)/SPD at baseline) × 100.

The maximum reduction in index lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anticancer therapy, as:

- Minimum of ((SPD at week XX – SPD at baseline)/SPD at baseline) × 100.

A waterfall plot of maximum percent reduction in the SPD from baseline will be created. This plot will display the best percentage change from baseline in the SPD for each patient with measurable disease at baseline and at least one adequate post-baseline assessment.

6.2.2.3. Duration of Response

Duration of Response (DR) is defined, for patients with OR, as the time from first documentation of objective response (CR or PR) to the date of first documentation of objective progression of disease (PD) or death due to any cause. If a patient has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are as described below for PFS in Table 3.

DR (months) = [date of event or censoring– first date of OR +1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rate at 3, 6 and 12 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DR will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

6.2.2.4. Time to Response

Time to response (TTR) is defined, for patients with OR, as the time from the 'start date' to the first documentation of objective response (CR or PR). For RECIST-defined response in solid tumors confirmation of response is required.

TTR (in months) = [first date of OR – 'start date' +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.5. Progression-free Survival

Progression-Free Survival (PFS) is defined as the time from 'start date' to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), or for patients with an event after 2 or more missing tumor assessments. For patients who start a new anti-cancer therapy prior to an event, PFS data will be censored on the date of the last adequate tumor assessment prior to starting the new anti-cancer therapy. Patients who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment will be censored on the 'start date' unless death occurred on or before the time of the second planned tumor assessment (ie, ≤16 weeks after 'start date') in which case the death will be considered an event (Table 3).

In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 8 weeks until disease progression regardless of initiation of subsequent anti-cancer therapy. After 10 months from 'start date', tumor assessments will be conducted less frequently, ie, at 16-week intervals.

The censoring and event date options to be considered for the PFS and DR analysis are presented in Table 3.

PFS (months) = [date of event or censoring– 'start date' +1]/30.4375

Table 3. Outcome and Event Dates for PFS and DR Analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	'Start date' [a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after 'start date'	Date of PD or death	Event
PD or death after 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the patient dies ≤16 weeks after 'start date' the death is an event with date on death date.

[b] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the 'start date'; if the criteria were met the censoring will be on the 'start date'

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rate at 3, 6, 9, 12 and 15 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 4 following the hierarchy shown.

Table 4. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/'start date'	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ 'start date' OR End of study (EOS) = Subject refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The PFS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for PFS

A plot will be generated to compare planned and actual relative day of tumor assessments by treatment group. A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the PFS censoring and event indicators.

6.2.2.6. Overall Survival

Overall survival (OS) is defined as the time from 'start date' to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– 'start date' +1]/30.4375.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rate at 3, 6, 9, 12, 15, and 18 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 5 following the hierarchy shown.

Table 5. OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [End of study (EOS) = Subject refused further follow-up]	Subject refused further follow-up
2	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 16 weeks]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the OS censoring and event indicators.

6.2.3. Pharmacokinetic Endpoints

6.2.3.1. Non-compartmental Analysis

Standard pharmacokinetic parameters (eg, C_{trough}, C_{max}, T_{max}, $t_{1/2}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, AUC_{tau}, CL, V_{ss} and Rac) will be estimated using non-compartmental methods. Pharmacokinetic parameters for PF-05082566 and rituximab will be evaluated.

Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean, its associated 95% CI and geometric %CV) of serum concentrations for PF-05082566 and rituximab will be presented in tabular form by study day, cycle, dose and nominal time. Concentrations with zero values will be excluded from the calculation of geometric means, its associated 95% CI and geometric %CV. Linear and semi-log plots of median serum concentrations vs nominal time will be prepared by study day, cycle and dose. Similar plots will be prepared for each individual patient's serum concentrations.

Pharmacokinetic parameters will be listed and summarized by cycle and dose using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, and geometric mean, its associated 95% CI and geometric %CV). Dose-normalized parameters (eg, C_{trough}, C_{max} and AUC) will also be listed and summarized. Pharmacokinetic parameters with zero values will be excluded from the calculation of geometric means, its associated 95% CI and geometric %CV.

$AUC_{0-\infty}$ (AUC_{tau} at steady state), AUC_{0-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.

