

Protocol B7861002

**A PHASE 1 DOSE ESCALATION STUDY TO
EVALUATE THE SAFETY,
PHARMACOKINETICS AND
PHARMACODYNAMICS OF INTRAVENOUS
PF-06747143, ADMINISTERED AS SINGLE AGENT
OR IN COMBINATION WITH
STANDARD CHEMOTHERAPY IN ADULT PATIENTS
WITH ACUTE MYELOID
LEUKEMIA**

Statistical Analysis Plan - Revised (SAP)

Version: 2.0

Author: PPD (Statistics, PPD, USA)

Revised: April 26, 2017 – Incorporates changes proposed in Amendment 2, march 6, 2017

Revised: October 26, 2017 – Added Appendix 3 (Disease Assessment), made minor changes in response to issues raised

Date: 29-August-2016

Revised: May 1, 2017 – Incorporates changes/comments suggested by PPD [redacted] on the Apr 26 version.

090177e18fcea1f7\0.1\Draft\Versioned On:20-Nov-2018 19:30 (GMT)

TABLE OF CONTENTS

LIST OF TABLES5

LIST OF FIGURES5

1. AMENDMENTS FROM PREVIOUS VERSION(S)6

2. INTRODUCTION6

 2.1. Study Overview6

 2.1.1. Part 16

 2.1.1.1. Starting Dose7

 2.1.1.2. Criteria for Dose Escalation7

 2.2. Part 29

 2.2.1. Part 2 Combination Cohorts Starting Dose9

 2.2.2. Part 2/Cohort 1 and 29

 2.2.2.1. Part 2/Cohort 1 - PF-06747143 Combination in Fit Treatment Naïve AML Patients.....10

 2.2.2.2. Part 2/Cohort 2 – PF-06747143 Combination in Unfit Treatment Naïve AML Patients.....10

 2.2.2.3. MTD Definition.....10

 2.2.2.4. Part 2/Cohort 3 – PF-06747143 Single Agent Expansion.....10

 2.2.3. Summary.....10

 2.3. Study Objectives and Endpoints11

 2.3.1. Part 1 Study Objectives11

 2.3.2. Endpoints – Part 1.....12

 2.3.3. Objectives – Part 2.....12

 2.4. Endpoints – Part 213

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING.....15

4. HYPOTHESES AND DECISION RULES15

 4.1. Statistical Hypotheses15

 4.2. Statistical Decision Rules.....15

 4.2.1. Part 115

 4.2.2. Part 216

5. SAMPLE SIZE DETERMINATION16

6. ANALYSIS SETS16

090177e18fcea1f7\0.1\Draft\Versioned On:20-Nov-2018 19:30 (GMT)



6.1. Full Analysis Set	16
6.2. ‘PER PROTOCOL’ Analysis Set.....	16
6.3. Safety Analysis Set.....	17
6.4. Other Analysis Sets	17
6.4.1. Modified Intent-to-Treat Set.....	17
6.5. Treatment Misallocations.....	17
6.6. Protocol Deviations	17
7. ENDPOINTS AND COVARIATES	18
7.1. Efficacy Endpoint(s)	18
7.2. Safety Endpoints	19
7.2.1. DLT Definitions.....	19
7.2.2. MTD Definition	20
7.2.3. Maximum Permitted Dose Definition	20
7.2.4. Recommended Phase 2 Dose (RP2D) Definition.....	20
7.2.5. Vitals Signs.....	21
7.2.6. Laboratory Data.....	21
7.2.7. Adverse Events	21
7.2.8. ECG and QTc Interval.....	22
7.2.9. Immunogenicity.....	23
7.3. PK Endpoints.....	23
7.4. PD Endpoints.....	24
7.5. Covariates.....	24
8. HANDLING OF MISSING VALUES	24
8.1. Missing Dates.....	24
8.2. Efficacy Analysis	24
8.3. Pharmacokinetics	24
9. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES	25
9.1. Statistical Methods	25
9.2. Statistical Analyses	26
9.2.1. Primary Analysis	26
9.2.2. Secondary Analyses.....	26

090177e18fcea1f7\0.1\Draft\Versioned On:20-Nov-2018 19:30 (GMT)



9.2.2.1. Efficacy Analysis26

9.2.2.2. Pharmacokinetics Analyses27

CCI

9.2.3. Safety Analyses29

9.2.4. Standard Analyses30

10. REFERENCES32

11. APPENDICES33

11.1. APPENDIX 1: CATEGORICAL CLASSES FOR ECG AND VITAL SIGNS33

11.2. APPENDIX 2: CENSORING DETAILS34

11.3. Appendix 3. Detailed Dose Escalation/De-Escalation Scheme for mTPI Design35

11.4. Disease Assessment37

LIST OF TABLES

Table 1. Possible Dose Levels8

Table 2. Overview of Efficacy Analysis27

Table 3. PK Parameter Summaries27

Table 4. Progression Free Survival and Duration of Response34

Table 5. Time to Progression34

LIST OF FIGURES

Figure 1. Part I schema7

090177e18fcea1f7\0.1\Draft\Versioned On:20-Nov-2018 19:30 (GMT)



1. AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable.

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol B7861002. This analysis plan is meant to supplement the study protocol. In this document, any text taken directly from the protocol is italicized. Any deviations from this analysis plan will be described in the Clinical Study Report (CSR).

2.1. Study Overview

PF-06747143 will initially be developed in patients with acute myeloid leukemia (AML). The diagnosis of AML will be according to the World Health Organization (WHO) classification (Ref (8)). The study will be conducted in two parts, Part 1 single agent dose escalation and Part 2 PF-06747143 in combination with standard chemotherapy with an option for single agent cohort expansion at the RP2D.

Assessment of anti-leukemia activity of PF-06747143 will be based on Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. (Ref (2)).

2.1.1. Part 1

Part 1, dose escalation, is an open-label, multi-center, single arm, non randomized, multiple dose, safety, pharmacokinetic and pharmacodynamic study of single-agent PF-06747143 in sequential dose levels of adult patients with refractory and/or relapsed AML in order to establish MTD/ RP2D or maximally permitted dose (MPD).

Patients will receive PF-06747143 as a weekly infusion (QW) in 28 day cycles at escalating doses. The proposed dosing scheme includes 0.3, 1.0, 3.0, 10, 15, and 20 mg/kg. Patients enrolled in the first two dose levels (0.3 mg/kg and 1.0 mg/kg) will be required to stay in the clinic/hospital overnight (minimum of 24 hours) after receiving the first dose of PF-06747143 to monitor for the potential risk of hyperleukocytosis that might be caused by the inhibition of **CCl** by PF-06747143. On an individual basis, patients may be monitored overnight for the additional doses in Cycle 1 at the treating physician's discretion.

