PROTOCOL B7971001

PHASE 1/2 OPEN-LABEL STUDY OF PF-06747775 (EPIDERMAL GROWTH FACTOR RECEPTOR T790M INHIBITOR) IN PATIENTS WITH ADVANCED EPIDERMAL GROWTH FACTOR RECEPTOR MUTANT (DEL 19 OR L858R ± T790M) NON-SMALL CELL LUNG CANCER

STATISTICAL ANALYSIS PLAN

(SAP)

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is Version 3.0. New study cohorts are incorporated in the protocol amendment 3 (dated Sept 20, 2016).

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol B7971001. 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 main analysis plan will be described in the Clinical Study Report.

2.1. Study Design

This is a Phase 1/2 study of PF-06747775 as a single agent and in combination with other cancer treatments in patients with advanced EGFRm non-small Cell lung cancer (*NSCLC*). *The overall clinical study consists of a Phase 1 single agent dose-escalation and expansion part to determine the* recommended Phase 2 dose (*RP2D*) *of PF-06747775 single agent in patients with previously-treated EGFRm NSCLC followed by sequential evaluations of PF-06747775 at the RP2D in 3 different clinical scenarios as detailed below:*

- *Cohort 1: Phase 2 evaluation of PF-06747775 as a single agent in previously untreated patients with advanced EGFRm NSCLC;*

- *Cohort 2: Phase 1b single arm evaluation of PF-06747775 in combination with palbociclib (Cohort 2A) followed by Phase 2 randomized evaluation of PF-06747775 in combination with palbociclib vs PF-06747775 single agent (Cohort 2B) in previously-treated patients with EGFRm NSCLC with a secondary T790M mutation (del 19 and T790M or L858R and T790M); and*

- *Cohort 3: Phase 1b evaluation of PF-06747775 in combination with avelumab for previously-treated patients with EGFRm NSCLC with a secondary T790M mutation (del 19 and T790M or L858R and T790M).*

Cohorts 2A and 3 will determine the RP2D of PF-06747775 in combination with either palbociclib or avelumab, respectively, based on safety and tolerability. Patients will be treated at dose level 1 (DL1) of the combination as noted in Table 14 of the protocol *(Cohort 2A) and Table 17* of the protocol *(Cohort 3). If the initial doses tested are tolerated, that will be the combination dose selected. Determination of the RP2D will be performed using the mTPI design as described in Section 2.1.3.1* of the protocol *(Cohort 2A) and* Section 2.1.4 of the protocol *(Cohort 3).*

For Cohort 2A, after determination of the RP2D for the PF-06747775 and palbociclib combination, a randomized evaluation of the combination vs PF-06747775 single agent (2:1 ratio) will be initiated (Cohort 2B). For Cohort 3, after determination of the RP2D for the PF-06747775 and avelumab combination, the dose level will be expanded to enroll an overall total of approximately 20 patients to further explore the safety, PK, and antitumor activity of the combination.

2.1.1. *Phase 1*

The Phase 1 part of this study is an open label, multi-center, multiple dose, non-randomized, safety, PK, CCI *and dose escalation study of PF-06747775 as a single agent in patients with advanced EGFRm NSCLC (del 19 or L858R, +/- T790M). PF-06747775 will be administered in successive cohorts as a single agent in 21-day cycles. The dose-escalation portion of Phase 1 includes a single dose lead-in period to assess single dose PK of PF-06747775, followed by continuous once daily dosing in a 21-day cycle. The Continual Reassessment Method (CRM) will be used to guide the dose assignment and estimate the* maximum tolerated dose (*MTD*) *based on cumulative data on* dose-limiting toxicities (*DLTs*) *in the first cycle.*

The target probability of dose-limiting toxicities *(DLTs) at the MTD will be 30%. The MTD will be the highest dose with ≤30% of patients experiencing a DLT for a 10 patient cohort. Approximately 36 patients will be treated during the dose escalation part of the study. An MTD expansion of up to 10 additional patients for the determination of the RP2D will be undertaken to better define the safety and provide enhanced early efficacy information.*

Phase 1 will also include a series of PK sub-studies:

1. *A sildenafil sub-study (PF-06747775 will be the CYP3A4 inducer/inhibitor and sildenafil the CYP3A4 substrate).*

2. *A food-drug and a CYP3A4 drug-drug interaction PK sub-study (CYP3A4 induction interaction with rifampin).*

3. *An antacid-drug and a CYP3A4 drug-drug interaction PK sub-study (CYP3A4 inhibition interaction with itraconazole).*

The sildenafil sub-study will be performed in the RP2D expansion cohort. RP2D may coincide with the MTD or could be lower than MTD as other factors might be taken into consideration when deciding the RP2D. In any case, the assessment of the potential CYP3A4 inhibitory effect of PF-06747775 at a dose that might be greater than the RP2D will not impact the estimation of the CYP3A4 inhibitory effect of PF- 06747775, on the contrary, it will show the maximum inhibitory effect that can be achieved at the RP2D. The dose selected for further development will undergo a series of sub-studies at the selected recommended RP2D to fully characterize the impact of food, antacid and CYP3A4 inhibitors/inducers.

Approximately 70 patients are expected to be enrolled in the Phase 1 part of the study. Approximately 36 patients will be enrolled into the dose escalation of the Phase 1 portion, depending on toxicity observed. At the MTD, up to an additional 10 patients will be enrolled to confirm the RP2D and participate in the sildenafil sub-study. Additional patients (approximately 24) will be enrolled at the RP2D to complete the drug-drug interaction (DDI), food and antacid effects studies. The sequencing of these studies relative to other portions of this protocol may be adjusted.

2.1.2. *Cohort 1: Phase 2 Evaluation of PF-06747775 Single Agent in Previously Untreated Advanced EGFRm NSCLC*

Upon determination of the RP2D of single-agent PF-06747775, Cohort 1 will be initiated. Cohort 1 of the study is an open-label, multi-center, single-arm Phase 2 evaluation of PF-06747775 single agent at RP2D in previously untreated patients with advanced EGFRm (del 19 or L858R, with or without T790M) NSCLC.