6.2.3.2. Population Pharmacokinetic Analysis

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-05082566 and rituximab exposure and CCI or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

6.2.4. Endpoints for Immunogenicity Data of PF-05082566 and Rituximab

ADA/ Nab data will be listed and summarized for PF-05082566 and rituximab by dose and for the entire study population. The percentage of patients with positive ADA and Nab will be summarized by dose and overall study population (eg. at baseline, post-dose, treatment-induced, treatment-boosted or anytime of the study). For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The impact of ADA/Nab on PK, safety/efficacy will also be assessed, if data permit.

CCI

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[redacted]

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[redacted]

6.4. Subset Analyses

The number of patients expected in each treatment group is small and therefore no subset analyses are planned in this study.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

The following analyses will be based on the FAS overall and separately by treatment group.

6.5.1.1. Demographic Characteristics

Demographic characteristics and physical measurements will be summarized by treatment group using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics:
  - Gender: Male, Female.
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Unknown.
  - Ethnic origin: Hispanic/Latino (Yes/No).
  - Age (years): summary statistics.
  - Age categories:
    - < 65 years, ≥ 65 years.
    - < 65, 65-<75, 75-<85, ≥ 85 years.

- Pooled Geographical Region (as applicable):
  - North America.
  - Europe.
  - Asia.
  - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including >10% of the overall randomized population).
- Geographic Region (as applicable):
  - North America.
  - Latin America.
  - Western Europe.
  - Eastern Europe.
  - Middle East.
  - Australasia.
  - Asia.
  - Africa.
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4.

- Physical measurements:
  - Height (cm).
  - Weight (kg).
  - Body Mass Index (BMI) (kg/m^2).
  - Body Surface Area (BSA) (m^2).

Site codes will be used for the determination of the patient's geographic region.

The listing of demographics and baseline characteristics will include the following information: patient identifier, treatment group, age, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2), BSA (m^2) and ECOG performance status.

6.5.1.2. Medical History

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of patients by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each patient will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease Characteristics

Information on disease characteristics collected on 'Primary Diagnosis', RECIST, and IWGRC eCRF pages will be summarized overall and by treatment group. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Site of primary tumor;
- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page);
- Time since initial diagnosis to 'start date' (months), defined as ('start date' – date of initial diagnosis)/30.4375;
- For Portion A solid tumors: Time since diagnosis of local/regional recurrence of disease (months), defined as ('start date' – date of diagnosis of local/regional recurrence of disease)/30.4375.

From the RECIST tumor assessment eCRF page:

- Measurable disease (lesions) at baseline (Yes, No);
- Involved tumor sites at baseline.

From the IWGRC tumor assessment eCRF page:

- Involved tumor sites at baseline.

6.5.1.4. Prior Anti-cancer Therapies

The prior anti-cancer therapies are collected under the 'Previous Systemic Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated:

- Patients with at least one type of prior anti-cancer treatment;
- Patients with at least one prior anti-cancer drug therapy;
- Patients with at least one prior anti-cancer radiotherapy;
- Patients with at least one prior anti-cancer surgery;

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- At least one prior anti-cancer drug therapy;
- Number of prior anti-cancer drug therapy regimens: missing / 1 / 2 / 3 / ≥4;
- Type of prior anti-cancer therapy;
- For Portion A solid tumors: Prior anti-cancer immune therapy (including PD-1, PD-L1, anti-CTLA4, others);
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Unknown / Not applicable. Best response is derived from the last treatment regimen.
- For the expansion cohort patients:
    - Response to prior checkpoint inhibitor therapy (patients with melanoma in Portion A): Refractory / Relapsed, collected on the 'Subject Stratification' page.
    - Response to prior rituximab therapy (patients with FL in Portion B): Refractory / Relapsed, collected on the 'Subject Stratification' page.

The prior anti-cancer drugs will also be summarized based on the number and percentage of patients by the drug class and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer treatments and procedures will be included in the listings that follow with a flag to identify prior therapies. These will include the patient identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of prior anti-cancer drug therapies;

- Listing of prior anti-cancer radiotherapy;
- Listing of prior anti-cancer surgeries.

6.5.2. Study Conduct and Patient Disposition

The following analyses will be performed based on the FAS overall and separately by treatment group.

6.5.2.1. Patient Disposition

For randomized cohorts

The percentages below will be calculated based on the number of patients in the FAS.