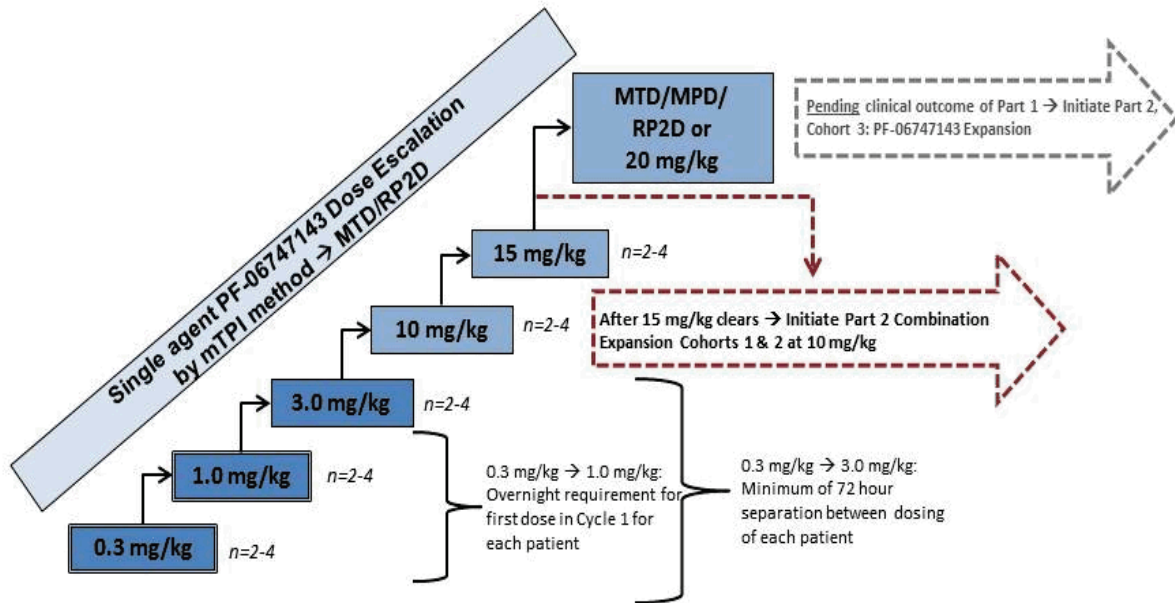
In the first three dose levels (ie, starting dose 0.3 mg/kg through 3.0 mg/kg), initiation of the first dose of PF-06747143 for each patient in the dose level must be at least 72 hours after the first dose of the previous patient. Patients enrolled in subsequent dose levels will be treated on an outpatient basis with no staggering of patients unless there are safety concerns based on findings at the lower doses.

Once MTD or MPD is identified, additional patients may be enrolled at that dose level (to a minimum of 9) to further investigate the anti-leukemia activity, safety, and PK profile of PF-06747143 prior to an expansion cohort with single agent PF-06747143 at the MTD/MPD/RP2D.

The total estimated number of patients to be enrolled for the Part 1 dose escalation study will be approximately 30-50 patients but it is pertinent to recognize that the exact sample size of the mTPI design in Part 1 cannot be pre specified in advance because it is a dynamic feature of the design.

Once the dose of 15 mg/kg in Part 1 is found safe and tolerable, the Part 2 combination cohorts will be initiated at 10 mg/kg while the Part 1 single agent dose escalation continues to 20 mg/kg for MPD or MTD assessment.

Figure 1. Part I schema



2.1.1.1. Starting Dose

The starting dose will be 0.3 mg/kg, administered QW in 28 day cycles.

2.1.1.2. Criteria for Dose Escalation

A modified toxicity probability interval method (mTPI) (Ref (7)) targeting a DLT rate of 25% with an equivalence interval (20%-30%) will be utilized in order to estimate MTD in dose escalation. For all dose levels, patients may be enrolled in cohorts of 2-4 (the target size of each cohort will be 3 patients). Intermediate dose levels to further evaluate the safety and/or PK may be evaluated following discussion between sponsor and Investigator.

The dose levels planned for Part 1 of the study are shown in Table 1 Additional dose levels may be explored, if appropriate based on emerging safety, PK or PD data. Intra-patient dose escalation of PF-06747143 or the backbone chemotherapy (in Part 2 combination cohorts) will not be permitted.

090177e18fcea1f710.1\Draft\Versioned On:20-Nov-2018 19:30 (GMT)



Table 1. Possible Dose Levels

Dose Level	PF-06747143 Dose (mg/kg) (QW)
1	0.3
2	1.0
3	3.0
4	10
5	15
6	20

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level to determine where future cohorts should be on dose escalation, no change in dose, or dose de escalation. The algorithm will stop if any of the following criteria is met:

- the maximum sample size has been achieved (approximately 50 patients total);
- at least 9 patients have been accumulated on a dose that is predicted to be the MTD;
- or
- all doses explored appear to be overly toxic and the MTD cannot be determined.

Although dose levels are capped at 20 mg/kg, this mTPI will continue to operate subject to the constraints detailed above while allowing for doses higher than specified. All clinically relevant adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the Sponsor and Investigators after each dose level is complete to determine if the dose allocation schedule requires modification.

The modified toxicity probability interval (mTPI) design uses a Bayesian statistics framework and a beta/binomial hierarchical model to tailor dose-escalation and de-escalation decisions.(Ref 7) These rules are conceptually similar to those used by the 3+3 design and all the dose-escalation decisions for a given trial and can be pre-calculated under the mTPI design and presented in a two-way table (Appendix 4).

Patients will continue with study treatment until disease progression, patient refusal or unacceptable toxicity occurs. Patients experiencing a DLT may be managed with dose modification (after dose interruption) or discontinuation. Subsequent dose levels may not be opened until all patients entered at the current dose level have been treated and observed for at least one complete cycle and the number of DLTs among those patients in their first cycle has been determined. Intra-patient dose escalation will not be permitted in this study.

2.2. Part 2

Part 2 dose expansion, is an open-label, multi-center, non randomized study to assess the safety and tolerability and preliminary anti-leukemia activity of PF-06747143 in three cohorts (two combination cohorts and one potential cohort of single agent PF-06747143).

Figure 2.

