Protocol C3661001

PF-06873600

PHASE 1/2 DOSE ESCALATION AND EXPANSION STUDY EVALUATING SAFETY, TOLERABILITY, PHARMACOKINETIC, PHARMACODYNAMICS AND ANTI TUMOR ACTIVITY OF PF 06873600 AS A SINGLE AGENT AND IN COMBINATION WITH ENDOCRINE THERAPY

Statistical Analysis Plan (SAP)

Version: 4.0

Author: PPD

Date: 23 March 2023

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Date	Author(s)	Summary of Changes/Comments
4.0	March 23,2023	PPD	• fuclude updates up through those incorporated in Protocol Amendment 9 dated 03 Mar 2023. • fuclude detailed infonnation regarding censonng efficacy endpoints for analysis based on sponsor decision to terminate study. (Section 7.1, Appendix 3)
3.0	October 19,2022	PPD r1	The pmpose of this amendment is to add additional analysis to include updates until Protocol Amendment 8 dated 08 July 2021.
2.0	Septemb er 25, 2019	DPD	The pmpose of this amendment is to add additional coho11s of patients to evaluate a modified release fonnulation of PF-06873600, as indicated, based on emerging and available prelimina1y clinical data, including safety/tolerability, laborato1y, PK and PD findings. fu addition, clarifications, administrative and typographical modifications were made.
			Section 2.1 Study Design. • Addition of Paii 1C description. • Overall Study Schema updated to include Part IC. • Study Schema (within Paii lC through Cycle 1). • Addition of Section 2.1.3. Paii lC PF 06873600 MR Fonnulation.
			Section 2.3. Study Objectives and Endpoints. Study Objectives and Endpoints were updated to reflect the addition of Pali 1C
			Modified the percentage requirement for planned doses from 70 to 75% based in order to be evaluable for DLT assessment. This modification is based on fustitutional Review Board (IRB) feedback.

			New dose levels for the immediate release fonnulation updated in Table 1
			TEAE definition in 7.2.6 was updated based on CDSB decision (UIMS 141184)
1.0	June 29, 2018	**PD**	First version

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol C3661001 (Ammendment 9, to be finalized Mar 2023). This analysis plan is meant to supplement the study protocol. fu 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 Design

This is a Phase I/2a, open-label, multi-center, non-randomized, multiple dose, safety, tolerability, pharmacokinetic, and pharmacodynamic study of PF-06873600 administered as a single agent in sequential dose levels and then in combination with endocrine therapy. In Part IA, successive cohorts of patients will receive escalating doses of PF-06873600 starting at I mg BID dosed on a continuous basis and then in dose finding (Part IB) with immediate release formulations of PF-06873600 in combination with endocrine therapy (ET) in an outpatient setting. In Part IC, successive cohorts of patients will receive escalating doses of PF-06873600 testing a modified release (MR) formulation in a MR cohort evaluation and then in dose finding (Part IB) with modified release formulations of PF-06873600 in combination with endocrine therapy (ET) in an outpatient setting.

This study contains 2 parts, dose escalation with single agent (Part IA and IC) and then dose finding with PF-06873600 in combination with endocrine therapy (letrozole and fulvestrant, independent y with both immediate and modified release formulations) (Part IB) followed by dose expansion arm in combination with endocrine therapy (Part 2). The overall study design is depicted in Figure 1 and Figure 2 *below.*

The Japan lead-in cohort (J-LIC) will be added separately as a sub-cohort in order to assess the safety of monotherapy of PF-06873600 in Japanese population. Detailed information is provided in the Appendix 7. Japanese participants will be able to enroll into Part 2 after safety and tolerability of monotherapy of PF-06873600 in Japanese participants is confirmed.

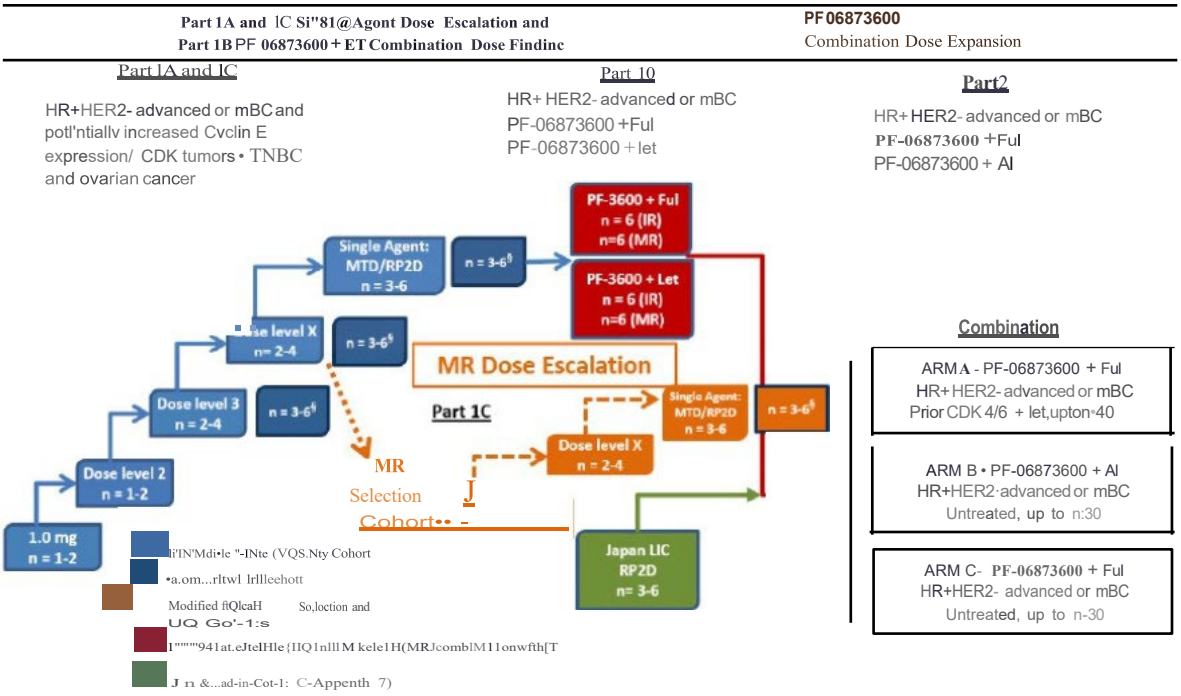
In Part IA, Part IB, and Part IC patients will partidpate in a dose escalation/finding phase aimed at estimating the MTD. The sample size for this component of the study will vary depending on the number of DLTs observed.

Approximate y 75 patients are expected to be enrolled in the dose escalation/finding safety cohorts and an additional 6-12 patients are expected in the biomarker cohorts in Parts IA and IC. The actual number of patients enrolled will depend on the tolerability of PF-O68736OO and the number of dose levels required to identify the MTDIRDE. Part IA, Part JC and each independent combination cohort in Part IB (PF-O68736OOin combination with letrozole and PF-O68736OOin combination withfulvestrant) can be stopped and MTD declared with approximately 6 to 12 patients. As for the number of patients treated at each dose, it is expected to be at I to 4 patients for the doses actually studied. However, since variable cohort size is allowed, the actual number of patients treated at each dose (including MTD) will va,y from I to 12..

