

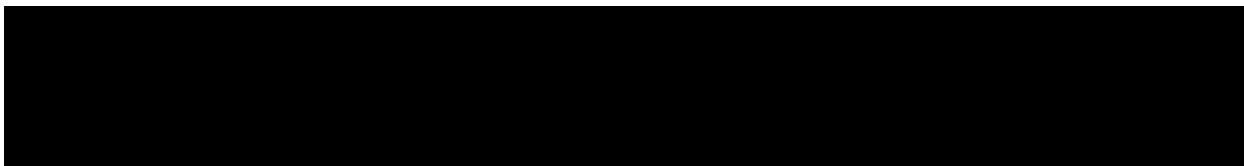


**B1641003**

**A PHASE 1 STUDY OF THE 4-1BB AGONIST PF-05082566 IN COMBINATION  
WITH THE PD-1 INHIBITOR MK-3475 IN PATIENTS WITH ADVANCED SOLID  
TUMORS**

**STATISTICAL ANALYSIS PLAN**

<b>Compounds:</b>	PF-05082566
<b>Compound Name:</b>	NA
<b>Version:</b>	Amendment 2
<b>Date:</b>	20-Mar-2017



## TABLE OF CONTENTS

LIST OF TABLES .....	5
LIST OF FIGURES .....	5
1. VERSION HISTORY .....	6
2. INTRODUCTION .....	8
2.1. Study Objectives .....	8
2.2. Study Design .....	9
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS .....	10
3.1. Primary Endpoints.....	10
3.2. Secondary Endpoints.....	11
3.2.1. Safety Endpoints.....	11
3.2.2. Efficacy Endpoints.....	11
3.2.3. Pharmacokinetic Endpoints .....	11
3.2.4. Immunogenicity Endpoints.....	12
3.2.5. Biomarker Endpoints .....	12
CCl	
3.4. Baseline Variables.....	13
3.4.1. Study Drug, Study Treatment and Baseline Definitions .....	13
3.4.2. Baseline Characteristics.....	14
3.5. Safety Endpoints .....	14
3.5.1. Adverse Events .....	14
4. ANALYSIS SETS .....	14
4.1. Full Analysis Set .....	15
4.2. Safety Analysis Set.....	15
4.3. Other Analysis Set.....	15
4.3.1. DLT-evaluable Set.....	15
4.3.2. PK Analysis Set .....	15
4.3.3. Biomarker Analysis Set .....	15
4.3.4. Immunogenicity Analysis Set.....	15
5. GENERAL METHODOLOGY AND CONVENTIONS.....	16
5.1. Hypotheses and Decision Rules .....	16
5.1.1. Hypotheses and Sample Size Determination .....	16

5.1.2. Decision Rules Using the TITE-CRM Method .....	16
5.2. General Methods .....	19
5.2.1. Data Handling After the Cut-off Date .....	20
5.2.2. Pooling of Centers .....	20
5.2.3. Presentation of Continuous and Qualitative Variables .....	20
5.2.4. Definition of Study Day.....	20
5.2.5. Definition of Start of New Anti-cancer Drug Therapy.....	20
5.2.6. Definition of Start of New Anti-cancer Therapy.....	21
5.2.7. Definition of On-treatment Period.....	21
5.2.8. Standard Derivations and Reporting Conventions .....	21
5.2.9. Unscheduled Visits .....	22
5.2.10. Adequate Baseline Tumor Assessment .....	22
5.2.11. Adequate Post-baseline Tumor Assessment.....	22
5.3. Methods to Manage Missing Data .....	22
5.3.1. Missing Data.....	22
5.3.1.1. Pharmacokinetic Concentrations.....	23
5.3.1.2. Pharmacokinetic Parameters .....	23
5.3.2. Handling of Incomplete Dates .....	24
5.3.2.1. Disease History .....	24
5.3.2.2. Adverse Events.....	24
5.3.2.3. Prior and Concomitant Medications.....	25
5.3.2.4. Exposure.....	26
5.3.3. Imputation Rules for Date of Last Contact and Efficacy Assessments .....	26
5.3.3.1. Date of Last Contact.....	26
5.3.3.2. Death Date.....	26
5.3.3.3. Tumor Assessments.....	27
5.3.3.4. Date of Start of New Anti-cancer Therapy .....	27
6. ANALYSES AND SUMMARIES .....	28
6.1. Primary Endpoints.....	28
6.1.1. DLT.....	28
6.1.1.1. Primary Analysis .....	28
6.2. Secondary Endpoint(s) .....	28
6.2.1. Safety Endpoints.....	28

6.2.2. Efficacy Endpoints.....	28
6.2.2.1. Objective Response as Assessed by the Investigator per RECIST v1.1 .....	28
6.2.2.2. Tumor Shrinkage.....	30
6.2.2.3. Duration of Response (Expansion Cohort Only) .....	30
6.2.2.4. Time to Response (Expansion Cohort Only) .....	31
6.2.2.5. Progression-Free Survival (Expansion Cohort Only) .....	31
6.2.3. Pharmacokinetic Endpoints .....	33
6.2.4. Population Pharmacokinetic Endpoints .....	34
6.2.5. Biomarker Endpoints .....	34
6.2.6. Endpoints for Immunogenicity Data of PF-05082566 and MK-3475 .....	34
6.3. Other Endpoints.....	35
6.4. Subset Analyses.....	35
6.5. Baseline and Other Summaries and Analyses .....	35
6.5.1. Baseline summaries .....	35
6.5.1.1. Demographic characteristics .....	35
6.5.1.2. Medical History.....	36
6.5.1.3. Disease Characteristics.....	36
6.5.1.4. Prior Anti-Cancer Therapies .....	36
6.5.2. Study Conduct and Patient Disposition .....	38
6.5.2.1. Patient Disposition .....	38
6.5.2.2. Protocol Deviations .....	38
6.5.3. Study Treatment Compliance and Exposure .....	39
6.5.3.1. Exposure to PF-05082566.....	40
6.5.3.2. Exposure to MK-3475 .....	41
6.5.3.3. Dose Reductions.....	42
6.5.3.4. Dose Delays.....	42
6.5.3.5. Infusion Rate Reductions .....	42
6.5.3.6. Infusion Interruptions .....	42
6.5.4. Concomitant Medications and Non-Drug Treatments.....	42
6.5.5. Subsequent Anti-cancer Therapies .....	43
6.6. Safety Summaries and Analyses .....	43
6.6.1. Adverse Events .....	44