- Total number of patients screened overall;
- Number of patients who discontinued from the study prior to randomization overall and by the main reason for discontinuation;
- Number and percentage of randomized patients in each of the analysis sets defined in Section 4;
- Number and percentage of randomized patients with study drug ongoing (separately for each study drug when administered in combination);
- Number and percentage of randomized patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug when administered in combination);
- Number and percentage of patients who entered follow-up;
- Number and percentage of patients who discontinued the study overall and by the main reason for discontinuation.

The results of the randomization algorithm (according to IRT) will be summarized as follows:

- Number and percentage of randomized patients overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region;
- Number and percentage of randomized patients by center;
- Cross tabulation: patients randomized (Arm A/Arm B/none) vs. patients treated (Arm A/Arm B/none).

For non-randomized cohorts

The percentages below will be calculated based on the number of patients in the FAS.

- Total number of patients screened overall.
- Number of patients who discontinued from the study prior to treatment with study drug overall and by the main reason for discontinuation.
- Number and percentage of treated patients in each of the analysis sets defined in Section 4.
- Number and percentage of patients with study drug ongoing (separately for each study drug when administered in combination).
- Number and percentage of patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug when administered in combination).
- Number and percentage of patients who entered follow-up.
- Number and percentage of patients who discontinued the study overall and by the main reason for discontinuation.

In addition the following will be summarized:

- Number and percentage of treated patients overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region.
- Number and percentage of treated patients by center.

6.5.2.2. Protocol Deviations

All protocol violations that impact the safety of the patients and/or the conduct of a study and/or its evaluation will be reported. These include:

- Patients who are dosed on the study despite not satisfying the inclusion criteria;
- Patients who develop withdrawal criteria whilst on the study but are not withdrawn;
- Patients who receive the wrong treatment or an incorrect dose;
- Patients who receive an excluded concomitant medication;
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

6.5.3. Study Treatment Compliance and Exposure

The following analyses will be based on the safety analysis set by treatment group.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. I.e., cycle is patient-dependent, rather than study-drug-dependent when study drugs are administered in combination.

For Cycle X, actual cycle start date for each patient is

- the earliest start date of dosing in the Cycle X day 1 visit CRF exposure page, if the patient received study treatment on that visit (ie, any study drug with dose>0 at that visit).

- the first day of assessments in the Cycle X day 1 visit, if the patient did not receive study treatment on that visit (ie, all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.

Actual cycle end date for each patient is,

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;

- for the last cycle, actual cycle end date = actual cycle start date + 28 days – 1 day.

Cycle duration (weeks) = (actual cycle end date – actual cycle start date + 1)/7.

When summarizing exposure for each study drug, only cycles from first dose of study treatment until the last cycle with non-zero dose of at least one of the study drugs should be included.

Exposure may be summarized (overall) as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The information that will be summarized depends on how the study drug is dosed (eg, infusion cyclical, oral daily, oral cyclical).

The formulae below should be applied to each study drug separately even when study drugs are administered in combination.

The derivations below are provided assuming 1 cycle = 4 weeks and for the following study drugs (administered alone or in combination):

- PF-05082566 administered as a 1-hour IV infusion (mg/kg) once every 4 weeks in 4-week cycles.

- Rituximab administered as a 1-hour IV infusion at a fixed dose of 375 mg/m^2 once every week (Day -7, Day 0, Day 7, Day 14) for the first cycle of treatment.

6.5.3.1. Exposure to PF-05082566

The dose level for PF-05082566 is calculated as actual dose administered/weight (mg/kg). The last available weight of the patient on or prior to the day of dosing will be used.

Intended duration of treatment with PF-05082566 (weeks) =

(end date–date of first dose of PF-05082566 +1)/7,

where end date = start date of last cycle with non-zero dose of PF-05082566 + 28 – 1.

Duration of exposure to PF-05082566 (weeks) =

(last dose date of PF-05082566 – first dose date of PF-05082566 + 28)/7.

Cumulative dose overall is the sum of the actual doses of PF-05082566 received overall.

Actual Dose Intensity (DI)

- Overall actual DI (mg/kg/4-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with PF-05082566 (weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg/kg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [d (mg/kg)] / [1 (4-week cycle)] = d (mg/kg/4-week cycle).

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [d (mg/kg/4-week cycle)].

where d ranges from 0.006 mg/kg to 10 mg/kg (see Section 3.7.1).