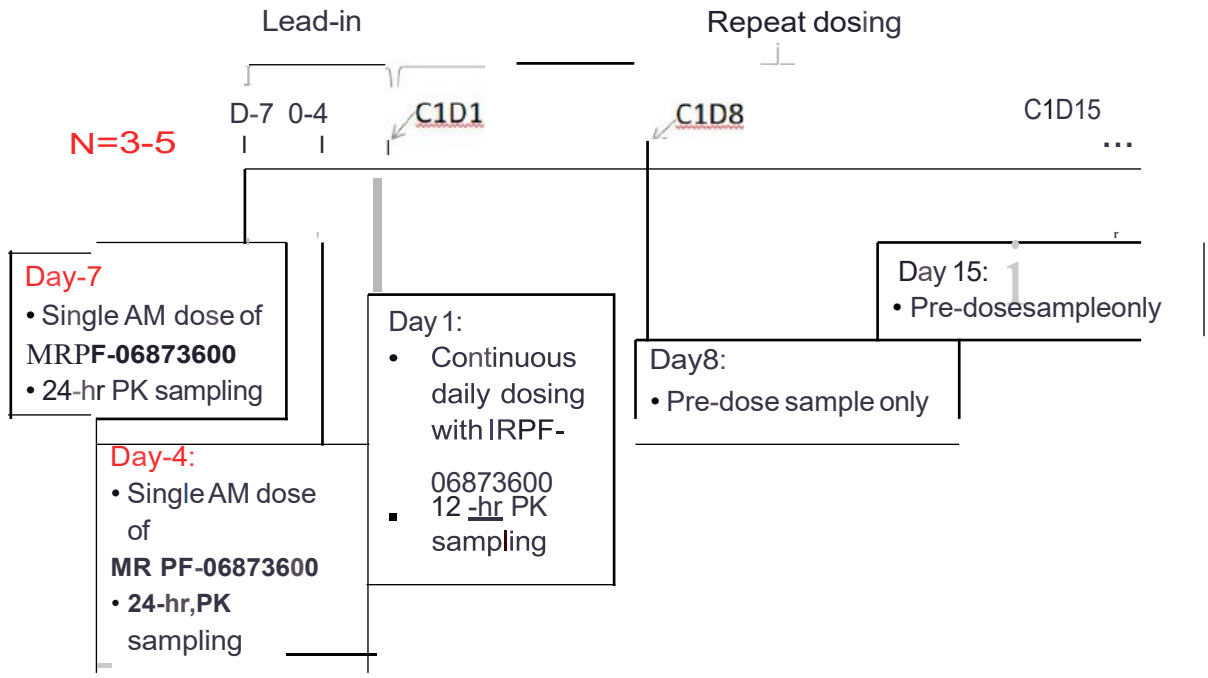
Part 2, the expansion arms will be conducted to assess efficacy as well as safety and tolerability of PF-O68736OOin single agent and combination therapy. The sample sizes for Part 2 are determined based on published historical data as benchmark data, I-sided type I error rate of a= 0.1 with 80% power or higher. Approximately JOO patients are expected to be enrolled in Part 2. Enrollment of participants into a given cohort may be discontinued if

minimal or no anti-tumor activity is observed.

Figure 1 Overall Study Schema



Figme 2 Modifed Release Selection Coho11 Study Schema (within Paii lC through Cycle 1)



2.1.1. *Part IA PF-06873600 Single Agent Dose Escalation*

Part IA consists of single agent dose escalation in dose escalation safety cohorts as well as biomarker cohorts. The dose escalation safety cohorts will be initiated in 1-2 patients for the first 2 planned dose levels starting at 1 mg BID orally on a continuous basis and dose escalation will proceed according to the modified toxicity probability interval (mTPI) method. When a dose level is deemed safe following a DLT observation period o/28 days and based on the discussion by the safety review team (comprised of the Investigators and the Sponsor), dose escalation will occur to the next dose level.

While patients enrolled in the dose escalation safety cohorts are being evaluated, patients may enroll into additional biomarker cohorts (approximately 6 patients in each cohort) requiring mandatory pre- and -on treatment tumor and skin biopsies. An end of treatment tumor biopsy is optional but encouraged. Initiation of enrollment into the first biomarker cohort will be based on observations of key pharmacodynamic (PD) findings (eg, neutropenia, gastrointestinal toxicities, and/or other PK/PD markers) and/or reaching a predicted active dose (noted in Figure 8 of the protocol as Biomarker Cohort). Enrollment into a biomarker cohort can occur after the dose level is deemed safe for escalation to a higher dose level or at the MTD. Biomarker cohorts will enroll women and men with HR-positive HER2-negative advanced or mBC. Because these additional patients will receive a dose lower than the concurrent dose escalation safety cohort or will be enrolled at a dose following the DLT evaluation period in the first 2-4 dose escalation safety cohort patients enrolled, their potential DLT observations may not be strict y used in the mTPI method for the ongoing dose finding. However, the safety profile from these additional patients will be used to establish the MTD or RDE.

2.1.2. *Part JB PF-06873600 Dose Finding in Combination with Endocrine Therapy*

After the single-agent PF-06873600 MTDIRDE has been determined for both the IR and MR formulations, enrollment will be initiated into Part JB which will evaluate the PF-06873600 in combination with letrozole and in combination with fulvestrant in independent cohorts in women with HR-positive HER2-negative advanced or mBC. PF-06873600 will be administered orally on a continuous basis (unless the dose schedule has changed during Part JA or Part 1C), while letrozole and fulvestrant will be administered per standard of care.
Available safety and clinical data will be reviewed by the safety review team. The PF-06873600 dose in combination with letrozole may be decreased if determined to not be tolerable. The PF-06873600 dose de-escalation in combination with letrozole will follow the mTPI method. Similarly, the PF-06873600 dose in combination withfulvestrant may be decreased if determined to not be tolerable. The PF-06873600 dose de-escalated in combination withfulvestrant will follow the mTPI method. The MTDIRDE of each of the PF-06873600 formulations (IR and MR) in combination with the respective endocrine therapy (letrozole and fulvestrant) will be declared when at least 6 patients have been enrolled at a dose level that is predicted to be the MTDIRDE for each of the respective combination per the mTPl Once the MTDIRDE of PF-06873600 in combination with letrozole and the MTDIRDE of PF-06873600 in combination withfulvestrant have been confirmed, a recommended dose for expansion for each combination will be declared and enrollment into Part 2 may be initiated. The decision to dose either the MR or IR or MR and IRformulation in Part 2 will be made following a careful review of all available clinical data and in alignment with C3661001 Safety Team.

Similar to Part JA and/or Part JC, dose escalation, all safety, PK and PD information from safety cohorts in Part JB available will be used to determine the PF-06873600 MTDIRDE for the respective combination treatments.

2.1.3. Part 1C PF-06873600 MR Formulation

A modified release (MR) formulation with two designed release rates shorter duration (eg, 6-hour) and longer duration (eg,12-hour) release, respectively) has been developed for PF-06873600 and were studied in the Part 1C MR Selection Cohort only. Compared to the Immediate Release (JR) formulation, the MR formulation has the potential to achieve more prolonged effective target inhibition during a dose interval. Emerging pharmacokinetics and safety data for the IRformulation suggest there is a large peak-to-trough fluctuation in steady-state concentations and a lower maximal concentration (Cmax) could potentially improve tolerability. Therefore, the MR formulation with the two release rates were evaluated in an MR selection cohort in this study.

The MR selection cohort enrolled 3 to 5 evaluable patients. These patients received two single doses of the MRformulation during a 7-day lead-in period (Day -7 to Day -1), prior to receiving the IR formulation of PF-06873600 twice dai y in 28-day cycles. During the 7-day lead-in period, patients will first received a single dose of the shorter release tablets on Day -7, and then another single dose of the longer release tablets on Day-4. The dose for the

shorter and longer release MR tablets to be administered during the lead-in period, as well as the IR dose to be administered startingfrom Cycle 1 Day 1, were no higher than the highest nominal dose tested found to be safe from the IR dose escalation. Serial PK sampling was performed for 24 hours following each of the MRformulation doses on Day -7 and Day -4, and for 12 hours following the IR formulation morning dose on Cycle 1 Day 1. PK were compared between the shorter and longer release MR tablets, and also between each of the two release rate MR tablets and IR. Based on the PK data from the MR selection cohort, 12-hour release rate provides a slower release compared to the 6-hour release rate, thus achieves more prolonged drug coverage during a dosing interval. Therefore, 12-hour release rate was selected to be further investigated during MR dose escalation.