6.6.1.1. All Adverse Events.....	44
6.6.1.2. Adverse Events Leading to Treatment Discontinuation.....	46
6.6.2. Deaths .....	46
6.6.3. Serious Adverse Events .....	47
6.6.4. Other Significant Adverse Events .....	47
6.6.5. Laboratory Data .....	48
6.6.5.1. Hematology and Chemistry Parameters .....	48
6.6.5.2. Other Laboratory Parameters .....	51
6.6.6. Vital Signs .....	52
6.6.7. Electrocardiogram.....	52
6.6.8. Physical Examination .....	54
6.6.9. ECOG Performance Status .....	54
7. INTERIM ANALYSES .....	54
7.1. Introduction .....	54
7.2. Interim Analyses and Summaries.....	54
8. REFERENCES .....	55

#### LIST OF TABLES

Table 1.	Summary of Major Changes in SAP Amendments .....	6
Table 2.	PK Parameters to be Determined for PF-05082566 and MK-3475.....	12
Table 3.	Outcome and Event Dates for PFS and DR Analyses .....	32
Table 4.	PFS Censoring Reasons and Hierarchy .....	33

#### LIST OF FIGURES

Figure 1.	Example Plot of Prior Dose Toxicity Curve.....	18
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## 1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B1641003 is based on the protocol amendment 2 dated 8JUL2014. The SAP amendment reflects updates to the imputation algorithms for missing data as applicable to the data collected in this study.

**Table 1. Summary of Major Changes in SAP Amendments**

Version	Version Date	Summary of Changes
1.0	16-Jun-2014	Not applicable (original SAP)
Amendment 1	09-Mar-2016	<ul style="list-style-type: none"><li>• Re-structured the content of the SAP for ease of review and to include additional details (new sections).</li><li>• Aligned content with revisions from protocol amendments 1 and 2.</li><li>• CCI [REDACTED]</li><li>• Removed the Response Evaluable set since efficacy analyses will be performed based on the Full Analysis Set.</li><li>• Added more details on the analyses of secondary endpoints including safety, efficacy.</li><li>• Added more details on the analyses of baseline and other summaries.</li><li>• Refinements made in endpoint definition and description of analysis methods.</li></ul>
Amendment 2	20-Mar-2017	<ul style="list-style-type: none"><li>• Section 3.5.1 and Section 6.6 referenced the pembrolizumab Even of Clinical Interest document to identify Adverse Events of Special Interest.</li><li>• Added Section 5.2.5 “Definition of start of new anti-cancer drug therapy” and Section 5.2.6 “Definition of start of new anti-cancer therapy” to provide specific details regarding these derivations.</li></ul>

Version	Version Date	Summary of Changes
		<ul style="list-style-type: none"> <li>Added Section 5.2.10 “Adequate baseline tumor assessment” and 5.2.11 “Adequate post-baseline tumor assessment” to provide derivation details.</li> <li>Section 5.3 “Methods to Manage Missing Data” and subsections - revised the imputation algorithms for missing data applicable to the data collected in the study.</li> <li>Section 6.2.2 “Efficacy endpoints” – added definitions for BOR for patients without measurable disease at baseline and separated reasons for BOR of ‘no post-baseline assessment’ between death and other reasons; provided more details regarding censoring reasons for PFS to take into account the change in schedule of tumor assessments and provided further details for the derivation of censoring reasons.</li> <li>Section 6.2.3 “Pharmacokinetic endpoints” – updated definitions and descriptions for consistency.</li> <li>Section 6.5.3 “Study treatment compliance and exposure” – added cycle definition and further details regarding derivations of DI and RDI; added derivations for infusion interruptions; changed the definition of infusion rate reductions to take into account the first infusion rate.</li> <li>Section 6.6.2 “Deaths” – aligned the primary reason for death with the wording in the associated eCRF.</li> <li>Section 6.6.5 “Laboratory data” and Section 6.6.7 “Electrocardiogram” provided further details regarding denominators used in the analyses.</li> <li>Section 6.6.7 “Electrocardiogram” – changed the study-specific correction from linear regression to log-linear regression.</li> <li>Deleted Appendix 1 since details are provided in Section 6.5.3.</li> </ul>

Version	Version Date	Summary of Changes
		<ul style="list-style-type: none"><li>Throughout all sections, corrected references to eCRF to use actual eCRF designation.</li></ul>

## 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B1641003. 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, biomarker 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 receive the first dose of the study drug. 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 first dose of study treatment.

### 2.1. Study Objectives

#### Primary Objectives

- To estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D) for the combination of PF-05082566 with MK-3475 in patients with advanced solid cancer.

#### Secondary Objectives

- To evaluate the overall safety profile;
- To characterize the single dose and multiple dose pharmacokinetics (PK) of PF-05082566 and MK-3475 given in combination following IV administration;
- To evaluate the immunogenicity of PF-05082566 and MK-3475 when given in combination;
- To assess the anti-tumor effect of PF-05082566 in combination with MK-3475 (by RECIST criteria);
- Expansion Cohorts Only:** To characterize the mechanism of sensitivity and/or resistance to PF-05082566 in combination with MK-3475 in tumor tissue.



CCI [REDACTED]

- CCI [REDACTED]
- CCI [REDACTED]

## 2.2. Study Design

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, pharmacokinetic CCI [REDACTED] study designed to estimate the MTD, and determine the RP2D of PF-05082566 in combination with MK-3475 in patients with advanced solid tumors.

PF-05082566 will be administered as a 1-hour intravenous infusion q3wks. On Day 1 of each dosing cycle, in which the drugs are co-administered, the MK-3475 infusion will start 30 minutes after completion of PF-05082566 infusion and after the post- PF-05082566 and pre-MK-3475 PK blood samples are drawn.