6.5.3.2. Exposure to Rituximab

The dose level for rituximab is calculated as actual dose administered/BSA (mg/m^2). The last available BSA of the patient on or prior to the day of dosing will be used.

Intended duration of treatment with rituximab (weeks) = 4 weeks

Duration of exposure to rituximab (weeks) =

(last dose date of rituximab – first dose date of rituximab + 7)/7.

Cumulative dose overall is the sum of the actual doses of rituximab received overall.

Actual Dose Intensity (DI)

- Overall actual DI (mg/m^2/4-week cycle) = [overall cumulative dose (mg/m^2)] / [intended duration of treatment with rituximab (weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg/m^2/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [375×4 (mg/m^2)] / [1 (4-week cycle)] = 375×4 (mg/m^2/4-week cycle).

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [375×4 (mg/m^2/4-week cycle)].

6.5.3.3. Dose Reductions

Applicable to PF-05082566 and rituximab.

Dose reduction is defined as actual non-zero dose < 90% of the planned dose.

The number and percentage of patients with at least one dose reduction as well as a breakdown of the number of dose reductions (1, 2, 3, ≥4) will be summarized.

6.5.3.4. Dose Delays

Applicable to PF-05082566 and rituximab.

Dose Delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

PF-05082566 in Portion A

Dose delay in Cycle x (days) = Date of first dose of PF-05082566 in Cycle x – Date of first dose of PF-05082566 in Cycle (x-1) – 28, where x >1.

PF-05082566 in Portion B

In Cycle 1,

Dose delay (days) = Study day of first dose of PF-05082566 – 9 [Note: Cycle 1 starts on Day -7 and the first dose of PF-05082566 is scheduled for Cycle 1 Day 1].

In Cycle x,

Dose delay in Cycle x (days) = Date of first dose of PF-05082566 in Cycle x – Date of first dose of PF-05082566 in Cycle (x-1) – 28, where x >1.

Rituximab

Dose delay for Dose x (days) = Date of Dose x – Date of Dose (x-1) – 7, where x >1.

Dose delays will be grouped into the following categories:

- No delay.
- 1-2 days delay.
- 3-6 days delay.
- 7 or more days delay.

For example, for PF-05082566, administered on a 4-week schedule, if one patient receives PF-05082566 on Day 1, then the next PF-05082566 administration date will be on Day 29; however, if the patient receives PF-05082566 at Day 30 or 31, this will be summarized in the 1-2 days delay category.

The number and percentage of patients with delayed study drug administration and maximum length of delay, ie, the worst case of delay if patients have multiple dose delays will be summarized.

6.5.3.5. Infusion Rate Reductions

Applicable to PF-05082566 and rituximab.

The number and percentage of patients with at least one infusion rate reduction of ≥50% compared to the first infusion rate reported in the CRF (first entry on the first dosing record page) as well as the frequency of patients with 1, 2, 3 or ≥4 infusion rate reductions of ≥50% will be summarized.

6.5.3.6. Infusion Interruptions

An infusion interruption is defined as an infusion that is stopped and re-started on the same day (ie, for a visit more than one infusion start time and infusion end time are recorded).

The number and percentage of patients with at least one infusion interruption as well as the frequency of patients with 1, 2, 3, or ≥4 infusion interruptions will be summarized.

6.5.4. Concomitant Medications and Non-drug Treatments

The following analyses will be based on the safety analysis set by treatment group.

Concomitant medications are medications, other than study medications, which started prior to first dose date of study treatment and continued on on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study medications and pre-medications for study drug, which are started before the first dose of study treatment.

Prior and concomitant medications will be summarized from the 'Prior and Concomitant Drug/Non-Drug Treatment' eCRF page.

Summary of prior and concomitant medications will include the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

A listing of concomitant medications will be created with the relevant information collected on the 'Prior and Concomitant Drug Treatment' eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the eCRF page 'Prior and Concomitant Non-Drug Treatment'.

A listing of concurrent procedures will be created with the relevant information collected on the 'Prior and Concomitant Non-Drug Treatment' eCRF page.

6.5.5. Subsequent Anti-cancer Therapies

The following analyses will be based on the FAS by treatment group.

Anti-cancer treatment will be provided in a data listing with data retrieved from 'Follow-up Systemic Therapy', 'Concomitant Radiation Therapy' and 'Concomitant Surgery' eCRF pages.