2.1.3. *Cohort 2: Phase 1b/2 Evaluation of PF-06747775 Plus Palbociclib*

Cohort 2 will be initiated upon completion of the antacid effect and itraconozole DDI PK sub-study. Cohort 2 of the study consists of a Phase 1b single-arm evaluation of the safety, PK, and CCI *of the RP2D of PF-06747775 in combination with palbociclib (Cohort 2A) followed by a Phase 2 randomized evaluation of antitumor activity and safety of the combination vs PF-06747775 single agent (Cohort 2B) in patients with previously-treated advanced EGFRm NSCLC (del 19 and T790M or L858R and T790M).*

2.1.3.1. Cohort 2A

Cohort 2A will evaluate PF-06747775 200 mg PO daily in combination with palbociclib continuous daily dosing in 21 day cycles to determine the RP2D. The starting dose (DL1) for palbociclib will be 100 mg PO daily.

2.1.3.2. Cohort 2B

Phase 2 Cohort 2B will be initiated once the RP2D of the PF-06747775 and palbociclib combination is determined. Approximately 39 patients with previously-treated advanced EGFRm NSCLC (del 19 and T790M or L858R and T790M) will be randomized in a 2:1 ratio to receive either the PF-06747775 plus palbocicib combination or PF-06747775 single agent. Patients will be treated continuously on a 21 day cycle with both agents and evaluated per the Schedule of Activities (SOA).

Approximately 49 patients will be enrolled to test in Cohort 2 (up to 10 patients in Cohort 2A and 39 patients [26 PF-06747775 plus palbociclib and 13 PF-06747775 single agent] in Cohort 2B).

2.1.4. *Cohort 3: Phase 1b Evaluation of PF-06747775 Plus Avelumab*

Cohort 3 will be initiated upon completion of enrollment to Cohort 2. Cohort 3 of the study consists of a Phase 1b single-arm evaluation of the safety, and PK to determine the RP2D of PF-06747775 in combination with avelumab 10 mg/kg Q2W in patients with previously-treated with advanced EGFRm NSCLC (del 19 and T790M or L858R and T790M).

The starting dose levels (DL1) for the Cohort 3 combination are PF-06747775 200 mg PO daily and avelumab 10 mg/kg IV Q2W in 4 week cycles.

2.2. Study Objectives

2.2.1. *Phase 1*

2.2.1.1. Primary Objective

- *To evaluate safety and tolerability at increasing dose levels of PF-06747775 as a single agent in order to estimate the MTD and RP2D in patients with advanced EGFRm NSCLC (del 19 or L858R, with or without T790M) following ≥1 prior line of therapy, which must have included an approved EGFR TKI.*

2.2.1.2. Secondary Objectives

- *To evaluate the overall safety profile of PF-06747775;*
- *To characterize the effects of single-agent PF-06747775 on QTc intervals;*
- *To characterize single dose and steady state PK profiles of single-agent PF-06747775;*
- *To evaluate the effect of PF-06747775 at steady state on the exposure of a single dose of sildenafil, a CYP3A4 probe;*
- *To characterize the effect of food on the exposure of PF-06747775 at the RP2D;*
- *To characterize the effect of esomeprazole, a proton pump inhibitor, on the exposure of PF-06747775 at the RP2D;*
- *To characterize the effect of itraconazole, a strong CYP3A4 inhibitor on the exposure of PF-06747775 at the RP2D;*
- *To characterize the effect of rifampin, a strong CYP3A4 inducer on the exposure of PF-06747775 at the RP2D;*
- *To assess in plasma the presence/absence of EGFR mutations;*
- *To evaluate the anti-tumor activity of PF-06747775 in both T790M-positive and T790M-negative NSCLC tumors;*
- *To evaluate tumor tissue biomarkers including, but not limited to, EGFR mutation by next generation sequencing.*

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2.2.2. *Phase 1b/2*

2.2.2.1. Primary Objectives

2.2.2.1.1. *Cohort 1 – PF-06747775 Single-Agent in Patients with Previously Untreated EGFRm NSCLC*

- *To assess the anti-tumor activity (*objective response rate [*ORR*]*) of PF-06747775 single agent in patients with EGFRm NSCLC (del 19 or L858R, with or without T790M).*

2.2.2.1.2. *Cohort 2A – PF-06747775 Plus Palbociclib: Dose Finding*

- *To evaluate safety and tolerability and determine the RP2D of PF-06747775 plus palbociclib in patients with EGFRm NSCLC with a secondary T790M mutation (del 19 and T790M or L858R and T790M).*

2.2.2.1.3. *Cohort 2B – PF-06747775 Plus Palbociclib vs PF-06747775 Single Agent (Randomized)*

- *To assess the* progression-free survival (*PFS*) *of PF-06747775 plus palbociclib versus PF-06747775 single agent in patients with EGFRm NSCLC with a secondary T790M mutation (del 19 and T790M or L858R and T790M).*

2.2.2.1.4. *Cohort 3 –PF-06747775 Plus Avelumab: Dose Finding*

- *To evaluate safety and tolerability and establish the RP2D of PF-06747775 plus avelumab in patients with EGRm NSCLC with a secondary T790M mutation (del 19 and T790M or L858 R and T790M).*

2.2.2.2. Secondary Objectives

- *To assess duration of response (DOR), and* overall survival (*OS*) *probability at 24 months (all Cohorts);*

- *To assess PFS (Cohort 1, Cohort 2A, and Cohort 3);*

- *To further characterize the* adverse event (*AE*) *profile of PF-06747775 when given as a single agent (Cohort 1 and Cohort 2B) and in combination with palbociclib (Cohort 2A and 2B) and avelumab (Cohort 3);*