Part 2 will assess the safety and tolerability and preliminary anti-leukemia activity of PF-06747143. In Part 2, PF-06747143 will be administered at 10 mg/kg QW (Section 3.1.2.1) on 28 day cycles in combination with chemotherapy in two separate cohorts each containing up to 30 patients with newly diagnosed AML, including Cohort 1 in fit treatment naïve AML patients, in which PF-06747143 will be combined with standard intensive 7+3 chemotherapy with cytarabine (100-200 mg/m² continuous infusion for 7 days) and daunorubicin (60-90 mg/m² daily for 3 days), and Cohort 2 in unfit treatment naïve AML patients who are considered to not tolerate or decline to receive standard intensive 7+3 treatment, in which case PF-06747143 will be combined with standard dose of azacitidine (75 mg/m² administered subcutaneously or intravenously daily for 7 days) or decitabine (20 mg/m² by continuous intravenous infusion over 1 hour daily for 5 days in a 4-week schedule) based on drug availability and institutional guidance.

Attributions to fit or unfit in Part 2 will be based on “Consensus-based definition of unfit to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of Italian SIE, SIES and GITMO group on a new tool for therapy decision making”²⁵ per Investigator judgement.

An additional single agent PF-06747143 expansion cohort, Cohort 3, at the MTD/RP2D may be initiated in Part 2 in 15-30 refractory and/or relapsed AML patients based on single agent PF-06747143 clinical benefit in Part 1.

2.2.1. Part 2 Combination Cohorts Starting Dose

After the DLT observation period in the first cycle of 15 mg/kg cohort is cleared, the dose of 10 mg/kg of PF-06747143 will be used to initiate the Part 2 combination studies, which may be escalated or de-escalated, depending on emerging data. Additionally, if an MTD in Part 1 is determined at or below the dose of 15 mg/kg, a lower dose than 10 mg/kg may be considered to move into Part 2 dose expansion combination studies.

2.2.2. Part 2/Cohort 1 and 2

In Part 2, Cohort 1 and 2 expansion cohorts (E) will start with a safety lead-in (S) in approximately 3-6 patients to assure the combination treatment regimen is safe and tolerable in each patient population (ie, fit and unfit AML). The safety lead-in will use the standard 3+3 dose escalation method to evaluate safety profile (using the DLT criteria described in Section 3.1.1.3) for a duration of up to 2 cycles.

2.2.2.1. Part 2/Cohort 1 - PF-06747143 Combination in Fit Treatment Naïve AML Patients

Cohort 1 safety lead-in group (S1) will start with 10 mg/kg dose of PF-06747143 and may be escalated to up to 20 mg/kg (the MPD) or de-escalated to below 10 mg/kg based on the predefined DLT criteria (see Section 3.1.1.3) and emerging data. After completion of the S1 cohort, PF-06747143 will be administered in combination with intensive therapy (ie, 7+3 daunorubicin and cytarabine) as induction and continue during consolidation and in maintenance for up to a maximum of 6 months (6 cycles) starting from the completion of consolidation, until disease progression or relapse, patient refusal or unacceptable toxicity occurs (whichever comes first) in newly diagnosed treatment naïve fit AML patients. The expansion cohort (E1) will enroll up to 30 patients.

2.2.2.2. Part 2/Cohort 2 – PF-06747143 Combination in Unfit Treatment Naïve AML Patients

Cohort 2 safety lead-in group (S2) will start with 10 mg/kg dose of PF-06747143 and may be escalated to up to 20 mg/kg (the MPD) or de-escalated to below 10 mg/kg based on the predefined DLT criteria (see Section 3.1.1.3) and emerging data. After completion of the S2 cohort, PF-06747143 will be administered in combination with a hypomethylating drug (ie, either azacitidine or decitabine, based on institutional guidelines) and may continue for up to 1 year (~12 cycles) from start of therapy or until disease progression or relapse, patient refusal or unacceptable toxicity occurs (whichever comes first) in newly diagnosed treatment naïve unfit AML patients). The expansion cohort (E2) will enroll up to 30 patients.

2.2.2.3. MTD Definition

In Part 2, the MTD of the combinations of PF-06747143 and intensive daunorubicin/cytarabine or PF-06747143 and decitabine/azacitidine will be determined separately within each cohort.

2.2.2.4. Part 2/Cohort 3 – PF-06747143 Single Agent Expansion

An additional single agent PF-06747143 expansion cohort, Cohort 3 (E3), at the MTD/RP2D may be initiated in Part 2 in 15-30 refractory and/or relapsed AML patients. The initiation of this cohort will require that single agent PF-06747143 demonstrates encouraging clinical benefit (eg, significantly improved CR and response duration compared to historical data) in the dose escalation Part 1. Patients in this cohort will be treated until disease progression or relapse, patient refusal or unacceptable toxicity occurs (whichever comes first).

2.2.3. Summary

Approximately 125-140 patients are expected to be enrolled in this study (approximately 30-50 patients in Part 1 (actual number of patients enrolled for Part 1 will depend upon tolerability of PF-06747143 and the number of dose levels required to identify the MTD) and approximately 87-102 patients in Part 2). The study will be conducted in approximately 4 sites for Part 1 and approximately 12-15 sites for Part 2.

Patients who complete the maximum number of cycles/months on study treatment (Section 3.1.2.2.1 and Section 3.1.2.2.2), demonstrate clinical benefit with manageable safety profile and are willing to continue receiving the assigned treatment may be given the opportunity to do so upon agreement between Investigator and sponsor and pending investigational product availability.

All patients who completed treatment will have a 60-day post dose follow-up period.

2.3. Study Objectives and Endpoints

2.3.1. Part 1 Study Objectives

Primary Objective

- To assess safety and tolerability at increasing dose levels of PF-06747143 in patients with refractory and/or relapsed AML for which no standard therapy is available in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile;
- To characterize the single-dose and multiple-dose pharmacokinetics (PK) of PF-06747143 following IV administration;
- To evaluate the immunogenicity of PF-06747143 following repeated administration;
- To document any anti-leukemia activity based on . Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet (Ref 2)

CCI



2.3.2. Endpoints – Part 1

Primary Endpoint

- Dose Limiting Toxicities (DLTs).

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03), timing, seriousness, and relationship to study therapy;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;
- PK parameters of PF-06747143: Single Dose (SD) - C_{max} , AUC_{last} , and if data permit, AUC_{inf} , V_d , CL , and $t_{1/2}$. Multiple Dose (MD) (assuming steady state is achieved) - $C_{max, ss}$, $C_{min, ss}$, $AUC_{\tau, ss}$, R_{ac} ($AUC_{\tau, ss} / AUC_{\tau}$, and if data permit, CL , V_{ss} , and $t_{1/2}$);
- Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against PF-06747143;
- Preliminary evidence of anti-leukemia activity including objective disease response; as assessed using the standardized response criteria including objective response rate (ORR), duration of ORR, and relapse free survival (RFS).(Ref 2)

CCI



2.3.3. Objectives – Part 2

Primary Objective

- To evaluate safety and tolerability and preliminary anti-leukemia activity (Dohner, et. al 2010)²² of PF-06747143 in combination with standard intensive chemotherapy (ie,

cytarabine and daunorubicin; D/C 7+3) in patients with newly diagnosed fit treatment naïve AML patients (Cohort 1) or with standard dose of decitabine or azacitidine in newly diagnosed unfit treatment naïve AML patients (Cohort 2) or PF-06747143 as a single agent ((Cohort 3) if data warrants).