The MR dose escalation, if to be performed, proceeded with one of the selected MR formulation release rates according to the mTPI method until a MTD is determined. The starting dose for the MR dose escalation was selected to achieve similar steady-state AUC during one dose interval (AUCss,J as the highest safe IR dose based on prediction. The dose increment will be no more than a 50% increase. After MTDIRDE is determined, a biomarker cohort may be open to enroll patients with HR-positive HER2-negative advanced or mBC requiring mandatory pre- and on-treatment tumor and skin biopsies.

During the Part 1C dose escalation, all available safety information from dose escalation safety and biomarker cohorts in will be used to determine the PF-06873600 MTDIRP2D as a single agent.

2.1.4. Dose Escalation and MTD Determination in Part 1A and 1B

The starting dose of PF 06873600 will be 1 mg administered orally BID on a continuous basis in 28 day cycles.

The MTD is defined as the highest dose associated with a DLT rate of 2 7.5% with an equivalence interval of (22.5%, 32.5%) following the mTPI method. During dose escalation/finding, patients will be enrolled in dose cohorts of 1-4 patients in Part JA and 2-4 patients in Part 1B and Part 1C in dose cohorts other than the MTDIRDE. Each MTDIRDE including single-agent and combination treatments will enroll 6-12 patients. Each patient will receive continuous doses of PF-06873600 eve1y 28 days. The dose finding decision will be based on]-cycle (28 days) DLT observation period. DLTs observed after the Cycle 1 (28-day) may also be considered in the final determination of the MTD as a single agent, in combination with letrozole, and in combination with fulvestrant.

A modified toxicity probability interval (mTPI) method will be utilized in Pait 1 of the study. Typically patients will be emolled in coho1ts of 2 to 4 patients. Intra patient dose escalation for patients emolled in dose level 1 and 2 may be considered in consultation with the sponsor. Once the respective dose level has been declared safe, patients who have completed at least 2 Cycles of treatment at the original emolled dose level may escalate to the next higher dose level that has cleared the DLT observation period of 28 days.

The potential dose levels planned for Pait 1 of the study are shown in Table 1. Additional dose levels, or inte1mediate doses, may be explored, if appropriate based on emerging safety, PK or PD data.

Table 1 PF-06873600 Dose Levels (Immediate Release Formulation)

DOSE LEVEL (DL)*	DOSE	TOTAL DAILY DOSE***
DL 1**	1 mg BID	2mg
DL2	2 mg BID	4mg
DL3	5 mg BID	10mg
DL4	10 mg BID	20mg
DL 5 and Beyond		Escalation to continue to the MTD or desired phaimacological activity

* The proposed doses, schedule(s), and PK time points may be reconsidered or amended during the study based on the emerging safety and PK data. Intennediate doses may be considered when deemed necessa1y based on on-going evaluation of safety and toxicity data.

** Staiting dose DLI.

*** Total daily dose may be administered in up to 3 divided doses.

The mTPI design uses a Bayesian decision-theoretic :framework and a beta/binomial hierai·chical model to tailor dose-escalation and de-escalation decisions. These rnles are conceptually similar to those used by the 3+3 design and all the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table.

The decision rnles to "dose escalate" (E), "no change in dose" (S), "dose de-escalate" (D) or "dose de-escalate, unacceptable toxicity" (U) are described below:

Table 2 Dose Escalation Decision Rules

DLT	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=l0	**n=ll**	n=12
0	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
1	S	S	S	S	**E**	**E**	**E**	**E**	**E**	**E**	**E**
2	**D**	**D**	**D**	S	S	S	S	S	S	S	**E**
3		u	u	**D**	**D**	S	S	S	S	S	S
4			u	u	u	u	**D**	S	S	S	S
5				u	u	u	u	u	**D**	S	S
6					u	u	u	u	u	u	u
7						u	u	u	u	u	u
8							u	u	u	u	u
9								u	u	u	u
10									u	u	u
11										u	u
12											u

Actions to be tak.en: D = De-escalate the dose; E = Escalate the dose; S = Stay at the dose. U = Unacceptable toxicity.

In prindple, all patients must be evaluated for a minimum DLT observation period of 28 days in both Part 1 and Part 2. However, in order to be evaluable for DLT assessment patients need to have received at least 75% of planned doses unless related to treatment emergent toxicity.

The dose escalation in Part IA and JC, dose finding in Part JB, and each arm of the dose expansion in Part 2 of the study will stop as the applicable following criteria are met:

- *The maximum sample size has been achieved (approximately 50 patients in Part 1, excluding patients enrolled in biomarker cohorts, and approximately 30 patients in each dose arm in Part 2);*
- *6 to 12 evaluable patients (for Parts IA, Part 1Band Part 1C) that have been enrolled at a PF-06873600 dose level (as a single agent, in combination with letrozole, and in combination withfulvestrant, each)) that is predicted to be the MTD per the mTPI method;*
- *All dose levels explored appear to be overly toxic, and the MTD cannot be determined.*

2.1.5. *Recommended Dose for Expansion (RDE) and Recommended Phase 2 Dose (RP2D) Definition*

The RDE is the dose chosen for further investigation based on Part 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the RDE may result in a RP2D dose lower than the RDE. A RP2D for PF-06873600 as a single agent, in combination with letrozole, and in combination with fulvestrant are planned to be individually determined based on the respective RDEIMTD and other considerations including available pharmacoldnetic, pharmacodynamic, and clinical benefit data.

2.2. *Part 2 PF-06873600 Combination Dose Expansion*

Part 2 dose expansion is an open-label, multi-center, non-randomized study to assess the prelimina,y anti-tumor activity and the safety and tolerability of PF-06873600. PF-06873600 will be administered at the RDE in 28 days cycles in combination with endocrine therapy in two separate dose expansion arms. Patients may be treated with IR or MRformulations depending on emerging data from Part 1 and availability.

2.2.1. *Part 2 Respective Starting Doses for PF 06873600 Combination Cohorts*

The single agent PF-06873600 RDEfrom Part IA will be used to initiate the Part 2 dose expansion arm studies, which may be de-escalated, depending on emerging data if indicated. Additionally, the PF-06873600 RDE in combination with letrozole and PF-06873600 RDE in combination withfulvestrantfrom Part JB will be used to initiate the Part 2 respective combination dose expansion arm studies, which may be de-escalated, depending on emerging data if indicated.

2.2.2. *Part 2/Arm A PF 06873600 in Combination with Fulvestrant in HR Positive HER2 Negative Locally Advanced or mBC (Second- or Third-Line Setting)*

PF-06873600 will be evaluated in combination withfulvestrant at the RDE in HR-positive HER2-negative advanced or mBC in patients who have received prior combined CDK4/6 inhibitor and a nonsteroidal aromatase inhibitor, and up to 1 prior line of chemotherapy in advanced/metastatic setting. This expansion cohort will enroll approximately 40 patients.

2.2.3. *Part 2/Arm B -PF 06873600 Part 2/Arm B -PF-06873600 in Combination with Letrozole in HR-Positive HER2-Negative Locally Advanced or mBC (naive to CDK4/6 inhibitors).*

PF-06873600 will be evaluated in combination with letrozole at the RDE in HR-positive HER2-negative advanced or mBC in patients, with supportive available prelimina,y PF-06873600 clinical data. Patients who have not received any prior treatment with a CDK4/6 inhibitor in the advanced or metastatic setting (prior adjuvant therapy with AI is permitted) will be enrolled. This expansion cohort will enroll approximately 30 patients.