Treatment with study drugs will continue until completion of 32 cycles (approximately 24 months) of treatment, confirmed objective disease progression, patient refusal, patient lost to follow up, unacceptable toxicity occurs, or the study is terminated by the Sponsor, whichever occurs first.

Once the MTD of PF-05082566 administered in combination with MK-3475 has been estimated with confidence, one or more expansion cohorts of patients with selected advanced solid tumors will be enrolled to further study the safety, tolerability, PK CCI [REDACTED] and preliminary anti-tumor activity for PF-05082566 in combination with MK-3475 to support RP2D selection, as well as to study tumor-associated biomarkers. The tumor types for further study could include NSCLC and potentially other tumor types based on emerging data from the dose escalation phase of this study.

Antitumor activity will be assessed by radiological tumor assessments conducted at baseline, at 9 weeks after the first dose of study drug, and every 6 weeks thereafter, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 6 weeks), using RECIST v1.1. Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits. PK CCI [REDACTED] blood endpoints will also be monitored in all patients.

For all patients in dose-expansion cohorts, a de novo biopsy will be required at study entry followed by a second biopsy at the time of the week 9 scans (after 3 cycles of treatment). Optional de novo biopsies may be collected from patients in dose-escalation cohorts to support the assessment of disease progression. CCI [REDACTED]

### **3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS**

#### **3.1. Primary Endpoints**

- First 2 cycles Dose-Limiting Toxicity (DLT) of PF-05082566 in combination with MK-3475.

Severity of adverse events (AEs) will be graded according to CTCAE v 4.03. any of the following AEs occurring during the DLT observation period (first 2 Cycles, ie, 6 weeks) that are attributable to one or both study drugs will be classified as DLTs:

- Hematologic:
  - Grade 4 neutropenia;
  - Febrile neutropenia, defined as absolute neutrophil count (ANC)  $<1000/\text{mm}^3$  with a single temperature of  $>38.3$  degrees C (101 degrees F) or a sustained temperature of  $\geq 38$  degrees C (100.4 degrees F) for more than one hour;
  - Grade  $\geq 3$  neutropenic infection;
  - Grade  $\geq 3$  thrombocytopenia with bleeding;
  - Grade 4 thrombocytopenia.
- Non-hematologic:
  - Grade  $\geq 3$  toxicities (non-laboratory);
  - Grade  $\geq 3$  nausea, vomiting or diarrhea despite maximal medical therapy;
  - Grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
- Other (non AST/ALT) non-hematologic Grade  $\geq 3$  laboratory value if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization.
- Inability to complete two infusions of MK-3475 and PF-05082566 during the DLT observation period.

## 3.2. Secondary Endpoints

### 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 in combination with MK-3475;

AEs will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA)

- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03);
- Vital signs, weight, ECOG Performance Status.

### 3.2.2. Efficacy Endpoints

- Objective tumor response by RECIST v1.1;

OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from ‘start date’ until documented disease progression. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

- Time-to-response (TTR, expansion cohorts only);

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) which is subsequently confirmed.

- Duration of response (DR, expansion cohorts only);

DR is defined, for patients with an objective response, 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.

- Progression-free survival (PFS, expansion cohorts only);

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.

### 3.2.3. Pharmacokinetic Endpoints

- PK parameters of PF-05082566 and MK-3475, including but not limited to C<sub>max</sub>, C<sub>trough</sub>, T<sub>max</sub>, AUC<sub>0-last</sub>, CL and V<sub>d</sub> (as data permits);

**Table 2. PK Parameters to be Determined for PF-05082566 and MK-3475**

Parameter	Definition	Method of Determination
$AUC_{last}$	Area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration ( $C_{last}$ )	Linear/Log trapezoidal method
$AUC_{\tau}$	Area under the serum concentration-time over dosing interval $\tau$	Linear/Log trapezoidal method
$C_{max}$	Maximum observed serum concentration	Observed directly from data
$T_{max}$	Time for $C_{max}$	Observed directly from data as time of first occurrence
$t_{1/2}^a$	Terminal half-life	$\text{Log}_e(2)/k_{el}$ ,  where $k_{el}$ is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
$C_{trough}$	Predose concentration during multiple dosing	Observed directly from data
CL	Clearance	Dose / $AUC_{\tau}$ for steady state
$V_d^a$	volume of distribution	Dose / ( $AUC_{\tau} \cdot k_{el}$ ) for steady state
$AUC_{last}(dn)$	Dose normalized $AUC_{last}$	$AUC_{last} / \text{Dose}$
$AUC_{\tau}$	Dose normalized $AUC_{\tau}$	$AUC_{\tau} / \text{Dose}$
$C_{max}(dn)$	Dose normalized $C_{max}$	$C_{max} / \text{Dose}$

<sup>a</sup> If data permit

### 3.2.4. Immunogenicity Endpoints

- Anti-Drug Antibody (ADA)/Neutralizing antibodies (Nab) titers for PF-05082566 and MK-3475.

### 3.2.5. Biomarker Endpoints

- Expansion Cohorts Only: Paired de novo tumor biopsy collection at sequential time points for analysis of exploratory mechanistic biomarkers such as IHC assessment of tumor-infiltrating lymphocytes, quantitation of T cell receptor sequences, and gene expression.

CCI

- CCI

- CCI

### 3.4. Baseline Variables

#### 3.4.1. Study Drug, Study Treatment and Baseline Definitions

In this study, ‘**study drug**’ refers to PF-05082566 or MK-3475 and ‘**study treatment**’ (or ‘**treatment group**’) refers to one of the following:

- Cohort -1: PF-05082566 0.2 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 1: PF-05082566 0.45 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 2: PF-05082566 0.9 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 3: PF-05082566 1.8 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 4: PF-05082566 3.6 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 5: PF-05082566 5 mg/kg q3wks + MK-3475 2mg/kg q3wks.