Secondary Objectives

- To characterize the single and multiple dose PK of PF-06747143 in combination with standard intensive cytarabine and daunorubicin 7+3 therapy in newly diagnosed fit treatment naïve AML patients or with standard dose of decitabine or azacitidine in newly diagnosed unfit treatment naïve AML patients;
- To collect PF-06747143 drug concentration data in patients from the dose expansion cohorts for evaluation of population PK;
- To evaluate the immunogenicity of PF-06747143 following repeated administration.



2.4. Endpoints – Part 2

Primary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.03), timing, seriousness, and relationship to study therapy;



- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;
- Preliminary evidence of anti-leukemia activity including objective disease response; as assessed using the standardized response criteria including objective response rate (ORR), duration of ORR, and relapse free survival (RFS).(Ref 2)

Secondary Endpoints

- PK parameters of PF-06747143: Single Dose (SD) - C_{max} , T_{max} , AUC_{last} , and if data permit, AUC_{inf} , V_d , CL , and $t_{1/2}$. Multiple Dose (MD) (assuming steady state is achieved) - $C_{max, ss}$, $C_{min, ss}$, $AUC_{\tau, ss}$, R_{ac} ($AUC_{\tau, ss}/AUC_{\tau}$), and if data permit, CL , V_{ss} , and $t_{1/2}$;
- Peak and trough PF-06747143 concentrations for selected doses;
- Incidence of ADA and Nab against PF-06747143.

CCI



CCI

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis or blinding is planned for this study. The final analysis will be conducted after the last subject last visit (LSLV).

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There are no statistical hypotheses. The emphasis of the final analyses will be on estimation of key summary statistics.

4.2. Statistical Decision Rules

4.2.1. Part 1

Decision rules are based on calculating unit probability mass (UPM) of three dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as $(0; p_T - e_1)$, the over-dosing interval $(p_T + e_2)$, and the proper-dosing interval $(p_T - e_1, p_T + e_2)$, where e_1 and e_2 are small fractions. For a target DLT rate of 0.25, the target equivalence interval is $(0.20, 0.30)$. The three dosing intervals are associated with three different dose-escalation decisions (Table 1). The under-dosing interval corresponds to a dose escalation (E), over-dosing corresponds to a dose de-escalation (D), and proper-dosing corresponds to remaining at the current dose (S). Given a dosing interval and a probability distribution, the unit probability mass (UPM) is defined as the ratio of the probability of the interval to the length of the interval. Once the safety assessment is complete for Cycle 1, the focus will be on allocation of new subjects to the dose most likely to be an MTD.

The study continues accruing until one of the three stopping conditions below is triggered. The algorithm will stop if any of the following criteria is met:

1. The maximum sample size has been achieved.
2. MTD has been identified with sufficient accuracy: at least 9 patients have been accumulated on a dose that is currently estimated to be the MTD, or
3. All doses explored appear to be overly toxic and the MTD cannot be determined.

Specifically the mTPI approach formalizes stopping rules as follow:

Rule 1 (early termination): if the first dose is too toxic $\rightarrow \Pr(p_1 > p_T / data) > \xi$; $\xi = 0.975$

Rule 2 (dose exclusion), if dose= i is too toxic $\rightarrow \Pr(p_i > p_T / data) > \xi$; $\xi = 0.975$
then exclude doses $\geq i$

4.2.2. Part 2

Part 2 of this study is intended to confirm the safety and tolerability of the dose selected in Part 1 while assessing the anti-leukemia activity of PF-06747143 in combination with standard dose of intensive chemotherapy. The DLT rate and its 95% confidence interval at the selected dose may be estimated. Part 2 data will also be used to determine the safety of combining PF-06747143 with standard chemotherapy in addition to justifying the efficacy of PF-06747143 monotherapy.

5. SAMPLE SIZE DETERMINATION

Approximately 125-140 patients are expected to be enrolled in this study (approximately 30-50 patients in Part 1 and 87-102 patients in Part 2).

The exact sample size of the mTPI design in Part 1 cannot be pre specified in advance because it is a dynamic feature of the design. The maximum sample size after which the Part 1 will be stopped and MTD declared is 30-50 patients. Also, a minimum of 9 patients is required to establish the MTD. The actual sample size of Part 1 will depend on the underlying dose toxicity profile and variability in actual data realization.

As for the number of patients treated at each dose, it is expected that the typical number will be 2 to 4 patients for the doses actually studied. For the dose declared as the MTD from Part 1, a minimum of 9 patients will be observed at this dose to further investigate the anti-leukemic activity, safety, and PK profile of PF-06747143. However, since not every dose listed will be studied and variable cohort size is allowed, the actual number of patients treated at each dose will vary.

6. ANALYSIS SETS

Several analysis sets are defined and will be considered for this study.

6.1. Full Analysis Set

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

6.2. 'PER PROTOCOL' Analysis Set

The per protocol analysis set includes all enrolled patients who receive at least one dose of study treatment at the dose level of MTD and who do not have major treatment deviations during first cycle. Patients with major treatment deviations in Cycle 1 are not evaluable for the MTD assessment and may be replaced. Major deviations include failure to satisfy major entry criteria (eg, confirmation of the target disease population; signed informed consent), administration of less than 3 out of the 4 doses in Cycle 1 or 80% of the planned Cycle 1 dose (provided that the reduction is not due to toxicity attributable to PF-06747143) or use of

other anti-cancer/anti-leukemia treatments during the active treatment and disease follow up phases other than as defined/allowed in this protocol.

PK analysis sets

The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest. The PK concentration population is defined as all patients who receive PF-06747143, have no major deviations affecting the PK assessment, and have at least one post-dose concentration measurement.

CCI



6.3. Safety Analysis Set

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

6.4. Other Analysis Sets

6.4.1. Modified Intent-to-Treat Set

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

6.5. Treatment Misallocations

Subjects who receive the wrong initial dose for whatever reason will be analyzed according to the initial dose actually received. Subjects who receive the wrong dose after the initial dose will be analyzed according to the initial dose received.

6.6. Protocol Deviations

All deviations will be listed in the CSR. Major treatment deviations include, but are not limited to, less than 80% of the planned Cycle 1 PF-06747143 dose provided the reduction/omission is not due to treatment-related toxicity. Subjects with major Cycle 1 treatment deviations are not evaluable for MTD.