2.2.4. *Part 2/Arm C-PF-06873600 in Combination with Fulvestrant in HR-Positive HER2-Negative Locally Advanced or mBC (nai've to CDK4/6 inhibitors)*

PF-06873600 will be evaluated in combination withfulvetsrant at the RDE in HR-positive HER2-negative advanced or mBC in patients who progressed on prior endocrine therapy in advanced/metastatic setting but have not previously received treatment with a CDK4/6 inhibitor in the advanced or metastatic setting. Participants who have prior treatment with CDK4/6 inhibitors,fulvestrant, everolimus, and any agents with MOA that inhibits PI3k mTORpathway are excluded. This expansion cohort will enroll up to 30 patients.

2.3. Study Objectives and Endpoints

Part lA: Single Agent Dose Escalation and Part JB: Combination Dose Finding	
Primary Objective(s):	***Primary Endpoint(s):***
Part JA and 1C: *To assess the safety and tolerability of increasing doses of PF-06873600 in patients with:* • *HR-positive HER2-negative advanced or mBC patients (third or fourth line setting).* • *Locally recurrent/advanced or metastatic TNBC.* • *Advanced platinum resistant epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer* • *In order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Dose for Expansion (RDE) for PF-06873600 as a single agent (Part JA and Part 1Conly).* *Part JB:* *To assess the safety and tolerability of PF-06873600 at the single agent MTD in combination with letrozole and in combination with fulvestrant (in a de-escalation manner, if indicated) in patients with:* • *HR-positive HER2-negative advanced or mBC (third or fourth line setting) in order to establish the MTD and select the RP2D for PF-06873600 in combination with letrozole and in combination with falvestrant, respectively.*	*Part JA, Part JB and Part JC:* • *Dose-Limiting Toxicities (DLTs).* • *Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy.* • *Laboratory abnonnalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing.* • *Vital sign abnormalities.* • *Heart rate corrected QT interval (eg, QTcF).*
Secondary Objective(s):	***Secondary Endpoint(s):***
• *To evaluate the single- and multiple- dose PK of PF-06873600 when given as a single agent (Part JA and Part 1C), in combination with letrozole, and in combination with falvestrant (Part JB).*	*Pharmacokinetic parameters of PF-06873600* • *Single Dose (SD) - Cmax, Tmax, AUC1asi and as data permit, t112, AUC;nJ, CUF, VzlF, and t112.* • *Multiple Dose (MD) (assuming steady state is achieved) - Css,max,Tss,max, AUCss,r, Css,min, CLsslF, and as data pennit, VsslF, t112, and Rae(A UCss,,IAUCs<i,-r}.*

Part lA: Single Agent Dose Escalation and Part JB: Combination Dose Finding	
• *To document any preliminary evidence of anti-tumor activity of PF-06873600.*	• *Objective Response (OR}, as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.* • *Time-to-event endpoints: eg, Duration of Response (DOR}, Progression-Free Survival (PFS}, Time to Progression (ITP).*
• *To evaluate the pharmacodynamic (PD} markers ofCDKpathway modulation following treatment with PF-06873600 in tumor.*	• *Modulation of PD biomarlrers (eg, pRb, Ki67} of CDK in tumor.*
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
	I [redacted]
[redacted]	I [redacted]

Part 2: PF-06873600 Single Agent and Combination Dose Expansion	
Primary Objective(s):	***Primary Endpoint(s):***

To evaluate the preliminary antitumor activity and confirm the safety and tolerability of PF-06873600:
In combination (at the RDEfrom Part lB) in patients with:
1. *HR-positive/HER2-negative advanced or mBC {PF-06873600 + falvestrant) (second or third line setting};*
2. *HR-positive/HER2-negative advanced or mBC {PF-06873600 + a nonsteroidal aromatase inhibitor) (CDK4/6i naive);*
3. *HR-positive/HER2-negative advanced or mBC {PF-06873600 + falvestrant)- (CDK4/6i naive).*
	• *Preliminary antitumor activity measure for efficacy includes OR, as assessed using RECIST 1.1.*
	• *Safety and tolerability:*
	  • *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.*
	  • *Lab abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) and timing.*
	  • *Vital sign abnonnalities.*
	  • *Heart rate corrected QT interval (eg, QTcF).*

Part 2: PF-06873600 Single Agent and Combination Dose Expansion	
Secondary Objective(s):	*Secondary Endpoint(s):*
• *To farther explore preliminary antitumor activity of PF-06873600.*	• *Time-to-event endpoints: eg, DOR, PFS, overall survival (OS) and TTP.*
• *To farther evaluate the **PK** of PF-06873600, in combination with letrozole, and in combination with falvestrant at the respective RDE.*	*Pharmacokinetic parameters of PF-06873600* • *SD - Cmax, Tmax.* • *MD (assuming steady state is achieved) - Css,m,u, Tss,max, Css,min, RacCmax,*
• *To evaluate pharmacodynamic (PD) markers of CDK pathway modulation following treatment with PF-06873600 in in combination with falvestrant or letrozole in tumor.*	• *Modulation of PD biomarkers (eg, pRb, Ki67) of CDK in tumor.*
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
I [redacted]	
[redacted] I [redacted]	

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No fo1mal 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 sUillllaiy statistics.

4.2. Statistical Decision Rules

4.2.1. Part 1

Decision mles are based on calculating unit probability mass (UPM) of three dosing inte1vals conesponding to under, proper, and over dosing in tenns of toxicity. Specifically, the underdosing inte1val is defined as (0; J)T-e1), the over-dosing inte1val (pr+e2), and the proper-dosing inte1val (pT-el, pr+ e2), where el and e2 are small fractions. For a target DLT rate of 0.275, the target equivalence inte1val is (0.225, 0.325). The three dosing inte1vals are associated with three different dose-escalation decisions (Table 1). The under-dosing inte1val conesponds to a dose escalation (E), over-dosing conesponds to a dose de-escalation (D), and proper-dosing conesponds to remaining at the cmTent dose (S). Given a dosing inte1val and a probability distribution, the unit probability mass (UPM) is defined as the ratio of the probability of the inte1val to the length of the inte1val. Once the safety assessment is complete for Cycle 1 (ie, 28 days after the first dose), the focus will be on allocation of new subjects to the dose most likely to be an MTD.

The dose escalation in Part IA and JC, dose finding in Part JB, and each arm of the dose expansion in Part 2 of the study will stop as the applicable following criteria are met:

- *The maximum sample size has been achieved (approximately 75 patients in Part 1, excluding patients enrolled in biomarker cohorts, and approximately 70 patients in Part 2);*
- *6 to 12 evaluable patients (for Parts IA, Part 1Band Part 1C) that have been enrolled at a PF-06873600 dose level (as a single agent, in combination with letrozole, and in combination withfulvestrant, each)) that is predicted to be the MTD per the mTPI method;*
- *All dose levels explored appear to be overly toxic, and the MTD cannot be determined.*

Specifically the mTPI approach fonnalizes stopping mies as follow:

Rule 1 (early tennination): if the first dose is too toxic $Pr(p1 > PT \mid data) >$; ; $= 0.975$

Rule 2 (dose exclusion), if dose= *i* is too toxic $Pr(Pi > PT \mid data) >$; ; $= 0.975$
then exclude doses *i*

4.2.2. Part 2

Part 2 dose expansion is an open-label, multi-center, non-randomized study to assess the prelimina,y anti-tumor activity and the safety and tolerability of PF-06873600. PF-06873600 will be administered at the RDE in 28 days cycles in combination with endocrine therapy in two separate dose expansion arms. Patients may be treated with IR or MR formulations depending on emerging data from Part 1 and availability.

Analyses may be perfo1med on data from both Part 1 and Pait 2 to explore the relationships between PK parameters, safety endpoints, and efficacy endpoints.

5. SAMPLE SIZE DETERMINATION

5.1. Pait 1

In Part IA, Part IB and Part IC, patients will participate in a dose escalation/finding phase aimed at estimating the MTD. The sample size for this component of the study will vary depending on the number of DLTs observed.