**Start of study treatment** is the first dose of study drug administered.

#### Definition of baseline:

The last available assessment prior to the start of study treatment is defined as ‘baseline’ value or ‘baseline’ assessment for safety and efficacy analyses. 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 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 (HR) and QT/QTc interval assessments will be derived from the visit where both HR 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 HR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

### **3.4.2. 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](#).

## **3.5. Safety Endpoints**

### **3.5.1. 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](#).

#### **Adverse Events of Special Interest (AESIs)**

AESIs are immune-related adverse events (irAE) and infusion-related reactions (IRRs). The criteria for classification of an AE as an irAE or IRR are documented separately in the pembrolizumab Event of Clinical Interest (ECI) document.

## **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**

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**

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. In this non-randomized 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 will include all patients who are eligible, receive both study treatments and who either experience a DLT during the first 2 cycles of PF-05082566 or complete the two cycles' DLT observation period. 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 two cycles' DLT observation period.

##### **4.3.2. PK Analysis Set**

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for PF-05082566 or MK-3475.

The PK parameter analysis set is a subset of the safety analysis set and will include patients who have at least one of the PK parameters of interest for PF-05082566 or MK-3475.

##### **4.3.3. Biomarker Analysis Set**

The biomarker analysis set is a subset of the safety analysis set and will include all patients who receive at least one dose of study drug and have baseline and at least 1 on study biomarker assessment.

##### **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 MK-3475.

## **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.

Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the Time-to-Event Continual Reassessment Method (TITE-CRM) cannot be determined in advance. The maximum sample size is set as 45 for dose escalation cohorts in order to have a reliable and accurate estimate of the MTD based on simulation results. Based on probability theory, a sample size of 45 will ensure the estimates of any binary variable (eg, objective response rate) have a 95% confidence interval of width  $<0.30$ . A sample size of 45 also enables the 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 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.

Additional patients will be required for expansion cohorts. The total number of patients in expansion cohorts will be determined based on emerging data from this study, cancer indication, and the patient population of interest.

#### **5.1.2. Decision Rules Using the TITE-CRM Method**

The doses of PF-05082566 will be assigned to each enrolled patient using a TITE-CRM method with an adaptive cyclical weight function (Huang and Kuan, 2014), a modified version of the original method proposed by Cheung and Chappell (2000).

Delayed-onset toxicities are a particular challenge for phase I trials of combination therapies. 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 patient 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.

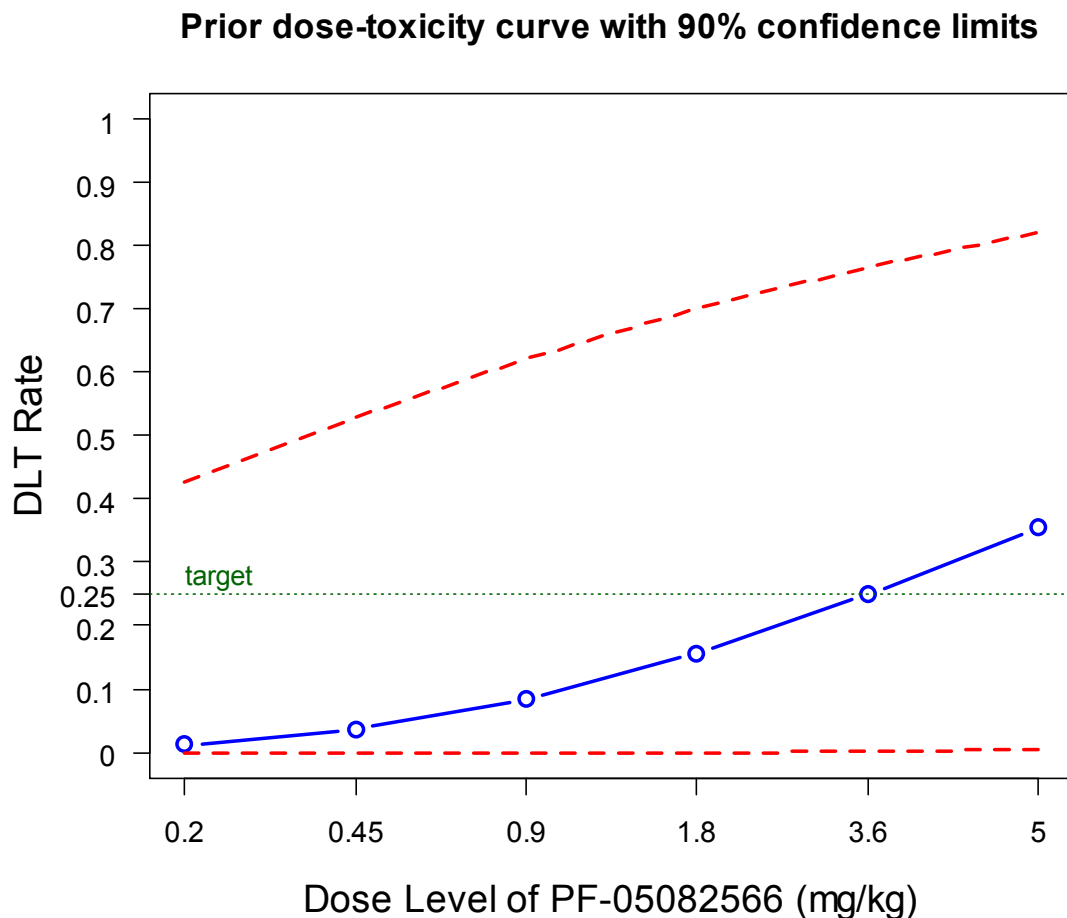
TITE-CRM is to be implemented as described by Cheung et al. and Normolle et al. for the dose-escalation of PF-05082566. PF-05082566 may be administered intravenously at the following available dose levels of 0.20, 0.45, 0.9, 1.8, 3.6, and 5 mg/kg on an every 3 week schedule (q3wk). PF-05082566 will be co-administered with MK-3475 on Day 1 of each treatment Cycle. MK-3475 will be administered at 2 mg/kg, MK-3475 will be administered q3wk. Higher dose levels may be available based on the emerging safety data from single agent PF-05082566 dosed at 5 mg/kg in the Phase 1 first-in-human study. The MTD is defined as highest dose that is associated with a DLT rate  $\leq 25\%$ . A power function modeling DLT rate at each dose  $d_i$  ( $i=1, \dots, 6$ ) expressed as  $\Pr(\text{DLT} \mid d_i) = F_i(\beta)$  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  $p_1 \leq p_2 \leq \dots \leq p_6$ . These estimates will be projected based model sensitivity to DLTs, together with single agent safety data for both study drugs.  $\beta$  is an unknown single parameter modeling the dose-toxicity relationship, with prior distribution  $N(0, \sigma_0^2)$ , where  $\sigma_0$  is the standard deviation of the normal prior distribution with mean=0. At the beginning of the trial, the initial prior value of  $\beta$  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  $\sigma_0$ , 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  $\beta$  (the posterior mean of  $\beta$  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  $\sigma_0$  upfront, the posterior toxicity probability estimates remain close to the prior estimates unless significantly discrepant data otherwise occur; with a large  $\sigma_0$ , the model will tend to be more immediately responsive to data. In this trial,  $\sigma_0=1$ , which provides a reasonably flat prior distribution of  $\beta$ , with 90% Bayesian credible interval of  $\exp(\beta) : [0.19, 5.21]$ , sufficiently wide to cover a wide spectrum of dose-toxicity scenarios. [Figure 1](#) illustrates the dose-toxicity curve (blue curve) with 90% upper and lower bounds (red curves) when the initial prior estimates  $p_i$  are (0.01, 0.04, 0.08, 0.16, 0.25, 0.35).