- *To further characterize PF-06747775 PK when given as a single agent (Cohort 1 and Cohort 2B) and in combination with palbociclib (Cohort 2A and 2B) and avelumab (Cohort 3);*

- *To characterize the PK of palbociclib in combination with PF-06747775 (Cohort 2A and 2B);*

- *To characterize the PK of avelumab in combination with PF-06747775 (Cohort 3);*

- *To further explore the effects of PF-06747775 on QTc intervals when given as a single agent (Cohort 1 and Cohort 2B) and in combination with palbociclib (Cohort 2A and 2B) and avelumab (Cohort 3);*
- *To assess in plasma the presence/absence of EGFR mutations (All Cohorts);*
- *To assess tumor markers of sensitivity and/or resistance to PF-06747775 (All Cohorts);*
- *To assess the immunogenicity of avelumab when given in combination with PF-06747775 (Cohort 3).*

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3. INTERIM ANALYSES, FINAL ANALYSES, AND UNBLINDING

This is an open label study therefore unblinding is not applicable. There is no formal interim analysis planned for this study.

The final analysis for the clinical study report will be done after all patient data have been submitted and cleaned, unless other arrangements are agreed upon by the Sponsor. The analysis will be performed at the time of official data base release.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There is no formal hypothesis testing for any phases or cohorts of the study.

4.2. Statistical Decision Rules

Phase 1:

In Phase 1 dose finding part of the study, the doses of PF-06477775 will be assigned to each enrolled patient using a CRM (O'Quigley el al, 1990). Statistical decision rules at the dose escalation/de-escalation stage will be discussed in detail in Section 8.1.

Phase 1b Cohort 2Aand Cohort 3:

In Cohorts 2A and 3**,** dose finding will follow the mTPI method (Ji Y el al, 2010) with adjustments using DLT rate. Statistical decision rules at the dose escalation/de-escalation stage will be discussed in detail in Section 8.1.

5. ANALYSIS POPULATIONS

Patients not enrolled to the study (ie, screen only patients) will not be included in any analysis.

5.1. Full Analysis Set

The full analysis set includes all enrolled patients. For Cohort 2B, the full analysis set will include all patients who are randomized. Patients will be classified according to the treatment assigned at randomization.

5.2. Safety Analysis Set

The safety analysis set includes all enrolled patients who receive at least one dose of study treatment. For Cohort 2B, patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case patients will be classified according to the first treatment received.

5.3. QTc Evaluable Analysis Set

QTc evaluable analysis set will include all treated subjects who had at least 1 ECG assessment undertaken pre-dose and 1 post dose at steady state in triplicate.

All ECGs obtained during the study will be evaluated for safety. ECG assessments will be documented by principal investigator at the site and by independent review (central read).

5.4. QTc-PK Evaluable Analysis Set

QTc-PK evaluable analysis set will include all treated subjects who had at least 1 ECG assessment undertaken pre-dose and 1 post dose at steady state in triplicate paired with a PK collection sample and resulting treatment concentration.

All ECGs obtained during the study will be evaluated for safety.

5.5. Per Protocol Analysis Set (Phase 1, and Cohorts 2A and 3)

For Phase 1/1b, the per protocol analysis set (evaluable for MTD/dose selection) includes patients who are eligible, receive study treatment and who either experience a DLT during

the first cycle of PF-06747775 or PF-06747775 plus avelumab or the first 2 cycles of PF-06747775 plus palbociclib, or complete the DLT observation period with no DLT. *Patients with major treatment deviations during the DLT observation period other than treatment related toxicity are not evaluable for the MTD/dose selection assessment and will be replaced as needed to permit MTD/dose selection estimation.*

5.6. Response Evaluable Analysis Set

The response evaluable analysis set will include all patients who received at least one dose of study medication, have measurable disease and adequate baseline assessment, and at least 1 post-baseline assessment during the study. For Cohort 2B, all randomized patients will be used. In the Phase 1b/2 portion of the study, patients must have T790M-positive NSCLC to be evaluable for response rate determination for the decision rules used in the study. Patients enrolled into Cohort 1 of the Phase1b/2 portion of the study are not required to have T790M-positive NSCLC.

5.7. PK Analysis Sets

The PK concentration population is defined as all treated patients who have at least one concentration in at least 1 treatment period for a particular analyte (ie, PF-06747775, sildenafil, palbociclib, or avelumab).

The PK parameter analysis population is defined as all treated patients who have sufficient information to estimate at least 1 of the PK parameters of interest for a particular analyte.

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5.9. Immunogenicity Analysis Set (Phase 1b Cohort 3 only)

The immunogenicity analysis set is a subset of the safety analysis set and will include patients who have at least one Anti-drug antibodies/neutralizing antibodies (ADA/Nab) sample collected for avelumab.

5.10. 4-β-Hydroxycholesterol and Cholesterol Analysis Set (Phase 1 only)

The analysis set for the ratio of blood 4-β-hydroxycholesterol/cholesterol concentration will include patients who have both measurable 4-β-hydroxycholesterol and cholesterol concentrations from at least 1 visit or treatment period.

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5.12. Treatment Misallocations

For Cohort 2B see Section 5.1 and 5.2.

5.13. Protocol Deviations

All deviations will be described when they appear and relate to the statistical analyses or analysis populations.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoints

Assessment of response will be made using RECIST version 1.1 (Appendix 3). All response statuses will be based on investigator assessment.

For the purposes of the definitions of endpoints, the term "on treatment" includes the period from the date of the first dose until 28 days after the last dose of each patient.

Start date for a patient is date of first treatment (if treatment start date is not available, date of enrollment is used) all cohorts (excluding Cohort 2B) and date of randomization for Cohort 2B.

- **Confirmed Overall response rate (ORR)** is defined as complete response (CR) or partial response (PR) according to RECIST 1.1 that must be confirmed ≥4 weeks later. Patients who do not have an on-treatment radiographic tumor assessment due to early progression, who receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR. Each patient will have an objective response status (0: no ORR; 1: ORR) and ORR) will be calculated as the percentage of patients with a confirmed CR or PR relative to the total number of response evaluable patients (which is defined as all randomized patients for Cohort 2B).