7. ENDPOINTS AND COVARIATES

7.1. Efficacy Endpoint(s)

Preliminary evidence of anti tumor activity including objective disease response; as assessed using the standardized response criteria for the hematologic disease under study including objective response rate (ORR), duration of ORR, time to progression (TTP) and progression free survival (PFS).

The above efficacy endpoints are derived based on the disease response per investigator evaluation on the CRF pages, which is the primary method of documentation of disease: Overall Response (OR) – Preliminary evidence of anti-leukemia activity including objective disease response will be assessed using the standardized response criteria, as recommended by an international expert panel, on behalf of the European LeukemiaNet (Dohner, et. al 2010), including objective response rate (ORR), duration of ORR, and relapse free survival (RFS) (section 7.6) All measurable disease must be documented at screening and re assesses at each subsequent tumor evaluation. Overall response is the best response recorded from first dose until disease progression/recurrence and it must include confirmation. To be assigned a status of PR or CR, changes in leukemia measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Progression Free Survival (PFS) - is defined as the time from Cycle 1 Day 1 (C1D1) to first documentation of disease progression or to death due to any cause, whichever occurs first. Subjects last known to be 1) alive 2) on treatment or within the post-treatment follow-up period and 3) progression-free, are censored at the date of the last disease assessment that verified lack of disease progression. Subjects who start new anti-cancer treatment prior to the end of post-treatment follow-up period and have adequate baseline and on-treatment objective disease assessments without evidence of progressive disease are censored at the date of the last objective disease assessment. Subjects with inadequate baseline or no on-study disease assessments are censored at C1D1 unless death occurred prior to the first planned assessment (in which case the death is an event). Subjects with at least one on-study disease assessment who discontinue treatment without disease progression and without death within 28 days of discontinuation are censored at the date of the last objective disease assessment that verified lack of disease progression (if progression or death is within 28 days of discontinuation the progression or death is an event). Subjects with documentation of progression or death after an unacceptably long interval (>16 weeks) since the previous disease assessment will be censored at the time of the previous assessment.

$PFS \text{ (days)} = [\text{progression/death date} - C1D1 + 1]$.

- **Overall survival (OS)** is defined as the time from initial dose until death from any cause, and is measured in the intent-to-treat population.

More details of censoring are provided in [Appendix 2](#).

7.2. Safety Endpoints

7.2.1. DLT Definitions

A DLT will be classified according to NCI CTCAE version 4.03 and is defined as any of the following adverse events unless the event can clearly be determined to be unrelated to drug occurring in the first cycle of treatment (within 28 days of first dose or until patient receives a second cycle if there are treatment delays). Data from all cycles of treatment will be analyzed for safety, delayed toxicity, and cumulative toxicity.

DLT is defined as:

- Hematologic:
 - Failure to achieve an ANC greater than 1,000/ul and/or a platelet count greater than 25,000/ul independent of platelet transfusion by day ≥ 42 after the start of therapy, with a hypocellular bone marrow (<10% marrow cellularity) and absence of persistent leukemia (ie, <5% marrow blasts) measured at the completion of Cycle 1 (approximately day 28-32);
 - If a subject with persisting cytopenias does not exhibit marrow hypoplasia on biopsy (or bone marrow aspirate) or demonstrates persisting leukemia, such subject will not be considered to have demonstrated a hematological toxicity and may continue to receive PF-06747143 at the scheduled time point for
 - Hyperleukocytosis (WBC $\geq 100,000$ /ul) not managed by hydroxyurea or leukapheresis and/or resulting in an adverse event.
 - Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding.
- Non-hematologic:
 - Grade 3 toxicities, except for:
 - Grade ≥ 3 nausea or vomiting that resolves to Grade ≤ 1 within 72 hours with appropriate supportive therapy;
 - Grade ≥ 3 diarrhea that resolves to Grade ≤ 1 within 72 hours with appropriate supportive therapy;
 - Grade ≥ 3 fatigue, asthenia, or other constitutional symptom that resolves to Grade ≤ 1 within 7 days with appropriate supportive therapy;
 - Alopecia of any grade;

- Grade ≥ 3 infection, fever (including febrile neutropenia), electrolyte abnormalities and ALT/AST elevation that returns to Grade ≤ 1 or baseline within 7 days;
- Delay by more than 14 days to receive the next scheduled dose due to a persisting drug-related AE.
- All Grade 4 toxicities.

In addition, clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by the investigators and sponsor. All DLTs need to represent a clinically significant shift from baseline.

Grade ≥ 3 cytokine release syndrome, infusion reaction, and allergic reaction will not be considered as DLTs (as it is unlikely to be dose related), but may be a reason for study discontinuation, protocol amendment (eg, pre-infusion treatments, infusion duration) and should be reviewed with the sponsor.

In principle, a patient needs to be on study for at least 28 days to be evaluable for DLT observation, and may be replaced if they terminate study participation earlier than 28 days without experiencing a DLT. Patients who are not able to receive at least 80% of the planned dose of the PF-06747143 and backbone chemotherapy (in Part 2 combination study) in the DLT assessment period are considered not evaluable for DLT and will be replaced. However, in some circumstances of a clear drug unrelated event (eg, traffic accident, clear disease progression, or withdrawal of consent) that leads to study termination close to or before 28 days, the patient might be deemed evaluable if the Investigators and Sponsor agree.

In addition, patients not evaluable for assessment of DLT, as described in Section 7.2.1, may be replaced.

7.2.2. MTD Definition

The MTD would be any doses with true toxicity probabilities in the Equivalence Interval (EI) where the EI is defined as [20%-30%].

In practice, the MTD will be the highest dose associated with the occurrence of DLTs $\leq 33\%$ (eg, 3/9 evaluable patients experience a DLT during the first treatment cycle).

7.2.3. Maximum Permitted Dose Definition

The Maximum Permitted Dose (MPD) for Part 1 and 2 is 20 mg/kg.

7.2.4. Recommended Phase 2 Dose (RP2D) Definition

The Recommended Phase 2 Dose (RP2D) is the dose chosen for further study based on Part 1 results. If the MTD proves to be clinically feasible for long term administration in a reasonable number of patients, such dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

7.2.5. Vitals Signs

Vital signs, See Schedule of Activities in the protocol for details.