**Figure 1. Example Plot of Prior Dose Toxicity Curve**



In the TITE-CRM paradigm, patients who have enrolled in the trial but have not experienced a DLT will be included in the probability calculation with an initial weight equal to the proportion of the 6-week (2 cycles) DLT observation period the patients have completed. However the weight function will be modified if safety data suggest different weight (toxicity) patterns in Cycle 1 and Cycle 2 of PF-05082566. An adaptive cyclical weight function as proposed by Huang et al. (2014) will be implemented.

Patients who experience a DLT or complete the observation period without a DLT will be assigned full weight (=1).

Extensive simulation results comparing the TITE-CRM using the adaptive cyclical weight function with the 3+3 design and other weight functions can be found in Huang et al. (2014).

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

- Dose skipping in escalation to untested doses is not allowed ( $k \rightarrow k+1$ ). In particular, at least three patients should have been treated at dose level  $k$  before escalation to dose level  $k+1$ ;
- At least three patients should have been on treatment (for a minimum of 3 weeks or 1 cycle) and observed DLT rate  $<33\%$  at dose level  $k$  before a patient is assigned to dose level  $k+1$  (*Note that the waiting window depends on our knowledge in the time-to-event pattern of toxicity and accumulating safety data, and thereby the confidence in the associated weights. However, intentional delay in enrollment in the absence of DLT or serious AEs should be minimized and discouraged*);
- Dose escalation recommendation by the TITE-CRM algorithm may be overruled by the sponsor if the nature of the existing data causes safety concern.

## 5.2. General Methods

As described in [Section 3.4](#), in this study ‘**treatment group**’ refers to one of the following:

- Cohort -1: PF-05082566 0.2 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 1: PF-05082566 0.45 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 2: PF-05082566 0.9 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 3: PF-05082566 1.8 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 4: PF-05082566 3.6 mg/kg q3wks + MK-3475 2mg/kg q3wks;
- Cohort 5: PF-05082566 5 mg/kg q3wks + MK-3475 2mg/kg q3wks.

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.

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

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

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:

$$\text{Study day} = \text{Date of the assessment/event} - \text{start of study treatment} + 1.$$

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:

$$\text{Study day} = \text{Date of the assessment/event} - \text{start of study treatment}.$$

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 'Prior and Concomitant Drug Treatment' eCRF page that is after the first dose of study treatment. This date will be identified based on clinical review.

### 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 6.2.2](#)).

The start date of new anti-cancer therapy is the earliest date after the ‘start date’ amongst the following:

- Start date of anti-cancer drug therapy as identified in [Section 5.2.5](#).
- Start date of radiation therapy as identified by clinical review based on data recorded in the ‘Prior and Concomitant Non-drug Treatment’ eCRF page
- 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.

### 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]:
  - $(\text{date of given informed consent} - \text{date of birth} + 1) / 365.25$
  - In case of missing day, day only: Age [years]:  $(\text{year/month of given informed consent} - \text{year/month of birth})$
  - In case only year of birth is given: Age [years]:  $(\text{year of given informed consent} - \text{year of birth})$

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

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

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 and non-missing lesions status at baseline for non-target lesions).
- Computerized tomography (CT) or magnetic resonance imaging (MRI) is required at baseline and may include chest, abdomen and pelvis CT or MRI scans, brain CT or MRI scan, and bone scans. The CT scans should be performed with contrast agents unless contraindicated for medical reasons.

### **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 6.2.2.1](#)). 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 confidence intervals. 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 1<sup>st</sup> day of the month.
- If both day and month are missing, the month and day will be imputed as January 1<sup>st</sup>.
- 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 1<sup>st</sup> 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 1<sup>st</sup> 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 withdrawal 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 withdrawal 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 1<sup>st</sup> 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 1<sup>st</sup> 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.
- 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: 1<sup>st</sup> day of the month and year of death.
  - Missing day and month: January 1<sup>st</sup> 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 1<sup>st</sup> 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, surgery) 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

##### 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.

### 6.2. 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.

##### 6.2.2.1. Objective Response as Assessed by the Investigator per RECIST v1.1

The following analyses will be based on the FAS by treatment group. Assessment of response will be made using RECIST v1.1.

**Best Overall Response (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:

- CR = at least two determinations of CR at least 4 weeks apart and before progression.
- PR = at least two determinations of PR or better 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)  $\geq 6$  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)  $\geq 6$  weeks after ‘start date’ and before progression (and not qualifying for CR or PR).