  - **CR**: Two objective statuses of CR a minimum of four weeks apart documented before progression and start of new anti-cancer therapy.

  - **PR**: Two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of four weeks apart documented before progression and start of new anti-cancer therapy, but not qualifying as CR. Sequences of PR- Stable- PR are considered PRs as long as the two PR responses are observed at a minimum of 4 weeks apart.

  - **SD**: At least one objective status of stable or better documented at least 6 weeks after start date and before progression and the start of new anti-cancer therapy but not qualifying as CR or PR.

  - **PD:** Progression documented within 12 or 16 weeks (for Cohort 3) after start date and not qualifying as CR, PR or SD

  - **Not Evaluable (NE):** All other cases. Note that reasons for NE should be summarized and the following reasons could be used:

    Early death (death prior to 6 weeks after start date)

No post-baseline assessments

All post-baseline assessments have overall response NE

New anti-cancer therapy started before first post-baseline assessment

SD too early (<6 weeks after start date)

PD too late (>12 or 16 weeks [for Cohort 3] after start date)

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

- All response statuses will be based on investigator assessment

  In Phase 1 part of the study, both confirmed and unconfirmed OR for patients with measurable diseases will be assessed.

- **Best Overall Response (BOR)** is the best response recorded from start date until disease progression or start of new anti-cancer therapy. For a patient to be called having a BOR of Stable Disease (SD), the patient must maintain the status of stable disease for at least 6 weeks after starting treatment as documented by a tumor assessment at or beyond this time point. The definition of overall response status at each assessment follows RECIST v1.1.
- **Duration of Response (DoR)** is measured in patients with an objective response from the time measurement criteria are first met for CR/PR (whichever occurs first) until the first date that progressive disease, or death (whichever occurs first) is objectively documented. If tumor progression data include more than 1 date, the first date will be used. Censoring for DoR is identical to the censoring rules presented for Progression-Free Survival (PFS) below when patients have at least 1 on study disease assessment.

  DoR (months) = [progression/death date – first date of OR +1]/30.4

- **PFS** is defined as the time from the start date to the date of the first documentation of PD or death due to any cause. In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 6 or 8 weeks (Cohort 3) until documented disease progression, start of a new anti-cancer treatment, death or lost to follow-up. The allowable time window for disease assessments is ±1week. Therefore time without adequate assessment is defined as 12 or 16 weeks (Cohort 3) plus 2 weeks. Therefore PD or death within 14 or 18 weeks (Cohort 3) of the last adequate tumor assessment will be counted as an event according to the tumor assessment date or date of death, as appropriate. For patients who do not have an adequate baseline tumor assessment or who do not have any post-baseline tumor assessments, censoring will occur on the start date unless death occurred on or before the time of the second planned tumor assessment (ie, on or before week 14 or 18 [Cohort 3]) in which case the death will be considered an event. In addition, if a new anti-cancer therapy is started prior to an event, the patient will be censored on the date of the last adequate tumor assessment that documented no progression prior to the start of the new anti-cancer therapy.

PFS (in months) will be calculated as (first event date – start date +1)/30.4.

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

- **Six-Month PFS** is defined as the PFS probability at six months based on Kaplan-Meier estimate.
- **Overall Survival (OS)** is defined as the time from the start date to date of death due to any cause. In the absence of confirmation of death (see the paragraph below for survival follow-up), survival time will be censored at the last date the patient was known to be alive.

  All patients should continue to be followed every 2 months. It is understood that not all patients will be available for continued clinic visits; however, every attempt should be made to collect survival information (alive or dead and date of last contact or death). This information may be obtained by telephone interview if the patient is unable to visit the clinic.

- **Two-Year Survival** is defined as the OS probability (alive, or not) at 2-years based on the Kaplan-Meier estimate.

6.2. Safety Endpoints

6.2.1. DLT (Phase 1 only)

Severity of adverse events will be graded according to CTCAE v 4.03. Adverse events meeting one of the definition criteria in protocol Section 3.2 occurring in the first cycle of treatment of PF-06747775, or PF-06747775 plus avelumab, or the first 2 cycles of PF-06747775 plus palbociclib, not related to progressive disease and attributable to PF-06747775 (Cohort 1) or that are attributable to one, the other or both compounds in Cohort 2A (PF-06747775 plus palbociclib) and Cohort 3 (PF-06747775 plus avelumab), respectively, will be classified as DLTs.

DLT is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dose level is used to estimate the MTD. AEs constituting DLTs will be listed by dose level.

6.2.2. Adverse Events

AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment Emergent Adverse Events

All deaths, regardless of cause, will be summarized from treatment start until 28 days after the last dose. Non-fatal events occurring after treatment start regardless of causes, will be summarized up until 28 days after the last dose or until start of new anti-cancer treatment,

whichever is first. Disease progression is not considered a treatment emergent adverse event unless the patient dies of disease within 28 days after the last dose. Events that are continuations of baseline abnormalities are considered treatment emergent adverse events only if there is an increase in grade over baseline, or if there is an increase following a decrease during the study.

Treatment Related Adverse Events

Treatment emergent adverse events will be summarized with causality related to treatment as judged by the investigator. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be due to treatment.

Immune-related Adverse Events (irAE)

For Cohort 3, irAEs are identified according to a pre-specified search list of MedDRA preferred terms, documented in the Safety Review Plan and finalized for analysis prior to database lock.

Infusion-related Reactions (IRR)

For Cohort 3, IRRs are identified by 3 preferred terms (infusion related reaction, drug hypersensitivity, and anaphylactic reaction) occurring on the date of the infusion of avelumab (not prior to infusion of avelumab) or the day following study drug infusion.