7.2.6. Laboratory Data

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal,

7.2.7. Adverse Events

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

Treatment Emergent Adverse Events

- All deaths from start of treatment until 28 days after the final dose.
- All treatment related SAEs.
- All unrelated SAEs from treatment start until 28 days after final dose of treatment.
- All non-fatal AEs occurring after treatment start up until 28 days after final dose of treatment or until start of new anti-cancer treatment, whichever is first.
- Disease progression is not considered a treatment emergent adverse event unless the subject dies of disease prior to 28 days after discontinuation of treatment.
- Events that are continuations of baseline abnormalities are considered treatment emergent adverse events only if there is an increase in grade over baseline.

Treatment Related Adverse Events

Treatment Related Adverse Events are treatment emergent adverse events with cause categorized by the investigator as related to study treatment. Events that are continuations of baseline abnormalities (signs and symptoms) are not considered treatment emergent, and hence are not considered treatment related, unless there is an increase in grade over baseline.

7.2.8. ECG and QTc Interval

The analysis of ECG results will be based on Safety Population patients with baseline and on-treatment ECG data.

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

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

1. The number of patients with maximum change from baseline in QTc (<30, 30-60, and \geq 60 ms).
2. The number of patients with maximum post-dose (post-baseline) QTc (<450, 450-<480, 480-<500, and \geq 500 ms).

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

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

If more than one ECG is collected at a nominal time post dose (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the three individual ECG tracings has a QTc value \geq 500 msec, but the mean of the triplicates is not \geq 500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the \geq 500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are \geq 500 msec will not be included in the categorical analysis unless the

average from those triplicate measurements is also ≥ 500 msec. Changes from baseline will be defined as the change between QTc post dose from Day 0, or the pre-dose values on Day 1.

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

7.2.9. Immunogenicity

The development of anti PF 06747143 antibodies will be measured using validated assays. Listings and summary tabulations of number of patients and incidence of ADA at baseline (pretreatment) and post treatment will be generated.

Potential impact of immunogenicity on PK and clinical responses including PD markers, safety/tolerability and efficacy of PF 06747143 will be explored, if data is warranted.

7.3. PK Endpoints

Serum pharmacokinetic parameters including the maximum concentration (C_{max}), time to maximum concentration (T_{max}), and area under the concentration versus time curve (AUC_{last} , AUC_{τ}) for PF-06747143 will be estimated using non compartmental analysis. If data permit, area under the concentration versus time curve to infinity (AUC_{inf}), terminal elimination half life ($t_{1/2}$), clearance (CL), apparent volume of distribution (V_{ss}), and accumulation ratio (Rac) will be also estimated. The PK parameters will be summarized descriptively by dose, cycle and day.

PF0-06747143 concentrations will be summarized descriptively (n, mean, SD, coefficient of variation(CV), median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time. Individual patient and median profiles of the concentration time data will be plotted by dose, cycle and day (single dose and steady state) using nominal times. Individual and median profiles will be presented on both linear linear and log linear scales.

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

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

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

CCI

7.5. Covariates

Not applicable.

8. HANDLING OF MISSING VALUES

8.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of onset cannot be prior to day one date). In this case, the date resulting in 0 time duration will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration). This excludes the pharmacokinetic, ECG, and pharmacodynamic analyses, which will only use the actual date collected or if date not available deem the data missing.

8.2. Efficacy Analysis

Censoring rules for time-to-event endpoints are detailed in Section [11.2 Appendix 2](#).

8.3. Pharmacokinetics

Concentrations below the limit of quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as “<LLQ”, where LLQ will be replaced with the value for the lower limit of quantification.)

Deviations, missing concentrations and anomalous values

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

- a. A concentration has been reported as ND (ie, not done) or NS (ie, no sample),
- b. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the drug is absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

QTc

For the QTc analyses, no values will be imputed for missing data.

CCI



9. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

9.1. Statistical Methods

No formal hypothesis testing will be performed in this exploratory study.

Analyses of Time-to-Event Endpoints

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint (Brookmeyer and Crowley, 1982) will be provided.

Analyses of Binary Endpoint

The rates of binary endpoints will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method.

Analyses of Continuous Data

Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints.

9.2. Statistical Analyses

9.2.1. Primary Analysis

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study, which will be summarized by dose level using the Per Protocol Analysis Set for patients in the dose escalation portion of the study. A listing of the DLTs will also be provided.

If necessary, a summary and listing of the DLT by malignancy may be provided using the Per Protocol Analysis Set for patients in the MTD expansion portion of the study.

9.2.2. Secondary Analyses

9.2.2.1. Efficacy Analysis

In this Phase 1 study efficacy is a secondary objective. Note that the efficacy analysis is to be conducted by malignancy for patients in the MTD expansion cohorts who are in the Safety Analysis Set and have baseline disease assessment and at least one post-baseline disease assessment. In the event that a large number of patients in the escalation portion of the study have the same malignancy, the efficacy analysis may be conducted.

Summary tables of best Overall Response Rate, Progression Free Survival, and Overall Survival will be provided overall and by malignancy. Efficacy listings will be provided that include best response, first CR/PR date, last date with CR or PR, most recent date without progression, progression date, death date, date of first response and last tumor assessment date, etc.

A response rate overall for Part 1 dose escalation and response rates by low, medium, and high dose groups may be presented.

The following table provides an overview of the efficacy analysis.

Table 2. Overview of Efficacy Analysis

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Interpretation
Overall response	Per Protocol, expansion cohorts, etc.	Exact CI	By dose range/ malignancy	Censored per Section 11.2	Secondary Analysis
Progression Free Survival (PFS)	Per Protocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per Section 11.2	Secondary Analysis
Time to Progression (TTP)	Per Protocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per Section 11.2	Secondary Analysis
Duration of Response (DR)	Per Protocol, expansion cohorts	Kaplan-Meier	By malignancy	Censored per Section 11.2	Secondary Analysis

9.2.2.2. Pharmacokinetics Analyses

Pharmacokinetic Parameters

To assess the pharmacokinetics of PF-06747143, PK parameters detailed in [Section 7.3](#) will be listed and summarized for subjects in the PK analysis set (as defined in [Section 9.1](#) of the protocol or [Section 6.2](#) in this document). Missing values will be handled as detailed in [Section 8](#). Each PK parameter will be summarized by dose and cycle and will include the set of summary statistics as specified in the table below:

Table 3. PK Parameter Summaries

Parameter	Summary statistics
AUC _{last} , AUC _∞ , AUC _τ , C _{max} , CL, V _{ss} , and R _{ac}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
t _{1/2}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum
T _{max}	N, median, minimum, maximum

There will be 1 summary table presenting all PK parameters. This will include data from all cohorts and will be summarized by dose group and cycle.

To assess the relationship between the PK parameters and dose, dose normalized AUC_∞, AUC_{last}, AUC_τ, and C_{max} will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means

will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg/kg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented are presented on the plot.