- PD = progression  $\leq 12$  weeks after start date (and not qualifying for CR, PR SD, or non-CR/non-PD).
- Not Evaluable (NE): all other cases.

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.

**Objective Response (OR)** is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from start date until documented disease progression. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

Patients who do not have an on-treatment radiographic tumor assessment (including due to early clinical progression), who receive anti-tumor treatments 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 also be calculated along with the two-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 BOR of CR, PR, SD, PD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), and NE (not-evaluable) will be tabulated. Patients with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- Inadequate baseline assessment (includes missing assessment or non-measurable disease at baseline).
- No post-baseline assessment due to death.
- No post-baseline assessments due to other reasons.
- All post-baseline assessments have overall response NE.
- New anticancer 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 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:

- $((\text{Sum of target lesions at week XX} - \text{sum of target lesions at baseline}) / \text{sum of target lesions at baseline}) \times 100$ .

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  $((\text{sum of target lesions at week XX} - \text{sum of target lesions at baseline}) / \text{sum of target lesions at baseline}) \times 100$ .

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.

#### 6.2.2.3. Duration of Response (Expansion Cohort Only)

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](#).

$$\text{DR (months)} = [\text{date of event or censoring} - \text{first date of OR} + 1] / 30.4375$$

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 two-sided 95% CIs. In particular, the DR rate at 3, 6 and 12 months will be estimated with corresponding two-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 (Expansion Cohort Only)**

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) which is subsequently confirmed.

$$\text{TTR (in months)} = [\text{first date of OR} - \text{‘start date’} + 1] / 30.4375$$

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

#### **6.2.2.5. Progression-Free Survival (Expansion Cohort Only)**

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 two 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 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, at 9 weeks after the first dose of study drug, and every 6 weeks until disease progression, and at the time of End of Treatment/Withdrawal (if not done in the previous 6 weeks). The allowable time window for disease assessments is  $\pm 7$  days while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration).

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

$$\text{PFS (months)} = [\text{date of event or censoring} - \text{start date} + 1] / 30.4375$$

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

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	'Start date' <sup>a</sup>	Censored <sup>a</sup>
PD or death <ul style="list-style-type: none"> <li>- After at most one missing or inadequate post-baseline tumor assessment, OR</li> <li>- <math>\leq 15</math> weeks after 'start date'</li> </ul>	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 <sup>b</sup> 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 <sup>b</sup> 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 <sup>b</sup> documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

<sup>a</sup> However if the patient dies  $\leq 15$  weeks after 'start date' the death is an event with date on death date.

<sup>b</sup> 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 two-sided 95% CIs. In particular, the PFS rate at 3, 6, 9, 12 and 15 months will be estimated with corresponding two-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 <sup>a</sup>
4	No event and 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 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

<sup>a</sup> 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.

### 6.2.3. Pharmacokinetic Endpoints

The following pharmacokinetic analyses will be conducted by treatment group.

Standard parameters including, but not limited to  $C_{max}$ ,  $C_{trough}$ ,  $T_{max}$ ,  $AUC_{\tau}$ ,  $t_{1/2}$ , CL, and  $V_{ss}$ , as data permit will be estimated using non-compartmental analysis.

Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean, its associated 95% confidence interval and geometric %CV) of serum concentrations for PF-05082566 and MK-3475 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% confidence interval 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% confidence interval 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% confidence interval and geometric %CV.

$C_{max}$  and  $C_{trough}$  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.

#### 6.2.4. Population Pharmacokinetic Endpoints

Pharmacokinetic CCI 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 MK-3475 exposure and biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

#### 6.2.5. Biomarker Endpoints

For tumor biopsy samples, the mean and standard deviation, median, and minimum/maximum levels of biomarker measures, including but not limited to percentage of CD3-positive T cells, will be determined at baseline and post-treatment. For each pair of specimens, the percent change from baseline of these same parameters will also be calculated. The minimum percent change from baseline needed to declare proof of pharmacology will be based on assay precision and size of the expansion cohort.

CCI The statistical approach will examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

CCI

#### 6.2.6. Endpoints for Immunogenicity Data of PF-05082566 and MK-3475

ADA/ Nab data will be listed and summarized for PF-05082566 and MK-3475 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.

### 6.3. Other Endpoints

CCI

### 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,  $\geq$  65 years.
    - < 65, 65-<75, 75-<85,  $\geq$  85 years.
  - 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<sup>2</sup>).
  - Body Surface Area (BSA) (m<sup>2</sup>).

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<sup>2</sup>), BSA (m<sup>2</sup>) 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' and RECIST 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.
- 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 eCRF page:

- Measurable disease (lesions) at baseline (Yes, No).
- 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.
- Any prior anti-cancer therapy regimens: missing / 1 / 2 / 3 /  $\geq 4$ .
- Type of prior anti-cancer therapy.
- Prior anti-cancer immune therapy (including PD-1, PD-L1, anti-CTLA4, others).
- Intent of Therapy: Neo-Adjuvant / Adjuvant / Advanced – Metastatic.
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Unknown / Not applicable (Adjuvant only). Best response is derived from the last treatment regimen.

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.

The listings of prior anti-cancer treatments and procedures will also be provided as follows. 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**

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 safety follow-up.
- Number and percentage of patients who discontinued safety follow-up overall and by the main reason for discontinuation.

In addition the following will be summarized:

- 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.

All dosing calculations and summaries will be based on 'DOSE\_PF-05082566' and 'DOSE\_MK-3475' eCRFs pages. A listing of study drug administration will be created with the information collected on the 'DOSE\_PF-05082566' and 'DOSE\_MK-3475' eCRF pages.

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

The formulae below should be applied to each study drug separately.

The derivations below are provided for the following:

- PF-05082566 administered as a 1-hour IV infusion at a dose of 0.20 mg/kg, 0.45 mg/kg, 0.9 mg/kg, 1.8 mg/kg, 3.6 mg/kg or 5 mg/kg once every 3 weeks in 3-week cycles.
- MK-3475 will be administered as a 30-minute IV infusion at a dose of 2 mg/kg once every 3 weeks.