Number and percentage of patients with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up anti-cancer Therapy' eCRF page.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the safety analysis set by treatment group.

All summaries of related AEs (PF-05082566 plus rituximab) will further be presented as PF-05082566-related, rituximab -related, or related to both study treatments.

All summaries described below by SOC and PT will further be presented by PT in decreasing frequency based on the frequencies observed in all treatment groups combined.

6.6.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event occurs during the on-treatment period as defined in Section 3.8.1.

All analyses described will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (ie, no answer to the question 'Relationship with study treatment').

- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).

- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).

- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest as described above, by treatment group, primary SOC and PT in decreasing frequency observed in all treatment groups combined.

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All Adverse Events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per patient, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a patient has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of patients with each of the following by treatment group:

    - TEAEs.

  - TEAEs, Grade ≥3.
  - Related TEAEs.
  - Related TEAEs, Grade ≥3.
  - TEAEs leading to permanent treatment discontinuation.
  - Related TEAEs leading to permanent treatment discontinuation.
  - Serious TEAEs.
  - Related Serious TEAEs.
  - TEAEs leading to death.
  - Related TEAEs leading to death.
- TEAEs by SOC and PT and worst grade.
- Related TEAEs by SOC and PT and worst grade.
- TEAEs leading to death by SOC and PT.
- Related TEAEs leading to death by SOC and PT.
- TEAEs by SOC and PT: displaying in separate columns the All TEAEs / Related TEAEs / Grade ≥ 3 TEAEs / Related Grade ≥3 TEAEs.
- TEAEs Excluding SAEs, with frequency ≥5% in any treatment group by SOC and PT.

6.6.1.2. Adverse Events Leading to Treatment Discontinuation

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment group:

- TEAEs leading to discontinuation of PF-05082566 by SOC and PT;
- Related TEAEs leading to discontinuation of PF-05082566 by SOC and PT;
- TEAEs leading to discontinuation of rituximab by SOC and PT;
- Related TEAEs leading to discontinuation of rituximab by SOC and PT;
- TEAEs leading to permanent discontinuation of study treatment;
- Related TEAEs leading to permanent discontinuation of study treatment.

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

6.6.2. Deaths

The frequency (number and percentage) of patients in the safety analysis set who died and who died within 30 days and within 60 days after last dose of study treatment as well as the primary reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs, by treatment group.

- All deaths;
- Deaths within 30 days after last dose of study treatment;
- Deaths within 60 days after last dose of study treatment;
- Reason for Death:
  - Disease under study;
  - Study treatment toxicity;
  - Unknown;
  - Other.

In addition, date and cause of death will be provided in individual patient data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5);
- Flags for death ≤30 days and 31-60 days after last dose of study treatment.

6.6.3. Serious Adverse Events

The frequency (number and percentage) of patients with each of the following will be presented for treatment-emergent SAEs by treatment group:

- SAEs by SOC and PT;
- Related SAEs by SOC and PT.

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.6.4. Laboratory Data

6.6.4.1. Hematology and Chemistry Parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Quantitative data will be summarized using simple descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each nominal visit over time (unscheduled measurements would therefore not be included in these summaries as described in Section 5.2.7). End of Treatment visit laboratory results will be summarized separately. The changes computed will be the differences from baseline. Qualitative data based on reference ranges will be described according to the categories (ie, Low, Normal, High).

Abnormalities classified according to NCI-CTCAE toxicity grading version 4.03 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) * (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥800/mm3.
- Neutrophil count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and

- % value < % LLN value, and
- derived absolute count ≥1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows:

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥3×ULN, ALT ≥5xULN, ALT ≥10×ULN, ALT ≥20×ULN;
- AST ≥3×ULN, AST ≥5xULN, AST ≥10×ULN, AST ≥20×ULN;
- (ALT or AST) ≥3×ULN, (ALT or AST) ≥5×ULN, (ALT or AST) ≥10×ULN, (ALT or AST) ≥20×ULN;
- TBILI ≥2×ULN;
- Concurrent ALT ≥3×ULN and TBILI ≥2×ULN;
- Concurrent AST ≥3×ULN and TBILI ≥2×ULN;
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN;
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and ALP >2×ULN;
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and (ALP ≤2×ULN or missing).

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, by graphically displaying.