6.2.3. Laboratory Abnormalities

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

6.2.4. ECG Results

For Phase 1, changes in QTc (QTcB, QTcF, and/or QTcS) from baseline to Day 11 of Cycle 1 and Day 1 of Cycles 2-4 will be used to characterize the potential effect of PF-06747775 on the QT interval with QTcF being the primary correction method. The baseline for Phase 1 is defined as the ECGs recorded on Day -8 pre-dose.

For Phase 1b/2, changes in QTc from baseline to Day 11 (Cohort 1) or Day 15 (Cohort 2A, 2B, and 3) of Cycle 1 and Day 1 of Cycles 2-3 (Cohort 3) or 2-4 (Cohort 1, 2A and 2B) will be used to characterize the potential effect of PF-06747775 on the QT interval with QTcF being the primary correction method. The baseline for Phase 1b/2 is defined as the ECGs recorded on Day -4 (Cohort 1) or Day 1 (Cohort 2A, 2B, and 3) pre-dose.

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. For all patients in the QTc evaluable analysis set, individual change in QTc (QTcB, QTcF and/or QTcS) will be calculated for each nominal post-baseline time point. ECG results will be reported by treatment/cohort, and may also be reported by treatment dose.

6.3. PK Endpoints

6.3.1. Phase 1 PF-06747775 PK Endpoints

6.3.1.1. Phase 1 Single and Multiple Dose PK (Dose Escalation)

PK blood samples for the determination of plasma PF-06747775 concentrations will be collected at the times specified in the protocol schedule of activities. PK parameters for PF-06747775 will be determined from the plasma concentration-time data using standard noncompartmental methods and be reported by dose.

PF-06747775 PK parameters for the analysis of single dose and steady state PK are listed in Table 1. Single dose parameters will be assessed on Day - 8 of the lead in period and steady state parameters will be assessed on Day 11 of Cycle 1. Steady state C_{trough} will also be assessed as the pre-dose concentration on Day 1 of Cycle 2-4. Dose-normalized parameters may be reported together for all dose levels.

Table 1. PF-06747775 Single Dose and Steady State Parameters

Parameter	State	Analysis Scale	Summary
AUC_{last}	sd	ln	D
AUC_{inf}*	sd	ln	D
AUC_{24}	sd	ln	D
AUC_{tau}	ss	ln	D
C_{max}	sd, ss	ln	D
T_{max}	sd, ss	R	D
t½*	sd	R	D
C_{trough}	ss	ln	D
CL/F*	sd, ss	ln	D
Vz/F*	sd, ss	ln	D
R_{ac}	ss	ln	D
R_{ss}*	ss	ln	D
AUC_{last}(dn)	sd	ln	D
AUC_{inf}(dn)*	sd	ln	D
AUC24(dn)	sd	ln	D
AUC_{tau}(dn)	ss	ln	D
C_{max}(dn)	sd, ss	ln	D
C_{trough}(dn)	ss	ln	D

sd=single dose; ss=steady state; ln=natural-log transformed; R=raw (untransformed); D=displayed with descriptive statistics; *=if data permits; dn=dose-normalized.

6.3.1.2. Multiple Dose PK (MTD Expansion Sildenafil Sub-Study)

PF-06747775 steady state PK parameters for the sildenafil sub-study are listed in Table 1 (excluding R_{ac} and R_{ss}) and will be assessed only on Day 11 of Cycle 1. On Day-8 patients received a single dose of sildenafil followed by continuous daily dosing of PF-06747775 starting on Day 1. On Day 11, patients receive another single dose of sildenafil along with PF-06747775 (steady state) under fasting conditions.

If more than one dose level of PF-06747775 was used for patients in the sub-study, steady state parameters will also be reported by dose, and dose-normalized steady-state parameters will also be reported.

6.3.1.3. Food-PF-0674777 and CYP3A4 Inducer-PF-06747775 Interactions

PF-06747775 PK parameters for the food effect and rifampin sub-study are listed in Table 2 and will be reported by treatment. For the food effect and rifampin sub-study, steady-state PF-06747775 PK parameters will be assessed on Days 8, 9, and 21 of Cycle 1. Days 8 and 9 are PF-06747775 administered alone under fasted or fed conditions according to the randomization schedule; Day 21 is PF-06747775 with rifampin.

6.3.1.4. Antacid - PF-06747775 and CYP3A4 Inhibitor - PF-06747775 Interactions

PF-06747775 PK parameters for the antacid effect and itraconazole sub-study are listed in Table 2 and will be reported by treatment. For the antacid and itraconazole sub-study, steady-state PF-06747775 PK parameters will be assessed on Days 8, 13, and 21 of Cycle 1. Day 8 is PF-06747775 alone, Day 13 is PF-06747775 with esomeprazole, and Day 21 is PF-06747775 with itraconazole. To prevent toxicity, during treatment with itraconazole the dose of concomitant PF-06747775 will be reduced, and relevant steady-state PF-06747775 PK exposure parameters will be dose-normalized for comparison to the reference treatment of PF-06747775 alone, or for any comparison across the 3 treatments in this sub-study.

Note the Days for these sub-studies may be modified based on the PK profile observed during the lead-in period in the earlier portions of the study.

Table 2. PF-06747775 Steady State Parameters for Food Effect/Rifampin and Antaaci/Itraconazole Sub-studies

Parameter	Analysis Scale	Plasma PF-06747775
AUC_{tau}	ln	A, D
C_{max}	ln	A, D
T_{max}	R	D
AUC_{tau}(dn)*	ln	A, D
C_{max}(dn)*	ln	A, D

ln=natural-log transformed; R=raw (untransformed); D=displayed with descriptive statistics; A=analyzed using statistical model; dn=dose-normalized; *=dose-normalized parameters will be used for itraconazole effect comparison to reference treatment of PF-06747775 alone in the antacid/itraconazole sub-study.