Analysis of exposure will be based on the calculated actual dose levels:

- PF-05082566 - total dose / weight.
- MK-3475 - total dose / weight.

#### 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) =**

$$(\text{end date} - \text{date of first dose of PF-05082566} + 1) / 7,$$

where end date = start date of last cycle with non-zero dose of PF-05082566 + 21 – 1

**Duration of exposure to PF-05082566 (weeks) =**

$$(\text{last dose date of PF-05082566} - \text{first dose date of PF-05082566} + 21) / 7$$

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

Each cycle for PF-05082566 is defined by a 3-week period. The dose intensity (DI) and the relative dose intensity (RDI) will be calculated for each patient across all cycles. **Actual Dose Intensity (DI)**

- Overall actual DI (mg/kg/3-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with PF-05082566 (weeks)/3].

**Relative Dose Intensity (RDI)**

- Intended DI (mg/kg/3-week cycle) = [intended cumulative dose per cycle] / [intended number of 3-weeks in a cycle] = [d (mg/kg)] / [1 (3-week cycle)] = d (mg/kg/3-week cycle).
- Overall RDI (%) =  $100 \times [\text{overall actual DI}] / [\text{intended DI}]$   
=  $100 \times [\text{overall actual DI}] / [d (\text{mg/kg/3-week cycle})]$ .

where d is 0.20 mg/kg, 0.45 mg/kg, 0.9 mg/kg, 1.8 mg/kg, 3.6 mg/kg or 5 mg/kg.

The summary of treatment exposure and compliance for PF-05082566 will include the following information:

- Treatment duration (weeks).
- Total number of infusions received.
- Cumulative dose (mg/kg).



- Dose intensity (mg/kg/cycle).
- Relative dose intensity (%).

### 6.5.3.2. Exposure to MK-3475

The dose level for MK-3475 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 MK-3475 (weeks) =**

$$(\text{end date} - \text{date of first dose of MK-3475} + 1) / 7,$$

where end date = start date of last cycle with non-zero dose of MK-3475 + 21 – 1

**Duration of exposure to MK-3475 (weeks) =**

$$(\text{last dose date of MK-3475} - \text{first dose date of MK-3475} + 21) / 7$$

**Cumulative dose** overall is the sum of the actual doses of MK-3475 received overall.

Each cycle for MK-3475 is defined by a 3-week period. The dose intensity (DI) and the relative dose intensity (RDI) will be calculated for each patient across all cycles.

#### **Actual Dose Intensity (DI)**

- Overall actual DI (mg/kg/3-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with MK-3475 (weeks)/3].

#### **Relative Dose Intensity (RDI)**

- Intended DI (mg/kg/3-week cycle) = [intended cumulative dose per cycle] / [intended number of 3-weeks in a cycle] = 2 (mg/kg/3-week cycle).
- Overall RDI (%) =  $100 \times [\text{overall actual DI}] / [\text{intended DI}]$   
=  $100 \times [\text{overall actual DI}] / [2 (\text{mg/kg/3-week cycle})]$ .

The summary of treatment exposure and compliance for MK-3475 will include the following information:

- Treatment duration (weeks).
- Total number of infusions received.
- Cumulative dose (mg/kg).
- Dose intensity (mg/kg/cycle).
- Relative dose intensity (%).

#### 6.5.3.3. Dose Reductions

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

Number and percentage of patients with at least one dose reduction as well as a breakdown of dose reductions (1 / 2 / 3 /  $\geq 4$ ) will be summarized.

#### 6.5.3.4. Dose Delays

Delays will be derived based on study drug administration date and will be grouped into the following categories based on the deviation of the actual to the planned treatment administration day (relative to the previous treatment administration date):

- No delay (including 1-2 days delays).
- 3-6 days delay.
- 7 or more days delay.

For example, for PF-05082566, administered on a 3-week schedule, if one patient receives PF-05082566 on Day 1, then the next PF-05082566 administration date will be on Day 22; however, if the patient receives PF-05082566 at Day 23 or 24, this is considered as 'no delay'.

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

The number and percentage of patients with at least one infusion rate reduction of  $\geq 50\%$  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  $\geq 4$  infusion rate reductions of  $\geq 50\%$  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  $\geq 4$  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 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 summarized according to the eCRF page 'Prior and Concomitant Non-drug Treatment'.

Number and percentage of patients with concurrent procedures will be tabulated overall and by reason for procedure as collected in 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**

Anti-cancer treatment will be provided in a data listing with data retrieved from 'Concomitant Drug Treatment', 'Prior and Concomitant Non-drug Treatment' and 'Concomitant Surgery' eCRF pages based on clinical review.

The earliest date of start of new anti-cancer drug therapy after 'start date' will be used for the definition of the on-treatment period and the earliest date of start of new anti-cancer therapy after 'start date' will be used for the censoring for efficacy analyses (see [Section 5.2.5](#) and [5.2.6](#)).

#### **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 MK-3475) will further be presented as PF-05082566-related, MK-3475 -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 is during the on-treatment period as defined in [Section 3.5.1](#).

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).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to a pre-specified search list of MedDRA PTs, documented in the Merck ECI document and finalized for analysis of the current studies data prior to DB lock).
- **Infusion-related Reactions (IRR):** IRRs (as identified according to a pre-specified search list of MedDRA PTs, documented in the Merck ECI document and finalized for analysis of the current studies data prior to DB lock) with onset on study drug dosing date (not prior to infusion of study drug) or the day following study drug infusion.