Approximate y 75 *patients are expected to be enrolled in the dose escalation/finding safety cohorts and an additional 6-12 patients are expected in the biomarker cohorts in Parts IA and IC. The actual number of patients enrolled will depend on the tolerability of PF-O68736OO and the number of dose levels required to identify the MTDIRDE. Part IA, Part JC and each independent combination cohort in Part IB (PF-O68736OOin combination with letrozole and PF-O68736OOin combination withfulvestrant) can be stopped and MTD declared with approximately 6 to 12 patients. As for the number of patients treated at each dose, it is expected to be at I to 4 patients for the doses actually studied. However, since variable cohort size is allowed, the actual number of patients treated at each dose (including MTD) will va,y from I to 12.*

5.2. Pait 2

Part 2, the expansion arms will be conducted to assess efficacy as well as safety and tolerability of PF-O68736OOin single agent and combination therapy. The sample sizes for Part 2 are determined based on published historical data as benchmark data, I-sided type I error rate of a= 0.1 *with 80% power or higher. Approximately JOO patients are expected to be enrolled in Part 2. Enrollment of participants into a ·ven cohort may be discontinued i f minimal or no anti-tumor activity is observed.* CCI

I

I

- CCI [redacted]

6. ANALYSIS SETS

6.1. Safety analysis set

The safety ana ysis set includes all enrolled patients who receive at least one dose of study treatment.

6.2. Full analysis set

The full analysis set includes all enrolled patients.

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

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

- *Administration of less than 75% of the planned number of doses of PF-06873600* during DLT observation period *(provided that the reduction in doses is not due to toxicity attributable to PF-06873600).*
- *Administration of more than 110% of the planned number of doses of PF-06873600* during DLT observation period.

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

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

6.5. Response Evaluable Set

The response evaluable population will include all paiiicipants who received at least one dose of study treatment and had baseline disease and at least one post baseline disease assessment.

6.6. 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 enrolled patients who are treated and have at least 1 analyte concentration.*

6.7. Biomarker analysis set(s)

- *The PD/Biomarker analysis population is defined as all enrolled patients with PD/Biomarkers evaluated at pre-and/post dose.*

6.8. Treatment Misallocations

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

6.9. Protocol Deviations

All deviations will be listed in the clinical study repo1i (CSR). Major treatment deviations requiring a patient to be excluded from the MTD evaluaton ai·e in Section 6.3.

7. ENDPOINTS AND COVARIATES

7.1. Efficacy Endpoint(s)

ill this First ill Patient study anti tumor activity is a primaiy objective for Pali 2 of the study. Tumor response will be presented in the fo1m of patient data listings that include, but are not limited to, tumor type, staiiing dose, tumor response at each visit, and best overall response. ill addition, progression date, death date, date of first response and last tumor assessment date, and date of last contact will be listed. Objective response rate (ORR), progression free survival (PFS), overall survival (OS), time to progression (TTP), and duration of response (DOR) will be summai·ized and presented if data pe1mits.

The above efficacy endpoints ai·e derived based on the disease response per investigator evaluation on the CRF pages, which is the primaiy method of documentation of disease.

- **Overall Response Rate (ORR)** -defined as the propo1iion of patients who achieved best overall response of complete response (CR) or paiiial response (PR) according to Appendix 2 RECIST 1.1. Overall response is the best response recorded from first dose until disease progression/recurrence.

Unconfi1med CR (uCR) is defined as one objective status of CR documented before PD, while confi1med CR requires two objective statuses of CR a minimum of four weeks apait documented before PD. Sequences of CR - Non-evaluable - CR ai·e considered confamed CR as long as the two CR responses are observed at a minimum of 4 weeks apa1t. Similai·ly, unconfamed PR (uPR) is defined as one objective status of PR documented before PD but not qualifying as uCR. Confi1med PR is defined as two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of four weeks apait documented before PD, but not qualifying as CR. Sequences of PR - Stable Disease or Non-evaluable - PR are considered PRs as long as the two PR responses are observed at a minimum of 4 weeks apait. Based on these definitions, the unconfi1med ORR analysis will include both confamed CR or PR and unconfamed CR or PR as responders, whereas the confi1med ORR analysis will only include confamed CR or PR as responders.

- **Progression Free Survival (PFS)** - is defined as the time from Cycle **1** Day 1 (ClDl) to first documentation of disease progression or death due to any cause, whichever occurs first. Patients 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. Patients who strut 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 ai·e censored at the date of the last objective disease assessment. Patients with inadequate baseline or no on-study disease assessments ai·e censored at ClDl unless death occuned prior to the first planned assessment (in which case the death is an event). Patients 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). Patients 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. If applicable, patients who ai·e still ongoing at time of study te1mination by sponsor ai·e censored at the date of study te1mination.
  PFS (days)= [progression/death date - ClDl + **1].**

  If last adequate tumor assessment is within 6 months of C1D1, any event of death or progression occmTing after more than 18 weeks of last tumor assessment, then it qualifies for 2 missing and we censor at last adequate tumor assessment.

  If last adequate tumor assessment is after 6 months and before 24 months of ClDl, any event of death or progression occmTing after more than 26 weeks of last tumor assessment, then it qualifies for 2 missing and we censor at last adequate tumor assessment.

  If last adequate tumor assessment is after 24 months of ClDl, any event of death or progression occmTing after more than 4 months and 2 weeks of last tumor assessment, then it qualifies for 2 missing and we censor at last adequate tumor assessment.

- **Duration of Response (DOR):** Time from the date of first documentation of CR or PR to the date of first documentation of objective progression or death due to any cause.

- **Time to Progression (TTP):** Time from randomization until disease progression.

More details of censoring are provided in Appendix 3.

7.2. Safety Endpoints

7.2.1. DLT Definitions

Severity of adverse events (AEs) will be graded according to Common Terminology Criteria for Adverse Events (CTCAE} version 4.03. The definition is provided in Section 3.1.6. of the protocol.

7.2.2. MTD Definition

The MTD is defined as the highest dose associated with a DLT rate of 2 7.5% with an equivalence interval of (22.5%, 32.5%) following the mTPI method. During dose escalation/finding, patients will be enrolled in dose cohorts of 1-4 patients in Part JA and 2-4 patients in Part 1B and Part 1C in dose cohorts other than the MTDIRDE. Each MTDIRDE including single-agent and combination treatments will enroll 6-12 patients. Each patient will receive continuous doses of PF-06873600 eve1y 28 days. The dose finding decision will be based on]-cycle (28 days) DLT observation period. DLTs observed after the Cycle 1 (28-day) may also be considered in the final determination of the MTD as a single agent, in combination with letrozole, and in combination with fulvestrant.

7.2.3. Recommended Dose for Expansion (RDE) and Recommended Phase 2 Dose (RP2D) Definition

The RDE is the dose chosen for further investigation based on Part 1 study results. If the RDE proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the RDE may result in a RP2D dose lower than the RDE. A RP2D for PF-06873600 as a single agent, in combination with letrozole, and in combination with fulvestrant are planned to be individually determined based on the respective RDEIMTD and other considerations including available pharmacoldnetic, pharmacodynamic, and clinical benefit data.

7.2.4. Vitals Signs

Vital signs to be obtained include temperature, blood pressure and pulse rate. See Schedule of Activities in the protocol for details.

7.2.5. Laboratory Data

Screening labs to be performed within 7 days of CJD1. Laboratory assessments can be performed earlier but will have to be repeated to be done within 7 days of CJD]. For subsequent cycles, pre-dose labs may also be drawn up to 3 days (-3 days/72 hours) in advance of scheduled dosing in order to obtain results prior to visit.