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.

- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI ≥2×ULN, ALT≥3×ULN or AST ≥3×ULN will be provided.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for CTCAE grading (ie, those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The summary of laboratory parameters by CTCAE grade table will include number and percentage of patients with Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4), laboratory abnormalities during the on-treatment period.

- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, ie:

- Hematology:

  Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased), Coagulation (activated partial thromboplastin time (aPTT) and prothrombin time (INR)).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia), Triglycerides (hypertriglyceridemia).

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of patients with:

- shifts from baseline normal to at least one result above normal during on-treatment period;
- shifts from baseline normal to at least one result below normal during on-treatment period.

In this study, these apply to the following parameters:

- Hematology: Absolute Monocytes, Absolute Eosinophils, Absolute Basophils;
- Serum Chemistry: Chloride, Total Urea, Uric Acid, Total Protein, C-Reactive Protein, Lactate Dehydrogenase (LDH).

6.6.4.2. Other Laboratory Parameters

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

- Urinalysis: all urinalysis parameters (except for Proteinuria, which will be summarized with CTCAE grades);
- Other parameters: hormone, and immunology parameters;
- Pregnancy test.

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each patient. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

In addition, listings of abnormal values will be provided for hematology, chemistry, urinalysis, coagulation parameters. If there is at least one abnormal assessment for any parameter, all the data for that laboratory parameter will be included into the listing.

For all tests not mentioned above but present in the clinical data, a listing of patients with at least one result for the relevant test will be provided.

6.6.5. Vital Signs

Weight for the purposes of dose calculation will be recorded at screening and within 7 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment. Height will be measured at screening only.

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each visit over time. End of Treatment visit will be summarized separately. The changes computed will be the differences from baseline.

6.6.6. Electrocardiogram

ECG summaries will include all ECG assessments from screening and the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing. QTcB and QTcF will be derived based on HR and QT (see below). The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as:

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Both formula produce similar results when the range of heart rates is not extreme. If QTcB and QTcF methods do not adequately correct QT for heart rate, an empirical correction specific to the study population can be derived.

These corrections were obtained by starting with the simple power model:

$$QT = a \times RR^b \qquad (1)$$

and then used the natural log transformation to derive the equation:

$$\ln(QT) = \ln(a) + b \ln(RR) \qquad (2)$$

The power model can be used to derive an empirical correction based on the reference group by fitting a linear mixed-effects regression model to the ln(QT) and ln(RR) data, estimating the slope b from Equation 2, and then applying that as a power in QTcP(msec) = $QT(msec)/RR(sec)^b$ to correct all the singlet data (on-drug as well as off-drug.)

Data will be summarized using QTcF and QTcB. However, if these are not appropriate correction method for the data set, the results will also be summarized using QTcP.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) by treatment group, during the on-treatment period. The denominator to calculate percentages for each category is the number of patients evaluable for the category.

- Pearson correlation between QT and RR, QTc (QTcB, QTcF and, if applicable, QTcP) and RR using individual (non-averaged) baseline assessments
- For each of the ECG parameters (HR, and QT, QTc, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of patients with notable ECG values according to the following categories:
    - QT/QTc increase from baseline >30 ms, >60 ms.
    - QT/QTc >450 ms, > 480 ms, >500 ms.
    - HR ≤50 bpm and decrease from baseline ≥20 bpm.
    - HR ≥120 bpm and increase from baseline ≥20 bpm.
    - PR ≥220 ms and increase from baseline ≥20 ms.
    - QRS ≥120 ms.

Patients with notable ECG interval values and qualitative ECG abnormalities will be listed for each patient and time point and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

6.6.7. Physical Examination

Number and percentage of patients with abnormal findings in physical examination will be summarized by body system.

6.6.8. ECOG Performance Status

The ECOG shift from baseline to highest score during the on-treatment period will be summarized by treatment group. ECOG performance status with shift from ECOG=0 or 1 to ECOG 2 or higher will also be presented in a data listing.

7. INTERIM ANALYSES

There is no formal interim analysis planned for this study. A Dose Escalation Steering Committee (DESC) was established to review safety data. Periodical DESC meetings will be scheduled to make decisions on escalation and de-escalation following the TITE-CRM design.

7.1. Introduction

Not Applicable.

7.2. Interim Analyses and Summaries

Not Applicable.

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