6.3.2. Phase 1 Sildenafil PK Endpoints

PK blood samples for the determination of plasma sildenafil concentrations will be collected at the times specified in the protocol schedule of activities for the MTD expansion sildenafil sub-study.

PK parameters for sildenafil will be determined from the plasma concentration-time data using standard noncompartmental methods (Table 3) Single dose parameters will be assessed on Day -8 for sildenafil alone, and on Day 11 of Cycle 1 for sildenafil with PF-06747775.

If more than one dose level of PF-06747775 was used for patients in the MTD expansion sildenafil sub-study, sildenafil PK parameters may also be reported by dose of PF-06747775 assigned.

Table 3. Single Dose Silenafil PK Parameters for Sildenafil Sub-study

Parameter	Analysis Scale	Plasma Sildenafil
AUC_{last}	ln	D
AUC_{inf}*	ln	A, D
C_{max}	ln	A, D
T_{max}	R	D
t½*	R	D
CL/F*	ln	D

ln=natural-log transformed; R=raw (untransformed); D=displayed with descriptive statistics; A=analyzed using statistical model; *=if data permits.

6.3.3. Phase 1b/2 PF-06747775 PK endpoints

6.3.3.1. Phase 2 Single Agent PF-06747775 in Previously Untreated Disease (Cohort 1)

PK blood samples for the determination of plasma PF-06747775 concentrations will be collected at the times specified in the protocol schedule of activities. PK parameters for PF-06747775 will be determined from the plasma concentration-time data using standard noncompartmental methods.

PF-06747775 PK parameters for the analysis of single dose and steady state PK are listed in Table 1 (excluding the dose-normalized parameters). Single dose parameters will be assessed on Day -4 of the lead in period and steady state parameters will be assessed on Day 11 of Cycle 1. Steady state C_{trough} will also be assessed as the pre-dose concentration on Day 1 of Cycle 2-4.

6.3.3.2. Phase 1b Single Arm PF-06747775 in Combination with Palbociclib (Cohort 2A)

PK blood samples for the determination of plasma PF-06747775 concentrations in combination with palbociclib will be collected at the times specified in the protocol schedule of activities. PK parameters for PF-06747775 will be determined from the plasma concentration-time data using standard noncompartmental methods.

PF-06747775 PK parameters for the analysis of steady state PK when given concomitantly with palbociclib are listed in Table 4 and will be assessed on Day 15 of Cycle 1. Steady state C_{trough} will also be assessed as the pre-dose concentration on Day 1 of Cycle 2-4, and both C_{trough} (the pre-dose concentration) and the concentration at 2 hours post-dose (approximate C_{max}) will be assessed on Day 15 of Cycle 2.

If more than one dose level of palbociclib was used in this dose-finding cohort, PF-06747775 PK parameters may also be reported by dose of palbociclib assigned.

All patients in this cohort will receive PF-06747775 and therefore they are eligible to meet the requirements of the PF-06747775 PK analysis set and have PF-06747775 PK reported.

Table 4 . PF-06747775 Steady State Parameters for Single Arm Combination with Palbociclib (Cohort 2A)

Parameter	Analysis Scale	Plasma PF-06747775
AUC_{tau}	ln	D
C_{max}	ln	D
T_{max}	R	D
C_{trough}	ln	D

ln=natural-log transformed; R=raw (untransformed); D=displayed with descriptive statistics.

6.3.3.3. Phase 2 Randomized PF-06747775 in Combination with Palbociclib vs PF-06747775 alone (Cohort 2B)

PF-06747775 steady state C_{trough} (pre-dose concentration) and the concentration at 2 hours post-dose (approximate C_{max}) when given concomitantly with palbociclib will be assessed on Day 15 of Cycle 1 and on Day 1 of Cycle 2-4.

All patients in this cohort will receive PF-06747775 and therefore they are eligible to meet the requirements of the PF-06747775 PK analysis set and have PF-067775 PK reported.

6.3.3.4. Phase 1b PF-06747775 in Combination with Avelumab (Cohort 3)

PF-06747775 steady state C_{trough} (pre-dose concentration) when given concomitantly with avelumab will be assessed on Day 15 of Cycle 1 and on Day 1 of Cycle 2-3.

If more than one dose level of PF-06747775 was used in this cohort, C_{trough} will be reported by dose level, and dose-normalized PF-06747775 C_{trough} may also be reported.

6.3.4. Phase 1b/2 Palbociclib PK Endpoints

PK blood samples for the determination of plasma palbociclib concentrations will be collected as specified in the schedule of activities and PK parameters for palbociclib will be determined using standard noncompartmental methods.

6.3.4.1. Phase 1b Single Arm PF-06747775 in Combination with Palbociclib (Cohort 2A)

Palbociclib PK parameters for the analysis of steady state PK when given concomitantly with PF-06747775 are listed in Table 5 and will be assessed on Day 15 of Cycle 1. Steady state C_{trough} (pre-dose concentration) will also be assessed on Day 1 of Cycle 2-4 and on Day 15 of Cycle 2.

If more than one dose level of palbociclib was used in this dose-finding cohort, palbociclib PK parameters will be reported by dose level, and dose-normalized PK parameters for palbociclib will be reported.

All patients in this cohort will receive palbociclib along with PF-06747775, and therefore they are eligible to meet the requirements of the palbociclib PK analysis set and have palbociclib PK reported.

Table 5. Steady State Parameters for Palbociclib for Single Arm Combination with PF-06747775 (Cohort 2A)

Parameter	Analysis Scale	Plasma Palbociclib
AUC_{tau}*	ln	D
AUC_{last}	ln	D
C_{max}	ln	D
T_{max}	R	D
C_{trough}	ln	D
AUC_{tau}(dn)*	ln	D
AUC_{last}(dn)	ln	D
C_{max}(dn)	ln	D
C_{trough}(dn)	ln	D

ln=natural-log transformed; R=raw (untransformed); D=displayed with descriptive statistics; *=if data permits; dn=dose-normalized. AUC_{last} for palbociclib following multiple doses will be reported since AUC_{tau} may not be estimable given the PK sampling times utilized in the combination study.