The laborato1y results will be graded according to the NCI CTCAE v4.03 severity grade. For labs for which an NCI CTCAE v4.03 scale does not exist, the frequency of patients with values below, within, and above the nonnal ranges will be summarized by dose. Baseline evaluations for laborato1y data are those collected:

- Within 28 days prior to Cycle 1/Day 1.
- Closest but prior to Cycle 1/Day 1 if there is more than one baseline evaluation.

7.2.6. Adverse Events

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

All AEs will be coded by system organ class (SOC) and prefe1Ted te1m using Medical Dictionaiy for Regualto1y Activities (MedDRA). The severity of all AEs will be graded by the investigator using NCI CTCAE Version 4.03 whenever possible. For other AEs without specific CTC definitions, results are identified according to CTCAE "other" categories. Adverse events will be assigned to the appropriate cycle based on Day 1 of each cycle.

Treatment Emergent Adverse Events

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event staiied during the effective duration of treatment (i.e., from the first dose of study treatment until last dose of study treatment+ 28 days or start of new anti-cancer therapy - 1 day, whichever occurs first).

Treatment Related Adverse Events

Treatment Related Adverse Events ai·e treatment emergent adverse events with cause categorized by the investigator as related to study treatment. Events that ai·e continuations of baseline abno1malities (signs and symptoms) ai·e not considered treatment emergent, and hence are not considered treatment related, unless there is an increase in grade over baseline.

7.2.7. ECG and QTc Interval

Standard electrocardiogram (ECG): 12-lead (with a JO-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities in the Protocol), *3 consecutive ECGs (except single ECG at screening and End of Treatment) will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged :?501 msec, ie, CTCAE Grade :?3}, then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate.*

7.3. Covariates

Not applicable.

7.4. Definition of baseline for efficacy and safety analyses

The last available assessment prior to the sta1t of study treatment is defined as 'baseline' value or 'baseline' assessment for safety and efficacy analyses. If an assessment is planned to be perfo1med prior to the first dose of study treatment in the protocol and the assessment is peifonned on the same day as the first dose of study treatment, it will be assumed that it was peifonned prior to study ti-eatment 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 dete1mine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the dete1mination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study ti·eatment administi·ation.

8. Handling of Missing Values

8.1. Missing Dates

ill 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). ill 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 phaimacokinetic, ECG, and pha1macodynainic analyses, which will only use the actual date collected or if date not available deem the data missing.

8.2. Efficacy Analysis

Censoring rnles for time-to-event endpoints are detailed in Section 11.3 Appendix 3.

8.3. Pharmacokinetics

Concentrations below the limit of quantification

ill all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (ill listings BLQ values will be repo1ted as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.).

Deviations, missing concentrations and anomalous values

Patients who experience events that may affect their PK (eg, incomplete dosing due to vomitting) may be excluded from the PK analysis.

ill mug concentration summaiy tables and plots of median PK profiles (plots of PK profiles will only be done for Part IA and lB patients), statistics will be calculated with concentrations set to missing if one of the following cases is ti11e:

1. A concentration has been repo1ied 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 anomalous by the phannacokineticist.

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

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other subjects. For example, a BLQ concentration that is between quantifiable values from the same

dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters. If a PK pai·ameter cannot be derived from a patient's concentration data, the pai·ameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

fu Sllllllla1y tables, statistics will not be presented for a paiiiculai· treatment group if more than 50% of the data ai·e NC. For statistical analyses, PK pai·ameters 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 an unexpected event such as vomiting before all the dose is absorbed in the body), this will be footnoted in summaiy tables and will not be included in the calculation of Sllllllla1y statistics or statistical analyses.

QTc

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

Pharmacodynamic parameters

Missing data for the phai"Inacodynamic parameters will be treated as such and no imputed values will be derived.

9. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

9.1. Statistical Methods

No fo1mal hypothesis testing will be perfonned in this explorato1y 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 ofbinaiy endpoints will be provided along with the conesponding 2-sided 95% confidence intervals using an exact method.

Analyses of Continuous Data

Descriptive statistics, such as the mean, standard deviation, coefficient of vai·iation, 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 primaiy endpoint of the study, which will be smnmai·ized by dose level using the Per Protocol Analysis Set for patients in the dose escalation po1iion of the study. A listing of the DLTs will also be provided.

9.2.2. Secondary Analyses

9.2.2.1. Efficacy Analysis

ill this First ill Patient study anti-tumor activity is a primaiy objective for Pait 2 of the study. Tumor response will be presented in the fo1m of patient data listings that include, but are not limited to, tumor type, staiiing dose, tumor response at each visit, and best overall response. ill addition, progression date, death date, date of first response and last tumor assessment date, and date of last contact will be listed. Objective response rate (ORR), progression-free survival (PFS), time to progression (TTP), and duration of response (DOR) will be summai·ized and presented. The definition of each response catego1y is provided in Appendix 2 (RECIST 1.1).

Efficacy analysis will be summai·ized by dose coho1ts for pa.ii 2 of the study (dose expansion). For paii 1 (dose escalation), no fo1mal efficacy analysis will be presented; instead, results will be listed.

For response-based metrics (BOR, ORR and DOR), analyses will be presented based on confnmed responses. Analysis of progression free smvival and time to progression ai·e defined as time from the date of first dose. Summai·ies of then and% of subjects with PFS, and TTP and data listing by tumor type and dose will be generated. If applicable, the PFS may also be summai·ized using the Kaplan-Meier method at all or some of the following timepoints: PFS, DOR, and TTP at 3, 6, 9, 12, 18, and then eve1y 6 months.

The 95% confidence inte1vals will be generated. Confidence inte1vals for medians and quaitiles will be based on the Brookmeyer-Crowley method. Confidence inte1vals for the estimated probability of an event at a pa1ticulai·time point will be generated using the

Greenwood fo1mula. Duration of response will be summarized with number of responders, number and percentage of event/censorship, mean, standard deviation, minimum, maximum and median of duration in unit of months. ORR will be summarized by number of subjects meeting respective criteria, percentage. The 95% confidence intervals will be generated for PFS, TTP, and ORR. Definitions of PFS, TTP, DOR, and ORR are outlined in section 7.1 of this SAP. Supportive figures depicting the change in tumor size may also be provided.

The following table provides an overview of the efficacy analysis.

Table 3 Summary of Efficacy Analysis

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Interpretation
Overall (confnmed) response	Full Analysis Set, Response Evaluable set.	Exact CI	By dose range/arms	Censored per Section 11.3	Secondruy Analysis
Progression Free Smvival (PFS)	Full Analysis Set.	Kaplan-Meier[1]	By dose range/arms.	Censored per Section 11.3	Secondruy Analysis
Time to Progression (TTP)	Full Analysis Set.	Kaplan-Meier	By dose range/arms.	Censored per Section 11.3	Secondruy Analysis
Dmation of (confnmed) Response (DOR)	Full Analysis Set.	Kaplan-Meier	By dose range/arms.	Censored per Section 11.3	Secondruy Analysis

[1] Kaplan EL, Meier P. Nonparametric estimation from incomplete obse1vations. J Am Stat Assoc 1958; 53:457-481.

9.2.2.2. Pharmacokinetics

Analyses Pharmacokinetic

Parameters

Plasma Concentration Summaiy

Presentations for plasma drng concentrations will include:

- a listing of all concentrations sorted by dose level, subject ID, cycle, day, and nominal time. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- median concentrations versus nominal time plots (on both lineai· and seini-log scales) for a dose inte1val after the morning dose on Cycle 1 Day 1 and Cycle 1 Day 15, sepai·ately, by dose level (all treatments on the same plot per scale, based on the SIlilllilalY of concentrations by dose level and time).

- mean concentrations versus nominal time plots (on both linear and semi-log scales) for a dose interval after the morning dose on Cycle 1 Day 1 and Cycle 1 Day 15, separately, by dose level (all ti·eatments on the same plot per scale, based on the summaiy of concentrations by dose level and time).