Pharmacokinetic Concentrations

To assess the PK profile of PF-06747143, total antibody and unconjugated payload, PK concentrations will be listed, summarized and plotted for subjects in the PK analysis set (as defined in Section 7.3) Presentations for PF-06747143, total antibody and unconjugated payload will include:

- a listing of all concentrations sorted by dose, subject ID, day and nominal time post dose. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.
- a summary of concentrations by dose, day and nominal time post dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv) and the number of concentrations above the lower limit of quantification.
- a plot of mean concentrations against nominal time postdose by dose (based on the summary of concentrations by dose and time postdose), preferably with all doses also on the same graph.
- a plot of median concentrations against nominal time postdose by dose (based on the summary of concentrations by dose and time postdose), preferably with all doses also on the same graph.
- a log-linear plot of mean concentrations against nominal time postdose by dose (on the same plot), preferably with all doses also on the same graph.
- a log-linear plot of median concentrations against nominal time postdose by dose (on the same plot), preferably with all doses also on the same graph.
- plots (linear and log scale) of individual concentrations against actual time postdose.

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PK concentration is quantifiable in the matrix.

In addition to the above, a median plot (linear and log scale) of the predose concentrations at each cycle against day will be provided for each dose, on the same plot, in order to assess the attainment of steady-state. Individual subject profiles will also be plotted.

For summary statistics and mean/median plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

CCI

CCI

9.2.3. Safety Analyses

Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 4.0 and coded using the MedDRA. The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). The Safety Analysis Set will be used.

Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test. The analyses will summarize laboratory tests both in the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory abnormalities. The Safety Analysis Set will be used.

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

Other Variables: Immunogenicity

The development of anti PF 06747143 antibodies will be measured using validated assays. Listings and summary tabulations of the anti PF 06747143 antibody data at baseline and post randomization will be generated.

Potential impact of immunogenicity on PK and clinical responses including CCI safety/tolerability and efficacy of PF 06747143 will be explored, if data is warranted.

9.2.4. Standard Analyses

Study Conduct and Patient Disposition

An accounting of the study patients will be tabulated. The subject evaluation groups will be listed. The Full Analysis Set will be used.

Subject discontinuation from treatment and study will be tabulated and listed separately with their reason for discontinuation. The Safety Analysis Set will be used.

Baseline Characteristics

Baseline characteristics such as demographics, prior medication, medical history, ECOG performance status, and primary diagnosis will be tabulated and listed. For ECOG performance status a shift table (worst post-baseline vs baseline may be produced). The Safety Analysis Set will be used.

Treatment Administration/Compliance

Listings and tables by dose level will be provided. Cycle length is 21 days. Day 1 of a cycle is the first date of dose within that cycle. The safety analysis set will be used.

Dose modifications may occur in the following ways:

- Cycle delay—Day 1 of current cycle starts later than 21 days from Day 1 of the previous cycle (only applies to cycle 2 and above);
- Dose reduction—A decrease in the administered total daily dose (non-zero) compared to the planned total daily dose upon enrollment. If in the CRF the prescribed dose unit is mg/kg, but the actual dose is in mg the actual dose mg/kg should be calculated considering the body weight of the patient at that visit.

Intra-patient dose escalation is not allowed in this study. The following will be summarized by subject for each dose level:

- Number of subjects per dose level;
- Median and range of number of cycles started per subject;
- Number (%) of subjects starting a cycle (1, 2, 3...);
- Number (%) of subjects with cycle delays;
- Number (%) of dose interruptions (include both known and unknown dates);
- Number (%) of subjects with dose reductions;
- Number (%) of each reason (AE vs. Other) for cycle delays, dose interruptions and dose reductions;

- Time on treatment (median, range).

The following will be summarized by cycle received for each dose level:

- Total number of cycles started;
- Number of cycles started per subject (median, range);
- Number of cycles before 1st delay (median, range);
- Number of cycles before 1st reduction (median, range);
- Number of cycles before 1st interruption (median, range).

The following will be summarized for cumulative dose by dose level and cycle:

- Summary statistics (mean, median, standard deviation and range) of cumulative dose and percent of starting dose (compared to Day 1 dose of each cycle)

Listings by subject (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0mg), administered total daily dose for each period, any missed doses with unknown dates (Y/N), number of missed doses with unknown dates, reason for any dosing changes.

Listings by subject and each cycle (ordered by dose level): cycle length, total planned dose, administered total dose, percentage of planned dose, dose delay (yes/no), dose reduction (yes/no), and dose interruption (yes/no).

Prior, Concomitant, and Further Therapies

Prior, concomitant, and further therapies (drug and non-drug treatments) will be coded by the World Health Organization (WHO) medical dictionary. Listings of prior, concomitant, and further therapies will be provided separately.

10. REFERENCES

1. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. *Biometrics* 1982; 38:29-41.
2. Döhner H1, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010 Jan 21; 115(3):453-74
3. E.A. Eisenhauer, P. Therasseb, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer* 45 (2009) 228–247
4. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.
5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-481.
6. NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE). http://evs.nci.nih.gov/ftp1/CTCAE/Documentation/CTCAE_Governance_2010-03-11.pdf
7. Y Ji, P Liu, Y Li, and BN Bekele. A modified toxicity probability interval method for dose-finding trials. *Clinical Trials*, 7:653 663, 2010.
8. Vardiman JW et al, The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009; 114(5):937-951.

11. APPENDICES

11.1. APPENDIX 1: CATEGORICAL CLASSES FOR ECG AND VITAL SIGNS

Categories for QTcB and QTcF

QTcB/QTcF (ms)	max. ≤ 450	$450 < \text{max.} \leq 480$	$480 < \text{max.} \leq 500$	max. > 500
QTcB/QTcF (ms) increase from baseline	max. < 30	$30 \leq \text{max.} < 60$	max. ≥ 60	

Categories for PR and QRS

PR (ms)	max ≥ 300	
PR (ms) increase from baseline	Baseline > 200 and max. $\geq 25\%$ increase	Baseline ≤ 200 and max. $\geq 50\%$ increase
QRS (ms)	max ≥ 200	
QRS (ms) increase from baseline	Baseline > 100 and max. $\geq 25\%$ increase	Baseline ≤ 100 and max. $\geq 50\%$ increase

Categories for Vital Signs

Systolic BP (mm Hg)	min. < 90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥ 30	max. increase ≥ 30
Diastolic BP (mm Hg)	min. < 50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥ 20	max. increase ≥ 20
Supine pulse rate (bpm)	min. < 40	max. > 120

Measurements that fulfil these criteria are to be listed in the study report.