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  $\geq 3$ ;
  - Related TEAEs;
  - Related TEAEs, Grade  $\geq 3$ ;
  - 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 of irAEs;
  - Related TEAEs of irAEs;
  - Treatment-emergent IRRs;
  - Related treatment-emergent IRRs.
- 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  $\geq 3$  TEAEs / Related Grade  $\geq 3$  TEAEs.
- TEAEs Excluding SAEs, with frequency  $\geq 5\%$  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 MK-3475 by SOC and PT.
- Related TEAEs leading to discontinuation of MK-3475 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 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.
- Primary 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),

- Flag for death within 30 days of 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. Other Significant Adverse Events**

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

- irAEs leading to death, by SOC and PT;
- Related irAEs leading to death, by SOC and PT;
- irAEs, by SOC and PT;
- irAEs, Grade  $\geq 3$ , by SOC and PT;
- Related irAEs, by SOC and PT;
- Related irAEs, Grade  $\geq 3$ , by SOC and PT;
- irAEs leading to permanent treatment discontinuation, by SOC and PT;
- Related irAEs leading to permanent treatment discontinuation, by SOC and PT;
- Serious irAEs, by SOC and PT;
- Related serious irAEs, by SOC and PT.

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

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

- IRRs leading to death, by PT;
- Related IRRs leading to death, by PT;

- IRRs, by PT;
- IRRs, Grade  $\geq 3$ , by PT;
- Related IRRs, by PT;
- Related IRRs, Grade  $\geq 3$ , by PT;
- IRRs leading to permanent treatment discontinuation, by PT;
- Related IRRs leading to permanent treatment discontinuation, by PT;
- Serious IRRs, by PT;
- Related serious IRRs, by PT;
- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later).

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

### **6.6.5. Laboratory Data**

#### **6.6.5.1. 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 5.2.9](#)). 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:

$$\text{Derived differential absolute count} = (\text{WBC count}) * (\text{Differential \%value} / 100)$$

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  $\geq 800/\text{mm}^3$
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count  $\geq 1500/\text{mm}^3$

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

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

**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  $\geq 3 \times \text{ULN}$ , ALT  $\geq 5 \times \text{ULN}$ , ALT  $\geq 10 \times \text{ULN}$ , ALT  $\geq 20 \times \text{ULN}$ .
- AST  $\geq 3 \times \text{ULN}$ , AST  $\geq 5 \times \text{ULN}$ , AST  $\geq 10 \times \text{ULN}$ , AST  $\geq 20 \times \text{ULN}$ .
- (ALT or AST)  $\geq 3 \times \text{ULN}$ , (ALT or AST)  $\geq 5 \times \text{ULN}$ , (ALT or AST)  $\geq 10 \times \text{ULN}$ , (ALT or AST)  $\geq 20 \times \text{ULN}$ .

- $TBILI \geq 2 \times ULN$ .
- Concurrent  $ALT \geq 3 \times ULN$  and  $TBILI \geq 2 \times ULN$ .
- Concurrent  $AST \geq 3 \times ULN$  and  $TBILI \geq 2 \times ULN$ .
- Concurrent  $(ALT \text{ or } AST) \geq 3 \times ULN$  and  $TBILI \geq 2 \times ULN$ .
- Concurrent  $(ALT \text{ or } AST) \geq 3 \times ULN$  and  $TBILI \geq 2 \times ULN$  and  $ALP > 2 \times ULN$ .
- Concurrent  $(ALT \text{ or } AST) \geq 3 \times ULN$  and  $TBILI \geq 2 \times ULN$  and  $(ALP \leq 2 \times ULN \text{ or missing})$ .

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of  $AST \geq 10 \times ULN$  will also appear in the categories  $\geq 5 \times ULN$  and  $\geq 3 \times ULN$ . 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  $ALT=3 \times ULN$  and total bilirubin  $=2 \times ULN$ .
- peak serum  $AST(/ULN)$  vs peak total bilirubin ( $/ULN$ ) including reference lines at  $AST=3 \times ULN$  and total bilirubin  $=2 \times ULN$ .

In addition, a listing of all  $TBILI$ ,  $ALT$ ,  $AST$  and  $ALP$  values for patients with a post-baseline  $TBILI \geq 2 \times ULN$ ,  $ALT \geq 3 \times ULN$  or  $AST \geq 3 \times ULN$  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/hpermagnesemia), 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).

**6.6.5.2. 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.

#### **6.6.6. Vital Signs**

Weight for the purposes of dose calculation will be recorded at screening and within 3 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.

#### **6.6.7. 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:

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

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

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

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  $QTcP(\text{msec}) = QT(\text{msec})/RR(\text{sec})^b$  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 HR 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.

- $QT/QTc > 450 \text{ ms}, > 480 \text{ ms}, > 500 \text{ ms}.$
- $HR \leq 50 \text{ bpm}$  and decrease from baseline  $\geq 20 \text{ bpm}.$
- $HR \geq 120 \text{ bpm}$  and increase from baseline  $\geq 20 \text{ bpm}.$
- $PR \geq 220 \text{ ms}$  and increase from baseline  $\geq 20 \text{ ms}.$
- $QRS \geq 120 \text{ ms}.$

Frequency (number and percentage) of patients with post-baseline qualitative ECG abnormalities (morphology) will be summarized.

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.

#### **6.6.8. Physical Examination**

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

#### **6.6.9. 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.

## 8. REFERENCES

1. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 53: 457-81, 1958.
2. Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*; 26, 404-413.
3. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. *Biometrics.* 38: 29-41, 1982.
4. Collet D (1994). *Modelling survival data in medical research*. London, Chapman & Hall
5. Kalbfleisch JD, Prentice, RL. *Statistical Analysis of Failure Time Data*, 2<sup>nd</sup> Edition. Hoboken, Wiley Interscience
6. O'Quigley J, Pepe M, Fisher L (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. *Biometrics* 46: 33-48, 1990.
7. Cheung YK, Chappell R (2000). Sequential designs for phase 1 clinical trials with late-onset toxicities. *Biometrics* 56(4):1177-82.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* Jan;45(2):228-47.
9. Lee S, Cheung YK (2009). Model calibration in the continual reassessment method. *Clinical Trials.* 6: 227-238.
10. Huang B, Kuan P. (2014). Time-to-event continual reassessment method incorporating treatment cycle information with application to an oncology phase I trial. *Biometrical Journal.* 6: 933-946.
11. Nishino M, Gargano M, Suda M, Ramaiya NH, Hodi FS. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? *J Immunother Cancer* 2014;2:17.