- median concenti·ations versus nominal time plots (on both linear and semi-log scales) after single dose on Cycle 1 Day -7, Cycle 1 Day -4 and Cycle 1 Day 1 (Paii 1C MR Selection Coho1i).

- mean concentrations versus nominal time plots (on both linear and semi-log scales) after single dose on Cycle 1 Day -7, Cycle 1 Day -4 and Cycle 1 Day 1 (Paii 1C MR Selection Coho1i).

Plasma dmg concenti·ation time data within a dose interval after the morning dose on Cycle 1, Day 1 (for all patients), Cycle 1, Day 15 (for all patients except Paii IC MR Selection Coho1i) and Cycle 1 Day -7/-4 (Paii IC MR Selection Cohort) will be analysed for individual patients using noncompaiimental methods. The noncompa1imental analysis will estimate PK parameters including the following:

1. Cycle 1, Day 1: the maximal concentration (Cmax), time to maximum plasma concentration (Tmax), and ai·ea under the plasma concenti·ation versus time curve from time 0 to the last sampling time point within the dose interval (AUClast), and if data pennit, area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUCinf), tenninal elimination half life (tl/2), apparent oral plasma clearance (CL/F), apparent volume of distribution (Vz/F);

2. Cycle 1, Day 15: steady state Cmax (Cmax,ss), Tmax, AUC within one dose inte1val (AUCr,ss), minimum plasma concenti·ation (Cmin,ss), oral CL (CLss/F), and if data permit, apparent volume of distribution (Vss/F), tl/2, and accumulation ratio (Rae);

3. Cycle 1, Day -7/-4: the maximal concenti·ation (Cmax), time to maximum plasma concentration (Tmax), and ai·ea under the plasma concenti·ation versus time cmve from time 0 to the last sampling time point within the dose inte1val (AUClast), and if data pennit, area under the plasma concentration versus time cmve from time 0 extrapolated to infinity (AUCinf), tenninal elimination half life (tl/2), apparent oral plasma clearance (CL/F), apparent volume of distribution (Vz/F).

PK parameters will be calculated from the PK concentration-time data using standard non compaiimental methods:

Parameter	Method of Determination
C.,.,.. Cmax ss C ,n ss	Observed directly from data
AUC1as1 AUC. ss	Linear/log trapezoidal method
AUCint	AUC1as1+ (C1as1*1ke1), where C1as1* is the predicted concentration at the last quantifiable time point estimated from the log-linear regression analysis, and ke1 is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. For the determination ofke1, only those data values that are consistent with the terminal log-linear phase of the log transformed concentration-time curve will be included. The tenninal log-linear phase will be determined from a minimum of 3 concentration-time data points, and will be verified with the r^2 value.
Tmax	Observed directly from data.
CLIP	Dose *I* AUCinf
CLsslF	Dose *I* AUC"s
t½"	ln21ke1
VJP	Dose/ (AUCinrkei)
V.p•	Dose/(AUC.·k.1)
Rae	AUc.lAUC1as1

• if data pemut

The actual time of sample collection will be used in PK parameter calculation. In the event that the actual sampling time is not available, the nominal time may be used if there is no evidence that the actual sampling time deviates substantially from the nominal time.

The single dose and steady state PK parameters will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometi·ic mean and its associated CV) by dose, cycle and day.

Pharmacokinetic/Pharmacodynamic (PK/PD) Correlation

PK and PD 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-06873600 exposure and biomarkers or significant safety endpoints. The results of these analyses, if peifonned, may be reported separately.

9.2.2.3. Biomarker Analyses

Level of pha1macodynamic (PD) markers, pRb and Ki67 from each dose will be analyzed at two time points, at screening and at cycle 2 day 1 of each patient. Percent changes of biomarkers at Cycle 2 Day 1 from Screening (baseline) will be calculated and summarized; actual biomarker levels will be listed by visit.

Summruy statistics for percentage change from baseline of biomru·ker level may include geometi-ic mean, 95% confidence interval, median, and minimum/maximum. Other explorato1y biomru·kers analyzed with the remaining tumor specimens will be described in the biomarker Statistical Analysis Plan (bSAP).

9.2.3. Safety Analyses

9.2.3.1. Adverse Events

Adverse Events (Aes) will be graded by the investigator according to the CTCAE version 4.03 and coded using the Med.ORA. The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, treatment related SAE, and any AEs leading to dose intenuptions, dose reductions, chug discontinuations, and/or death will be summarized according to worst toxicity grades. The summaries will present AEs based on the entire study period (all cycles). The Safety Analysis Set will be used.

9.2.3.2. Laboratory Tests Abnormalities

The number and percentage of patients who experienced laborato1y test abnonnalities will be summarized according to worst toxicity grade observed for each laborato1y test. The analyses will summarize laborato1y tests based on the entire study period (all cycles). Shift tables will be provided to examine the distribution of laborato1y abnonnalities, and worst on-study abnonnalities will be summarized. The Safety Analysis Set will be used.

For laborato1y tests without CTC grade definitions, results will be categorized as nonnal, abnonnal high/low or not done.

9.2.3.3. Vital Signs

Vital signs data will be presented as summaries for change from baseline and as categorical summaries for absolute value, decrease and increase from baseline. The Safety Analysis Set will be used.

9.2.3.4. Electrocardiogram

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

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

QT intervals will be corrected for hea1t rate (QTc) using standard correction factors (ie, Fridericia's and possibly a study specific factor). Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF and QTcB by treatment and dose. fudividual QTc (QTcF and QTcB) intervals will be listed by compound, time and dose. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTcF value and changes from baseline in QTcF 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. Categorical outlier analysis of the QTcF data will be conducted and summarized as follows:

- The number of patients with maximum change from baseline in 30ms < QTcF 60 ms, QTcF > 60 ms.
- The number of patients with maximum post-dose (post-baseline) 450ms QTcF 480 ms, 481 QTcF 500 ms and QTcF 501 ms.

fu addition, the number of patients with coITected and uncoITected QT values501 msec will be summarized.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction methods will be used) using maximum CTCAE (version 4.03) *Grade. Shift tables will also be provided for ECG abnormality at baseline vs on treatment (yes, no, not done: (n, %)). Patients experiencing clinically relevant morphological ECG changes will be summarized (includingfrequency and percentage).*

If more than one ECG is collected at a nominal time post dose (for example, ti·iplicate 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 QTcF value501 msec, but the mean of the ti·iplicates is no501 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the501 msec value in appropriate clinical context. However, values from individual tracings within ti·iplicate measurements that are500 msec will not be included in the categorical analysis unless the average from those u-iplicate measurements is also500 msec. Changes from baseline will be defined as the change between QTcF post dose from Day 0, or the pre-dose values on Day 1.

The effect of chug concenti·ations on QTcF change from baseline will be explored graphically. fu addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QTcF interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of subject factors (covariates) on the relationship will be examined.

Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

Changes from baseline for the ECG parameters QT interval, heali rate (HR), QTc interval, PR interval and QRS interval will be summarized by coho1t and timepoint. Categorical data analysis will follow Appendix 1.

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.

Patient discontinuation from ti·eatment 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 histo1y, ECOG peifonnance status, HER2 status, and prima1y diagnosis will be tabulated and listed. For ECOG perfo1mance 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 28 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 cmTent cycle staiis later than 28+3 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) compai·ed to the planned total daily dose upon enrollment.

fun-a-patient dose escalation is not allowed in this study. The following will be smrunai·ized by patient for each dose level:

- Number of subjects per dose level
- Median and range of number of cycles staiied per subject
- Number(%) of subjects staiiing a cycle (1, 2, 3...)
- Number(%) of subjects with cycle delays
- Number (%) of dose inte1n1ptions (include both known and unknown dates)
- Number(%) of subjects with dose reductions
- Number (%) of each reason (AE vs. Other) for cycle delays, dose intenuptions and dose reductions
- Time on u-eatinent (median, range)

The following will be smmnai·ized by cycle received for each dose level:

- Total number of cycles staiied
- Number of cycles staiied 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 inte1n1ption (median, range)

The following will be smmnai·ized for cumulative dose by dose level and cycle:

- Summruy statistics (mean, median, standru·d deviation and range) of cumulative dose and percent of staiiing dose (compai·ed to Day **1** dose of each cycle)

Listings by patient (ordered by dose level): staii 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 (yes/no), number of missed doses with unknown dates, reason for any dosing changes will be provided.