6.3.4.2. Phase 2 Randomized PF-06747775 in Combination with Palbociclib vs PF-06747775 alone (Cohort 2B)

Palbociclib steady state C_{trough} (pre-dose concentration) will be assessed on Day 15 of Cycle 1 and on Day 1 of Cycle 2-4.

Only the patients randomized to receive palbociclib along with PF-06747775 will be eligible for the PK analysis set for palbociclib and have palbociclib PK reported.

6.3.5. Phase 1b Avelumab PK Endpoints (Cohort 3)

PK blood samples for the determination of serum avelumab concentrations will be collected as specified in the schedule of activities.

PK parameters for avelumab during Cycle 1 include pre-dose concentration ($C_{trough)}$ and end of infusion peak concentration (C_{max}) and will be assessed on Day 1 and Day 15 of Cycle 1. Multiple dose (steady state) parameters will be assessed on Day 1 of Cycle 2 (C_{trough} and C_{max}) and on Day 1 of Cycle 3 (C_{trough} only). After Cycle 3, C_{trough} will be assessed every 3 cycles thereafter.

Avelumab PK parameters (pre-dose and end of infusion [EOI] serum concentration) may also be reported by presence and/or magnitude (titer) of avelumab ADA/nAb.

If more than one dose level of PF-06747775 was used for patients in this cohort, avelumab PK parameters/serum concentrations may also be reported by dose of PF-06747775 assigned.

6.4. Other Endpoints

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[redacted]

6.4.2. Endpoints for Immunogenicity Data of Avelumab (Phase 1b Cohort 3 only)

Blood samples for the determination of serum anti-drug antibody (ADA) and neutralizing antibody (Nab) levels for avelumab will be collected as specified in the schedule of activities.

ADA/ Nab data will be listed and summarized, with the percentage of patients with positive ADA and neutralizing antibodies. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit.

6.4.3. Endpoints for 4-β-Hydroxycholesterol and Cholesterol (Phase 1 only)

Blood samples for the determination 4-β-hydroxycholesterol and cholesterol concentrations will be collected as specified in the schedule of activities, and the molar ratio of 4-β-hydroxycholesterol: cholesterol will be reported by patient and visit, according to treatment/cohort and dose. The ratio may also be reported in individuals as change in ratio over time compared to baseline or first sample collected.

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6.4.6. Baseline Characteristics

The following baseline characteristics will be presented: age, sex, race, height, weight, performance status, primary diagnosis, time from initial diagnosis to first dose, stage of disease, number of prior systemic therapies, number of prior surgeries, prior radiotherapy (yes/no), and involved disease sites.

6.4.7. Study Treatment Exposure

6.4.7.1. Treatment Exposure

The summary of treatment exposure and compliance for PF-06747775 or palbociclib will include the following information:

- Duration (weeks)
- Cumulative dose (mg)
- Dose intensity (mg/week)

The summary of treatment exposure and compliance for avelumab will include the following information:

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

Detailed algorithm will be presented in Appendix 5.

6.4.7.2. Dose Reductions and Interruptions

Dose reduction is as a day when the actual dose taken is less than the initial prescribed dose for any reason with the exception that a day with total dose administered of 0mg is not considered a dose reduction. Number of patients with at least one dose reduction as well as a breakdown of dose reductions (1 / 2 / 3 / ≥4) will be summarized by treatment /cohort.

A dose interruptions/missed dose is defined as a planned dosing day with 0 mg total dose administered. Number of patients with at least one dose interruption as well as a breakdown of interruptions (1 / 2 / 3 / ≥4) will be summarized by treatment /cohort.

6.4.7.3. Infusion rate reductions

For Cohort 3, the frequency (number and percentage) of patients with at least one infusion rate reduction of 50% or more as well as the frequency of patients with 1, 2, or ≥3 infusion rate reductions of 50% or more will be summarized by treatment.

6.5. Covariates

None.

7. HANDLING OF MISSING VALUES

7.1. Missing Dates

Missing or Partial Death Dates

It is recommended that the database be designed to mandate a complete death date. If there is a record for death, but the date is missing or is partial, it will be imputed based on the last contact date ().

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

Date of Last Dose of Study Drug

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use

the cutoff date for the analysis as the last dosing date. Note: teams should confirm that the patient is actively receiving dose at the time of the data cutoff.

- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the data cutoff date), then impute this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < Month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

Date of Start of New Anti-cancer Therapy

Incomplete dates for start date of new anti-cancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For patients who have not discontinued study treatment at the analysis cutoff date, last dose of study treatment is set to the analysis cutoff date is the imputations below
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is:

  = 31DECYYYY, if only Year is available and Year < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

  = Last day of the month, if both Year and Month are available and

  Year = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

  Month < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

  = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], for all other cases.

Other Missing or Partial Dates

In compliance with Pfizer standards, imputation methods generally apply to partial dates as follows:

- If the day of the month is missing for a start date used in a calculation, the 1st of the month will be used to replace the missing date.
- If both the day and month are missing, the first day of the year is used.
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

These rules are used unless the calculations result in negative time durations (eg, date of resolution cannot be prior to date of onset). In these cases, the resolution and onset dates will be the same and the duration will be set to 1 day.

7.2. Missing Efficacy Endpoint Values

For all efficacy analyses no values will be imputed for missing data, except as specified in Section 6. For ORR, patients with no post-baseline tumor evaluations due to early progression will be counted as non-responders.

7.3. Pharmacokinetics

Concentrations Below the Limit of Quantification

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

Deviations, Missing Concentrations and Anomalous Values

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

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

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

For steady state PK assessment, if a pre-dose PK sample (0 hr or 24 hr) was missed, taken erroneously after dosing, or the reported concentration appears anomalous, the plasma concentration reported for the other pre-dose PK sample (24 hr or 0 hr) from that visit, if available, will be imputed to replace the missing or erroneous pre-dose concentration. This will be done only if deemed appropriate by the PK analyst or clinical pharmacologist in order to allow for steady state PK evaluation.