11.2. APPENDIX 2: CENSORING DETAILS**Table 4. Progression Free Survival and Duration of Response**

Situation	Date of Progression/Censoring ¹	Outcome
Inadequate baseline assessment	Start date (C1D1)	Censored
No on-study assessments	Start date (C1D1)	Censored
Alive, on treatment ² and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation ²	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation ²	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation ²	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation ²	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1: For date of censorship, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.

2: or within 28 days of discontinuation of treatment.

Table 5. Time to Progression

Situation	Date of Progression/Censoring ¹	Outcome
Inadequate baseline assessment	Start date (C1D1)	Censored
No on-study assessments	Start date (C1D1)	Censored
Alive, on treatment ² and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation ²	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation ²	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation ²	Censored
New anticancer treatment <28 days after discontinuation of treatment without progression	Date of last objective tumor assessment prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Start date (C1D1)	Censored
Death without objective progression prior to treatment discontinuation ²	Date of last objective tumor assessment prior to death	Censored
Progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1: For censoring date, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.

2: or within 28 days of discontinuation of treatment.

11.3. Appendix 3. Detailed Dose Escalation/De-Escalation Scheme for mTPI Design

Number of Patients

Number of Toxicities

	1	2	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	S	S	E	E	E	E	E	E
2		DU	D	D	S	S	S	S	S	S	S	S
3			DU	DU	DU	D	S	S	S	S	S	S
4				DU	DU	DU	DU	DU	D	S	S	S
5					DU	DU	DU	DU	DU	DU	D	S
6						DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

E=Escalate to the next higher dose
 S=Stay at the current dose
 D=De-escalate to the next lower dose
 DU=The current dose is unacceptably toxic
 Probability of target toxicity=0.25

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

- With 2 patients treated at current dose level
 - 0 DLT -> escalate
 - 1 DLT -> de-escalate to the lower dose
 - 2 DLTs -> de-escalate and consider current dose as intolerable
- With 3 patients treated at current dose level
 - 0 DLT -> escalate
 - 1 DLT -> remain at the same dose
 - 2 DLTs -> de-escalate
 - 3 DLTs -> de-escalate and consider current dose as intolerable
- With 4 patients treated at current dose level
 - 0 DLT -> escalate
 - 1 DLT -> remain at the same dose



- 2 DLTs -> de-escalate
 - 3-4 DLTs -> de-escalate and consider current dose as intolerable
- With 5 patients treated at current dose level
 - 0 DLT -> escalate
 - 1-2 DLTs -> remain at the same dose
 - ≥ 3 DLTs -> de-escalate and consider current dose as intolerable
- With 6 patients treated at current dose level
 - 0 DLT -> escalate
 - 1-2 DLTs -> remain at the same dose
 - 3 DLTs -> de-escalate
 - 4-6 DLTs -> de-escalate and consider current dose as intolerable
- With 7 patients treated at current dose level
 - 0-1 DLT -> escalate
 - 2-3 DLTs -> remain at the same dose
 - ≥ 4 DLTs -> de-escalate and consider current dose as intolerable
- With 8 patients treated at current dose level
 - 0-1 DLT -> escalate
 - 2-3 DLTs -> remain at the same dose
 - ≥ 4 DLTs -> de-escalate and consider current dose as intolerable
- With 9 patients treated at current dose level
 - 0-1 DLT -> escalate
 - 2-3 DLTs -> remain at the same dose
 - 4 DLTs -> de-escalate
 - 5-9 DLTs -> de-escalate and consider current dose as intolerable
- With 10 patients treated at current dose level
 - 0-1 DLT -> escalate
 - 2-4 DLTs -> remain at the same dose
 - ≥ 5 DLTs -> de-escalate and consider current dose as intolerable
- With 11 patients treated at current dose level
 - 0-1 DLT -> escalate
 - 2-4 DLTs -> remain at the same dose
 - 5 DLTs -> de-escalate
 - 6-11 DLTs -> de-escalate and consider current dose as intolerable
- With 12 patients treated at current dose level
 - 0-1 DLT -> escalate
 - 2-5 DLTs -> remain at the same dose

- 6-12 DLTs -> de-escalate and consider current dose as intolerable

11.4. Disease Assessment

The following section describes the CRF completion guidelines and the corresponding response criteria.

If assessment was done, place 'X' in one box only (unless otherwise specified for that selection), to record the disease assessment. Select from the following:

1. Morphologic Complete Remission (CR): This is morphologic leukemia-free state with bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease (EMD); absolute neutrophil count >1000/ul and platelet >100,000/ul; independence from red cell transfusions.

If the CR box is checked, check the box(es) below if patient achieved the following:

- a. Cytogenetic CR (CRc): Reversion to a normal karyotype at the time of morphologic CR, as defined above, in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow.
- b. Molecular CR (CRm): Reversion to a molecular-negative phenotype at the time of morphologic CR, as defined above.

Note: Even if the CRc and/or CRm box(es) are checked, the CR box must still be checked.
OR

2. Morphologic Complete Remission with incomplete blood count recovery (CRi): All CR criteria met except for residual neutropenia (absolute neutrophil count <1000/ul) or thrombocytopenia (platelets <100,000/ul).

OR

3. Morphologic Leukemia-Free State: Bone marrow blasts <5%; absence of blasts with Auer rods; absence of EMD; no hematologic recovery required.

OR

4. Partial Remission (PR): Absolute neutrophil count >1000/ul and platelet >100,000/ul; bone marrow blasts decreased to 5-25% and $\geq 50\%$ decrease from pre-treatment levels.

OR

5. Partial Remission with incomplete blood count recovery (PRI): residual neutropenia (absolute neutrophil count $<1000/\text{ul}$) or thrombocytopenia (plateletes $<100,000/\text{ul}$); bone marrow blasts decreased to 5-25% and $\geq 50\%$ decrease from pre-treatment levels.

OR

6. Treatment Failure (TF): If TF box is checked, one of the options below must be chosen:

a. TF due to resistant disease: Failure to achieve CR, CRi, PR or PR; Only includes patients surviving ≥ 7 days following completion of initial course of treatment with evidence of persistent leukemia by blood and/or bone marrow examination. Initial course of treatment completion is defined as completion of Cycle 1.

b. TF due to aplasia: Deaths occurring ≥ 7 days following completion of initial course of treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death and without evidence of persistent leukemia. Initial course of treatment completion is defined as completion of Cycle 1.

c. TF indeterminate cause: Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial course of treatment with no blasts in the blood, but no bone marrow examination available. Initial course of treatment completion is defined as completion of Cycle 1.

Note: If TF applies, the TF box should always be checked along with one of the three options.

OR

7. Relapse: Bone Marrow blast $\geq 5\%$; or reappearance of blast in the blood; or development of EMD