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 intenuption (yes/no) will be provided.

Prior, Concomitant, and Further Therapies

Prior, concomitant, and further therapies (diug and non-diug treatments) will be coded by the World Health Organization (WHO) medical dictiona1y. Listings of prior, concomitant, and fmther therapies will be provided separately.

10. REFERENCES

Brookmeyer R, Crowley JJ. A confidence interval for the median smvival time. Biometrics 1982; 38:29-41.

E.A. Eisenhauer, P. Therasseb, J. Bogae1is, L.H. Schwaiiz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankru·, L. Dodd, R. Kaplan, D. Lacombe, J. Ve1weij: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Jomnal of Cancer 45 (2009) 228-247

ICH E14 - The clinical evaluation of QT/QTc inte1val prolongation and proaIThythmic potential for non-antianhythmic di11gs. CHMP/ICH/2/04.

Kaplan EL, Meier P. Nonpai·ametric estimation from incomplete obse1vations. J Am Stat Assoc 1958; 53:457-481.

NCI Common Terminology Criteria for Adverse Events v4.03 (CTCAE). https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/

11. APPENDICES

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

Categories for QTcF

QTcF(ms)	450< max. <480	481< max. <500	max. >501
QTcF(ms) change from baseline	30<max. '.S60	max. >60	

Categories for PR and QRS

PR(ms)	max>300	
PR (ms) increase from baseline	Baseline >200 and max. >25% increase	Baseline '.S200 and max. c:::50% mcrease
ORS (ms)	max>200	
QRS (ms) increase from baseline	Baseline >100 and max. >25% increase	Baseline '.Sl00 and max. c:::50% mcrease

Categories for Vital Signs

Svstolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease c:::30	max. increase c:::30
Diastolic BP (mm Hg)	min. *<50*	
Diastolic BP (mm Hg) change from baseline	max. decrease c:::20	max. increase c:::20
Supine pulse rate (born)	min. <40	max. >120

Measurements that fulfil these criteria are to be listed in the study repo1t.

11.2. APPENDIX 2: RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

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

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 Illill or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.

- Superficial lesions with longest diameter 10 rmn or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 rmn or greater when assessed by CT.

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

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with sho1i axis between 10 and 14.9 rmn) and tiuly non-measurable disease such as pleural or pericardia! effusions, ascites, inflarmnato1y breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

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

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are prefened as target lesions.
- Nonnal nodes: Nodes with sho1i axis <10 mm are considered nonnal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study sta1i. For an adequate baseline assessment, all required scans must be done within 28 days prior to randoinization and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be non-evaluable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, sho1i axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments perf01med on study.

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

- Measurements for tai·get lesions that become small should continue to be recorded. If a tai·get lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; othe1wise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 nun (no1mal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements ai·e not required but rather assessments will be expressed as CR, Non-CR/Non-PD, PD, Non-evaluable (NE). Multiple non-tai·get lesions in one organ may be recorded as a single item on the case repo1i fo1m (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target Disease

1. Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All tai·get nodes must decrease to n01mal size (sho1i axis <10 mm). All tai·get lesions must be assessed.

2. Paiiial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The sho1i diameter is used in the sum for tai·get nodes, while the longest diameter is used in the sum for all other tai·get lesions. All tai·get lesions must be assessed.

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

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

5. Non-evaluable (NE): Progression has not been documented, and

   - One or more target measurable lesions have not been assessed; or
   - One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or
   - One or more target lesions were excised or i1rndiated.

Non-target disease

6. CR: Disappearance of all non-target lesions and n01malization of tumor marker levels. All lymph nodes must be 'nonnal' in size (<10 mm sho1i axis).

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

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

9. NE: Progression has not been dete1mined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

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

Supplemental Investigations

- If CR dete1mination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

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

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be repo1ied as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Eve1y effo1i should be made to document objective progression even after discontinuation of treatment.

Table 4 Objective Response Status at each Evaluation

Tarn:et Lesions	Non-tarn:et Disease	New Lesions	Obiective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE or Missing	No	PR
PR	Non-CR/Non-PD, NE or Missing	No	PR
SD	Non-CR/Non-PD, NE or Missing	No	Stable
NE or Missing	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table 5 Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

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

Best Overall Response

The best overall response (BOR) is the best response recorded from the randomization until disease progression or death due to any cause. This is derived from the sequence of objective

statuses. Objective statuses are not considered after objective progression is documented or after sta1t of the first anticancer treatment post discontinuation of protocol treatment. BOR for each patient will be derived as one of the following categories.

- **Complete response (CR):** At least one objective status of CR documented before progress10n.
- **Partial response (PR):** At least one objective status of PR documented before progress10n.
- **Stable disease (SD):** At least one objective status of stable documented at least 8 weeks after randomization date and before progression but not qualifying as CR, PR.
- **Progressive Disease (PD):** Objective status of progression within 16 weeks of randomization, not qualifying as CR, PR or SD.
- **Non-evaluable (NE):** Progression not documented within 16 weeks after randomization and no other response catego1y applies.

Appendix 1. List of High Risk Medications for QTc Prolongation

Antianhythmics:	Miscellaneous:
• amiodarone • disopyramide • dofetilide • ibutilide • procainamide • quinidine • sotalol	• arsemc • cisapride • droperidol • thioridazine • pentamidine

Adapted from:
https://cpnp.org/sites/default/files/shared/2013/QTc_Prolongation_Med_Managment_Guideline.doc Regions Guidelines for Managing Medications and QTc prolongation.

11.3. APPENDIX 3: CENSORING DETAILS

Table 6 Progression Free SU1vival and Dmation of Response

Situation	Date of Progression/Censoring[1]	Outcome
Inadeauate baseline assessment	Sta1t date (ClDl)	Censored
No on-studv assessments	Sta1t date (ClDl)	Censored
Alive, on treatment[2] and no Progression	Date oflast objective tumor assessment	Censored
Progression Documented on or betv.•een 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 oflast objective tumor assessment prior to discontinuation[2]	Censored
Treatment discontinuation due to toxicity or other reason	Date oflast 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 oflast objective tumor assessment prior to the event	Censored
Ongoing at time of study tel'lllination by sponsor	Date of study tennination	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 7 Time to Progression

Situation	Date of Progression/Censoring[1]	Outcome
Inadeauate baseline assessment	Sta1t date (ClDl)	Censored
No on-study assessments	Sta1t date (ClDl)	Censored
Alive, on treatment[2] and no Progression	Date oflast objective tumor assessment	Censored
Progression Documented on or betv.re.en 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 oflast objective tumor assessment prior to discontinuation[2]	Censored
Treatment discontinuation due to toxicitv or other reason	Date oflast objective tumor assessment prior to discontinuation[2]	Censored
New anticancer treatment <28 days after discontinuation of treatment without progression	Date oflast objective tumor assessment prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Sta1t date (ClDl)	Censored
Death without objective progression prior to treatment discontinuation[2]	Date oflast objective tumor assessment prior to death	Censored
Progression after 2 or more missed	Date oflast obiective tumor assessment	Censored

tumor assessments	orior to the event	
Ongoing at time of study termination by sponsor	Date of study tennination	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.