Pharmacokinetic Parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses. If a PK parameter cannot be derived from a 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 be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level or interruption of daily dosing so that steady-state cannot be assumed), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

7.4. ECG

For analyses using the QTc analysis set, no values will be imputed for missing data except for averaging of triplicate measurements. If one or two of the triplicate measurements for an ECG parameter are missed, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing at a time point for an ECG parameter, no values will be imputed for this time point and no analyses related to this time point will be performed.

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8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Statistical Methods for Dose Escalation/De-escalation

8.1.1.1. CRM (Phase 1)

The Phase 1 portion of this study employs a CRM approach to estimate the MTD. The CRM algorithm utilizes the Bayesian methodology to continuously learn about the dose-toxicity relationship after each cohort's DLT data becomes available. The underlying model assumption is that DLT rate at each dose can be expressed as Pr (DLT|dose x) =f(x, β), where f is a monotonically increasing function in dose x and β is an unknown parameter with prior distribution placed on it at the beginning of the trial. The first two cohorts patients will be assigned to 25 mg/QD and 50 mg/QD respectively if the DLT data warrants dose escalation. After the DLT data of the 25 mg/QD and 50 mg/QD cohorts becomes available (~3 wks), the prior distribution of β is updated based on their DLT responses and becomes a posterior distribution. The current estimate of MTD is calculated and the next cohort's dose assignment is chosen as the dose closest to this estimated MTD but not exceeding it. This process is continued until 1 of the stopping rules below is triggered.

- *Maximum sample size of 36 patients has been reached; or*
- *10 evaluable patients have been treated at the estimated MTD; or*
- *All doses appear to be overly toxic and the MTD cannot be determined in the current trial setting.*

The above described CRM algorithm constantly incorporates additional information about dose-DLT relationship learned from the data via modeling and that is reflected on the projected MTD. By design, such dose allocation procedure will eventually cluster dose assignments around the dose yielding a DLT rate closest to but no more than 30%.

Once one of the aforementioned conditions for stopping the CRM is met, the dose identified as MTD will be evaluated together with information gathered from PK analyses and the overall safety profile in order to determine the RP2D. The dose(s) likely to be considered the RP2D will be expanded to 10 patients if not already tested within the CRM context in order to confirm the RP2D.

Extensive simulation results assessing the CRM properties can be found in O'Quigley et all (1990).

8.1.1.2. mTPI (Phase 1b)

The mTPI design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.30). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to target probability (pT), the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend

de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model.

Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a two-way table (see Appendix 4)*. Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement.*

Decision rules are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as (0; pT-e_1), the overdosing interval (pT+e_2, 1), and the proper-dosing interval (pT- e_1, pT+ e_2), where e_1 and e_2 are small fractions. Based on the expected safety profile of PF-06459988 as a single-agent, e1 is selected as 0.05, and e2 is selected as 0.03. Therefore, the target interval for the DLT rate is (0.25, 0.33).

The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing 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, UPM of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the under-dosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Ji et al. have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

The dose-finding portion of the study uses a modified version of the mTPI design that maximizes the number of evaluable patients treated at each dose to 6 patients. Dose finding is complete when at least 6 evaluable patients have been treated at the highest dose with DLT rate ≤33%. In case de-escalation is required from the initial starting DL1, it is estimated that up to approximately 10-12 DLT-evaluable patients will need to be enrolled to estimate the MTD for the PF-06747775 plus palbociclib combination. For the PF-06747775 plus avelumab combination, up to approximately 10 – 12 patients may be enrolled.

8.1.2. Sample Size Determination

8.1.2.1. Phase 1 Sample Size

Due to the dynamic nature of the Bayesian allocation procedure, the sample size of CRM approach cannot be determined in advance. The maximum sample size is set as 36 for dose escalation cohorts.

In Phase 1 portion of the study, patients will participate in a dose escalation phase aimed at estimating the MTD. The sample size for this portion of the study will vary depending on the number of DLTs observed. It is expected that about 36 patients will be required.

In addition to dose escalation, additional patients (approximately 24) will be enrolled with the aim of evaluating the DDI, food and antacid effects studies at RP2D prior to initiating the Phase 1b/2 portion.

The planned sample size for the MTD expansion cohort is 10 evaluable patients. An evaluable patient will have both a baseline and on-treatment tumor assessment. This expansion cohort will also be used to conduct the sildenafil sub-study.

8.1.2.2. Phase 1b/2 Sample Size

The sample size planned for Phase 2 Cohort 1 is about 20 patients to provide preliminary information on efficacy, safety, and PK endpoints in previously untreated patients with advanced EGFRm NSCLC. With 20 patients the maximum width of the exact 2-sided 90% confidence interval for ORR will be ≤0.396.

The sample size planned for the Phase 1b (Cohort 2A and Cohort 3) dose finding part arises from logistic feasibility and is not entirely driven by statistical considerations. Due to the dynamic nature of the dose allocation procedure and unknown safety profile of the combination, the sample size of the interval design cannot be determined in advance. It is expected that approximately 10 DLT evaluable patients will be required for each of the dose finding cohorts.

After dose selection determined for Cohort 3, the Dose Expansion Phase will continue to enroll patients until approximately 20 patients in total have been treated to further assess the safety, PK, CCI *of the combination.* Phase 2 (Cohort 2B), the planned sample is about 39 patients. These patients will be randomized with a 2:1 ratio for the combination of PF-06747775 and palbociclib vs PF-06747775 single agent. The primary objective is to estimate the hazard ratio (HR) and its corresponding confidence interval for PFS. For a target sample size of 39 patients randomized in ratio of 2:1 and 26 events, the approximate width of the 2-sided 90% CI for the logHR for PFS will be 1.37 which corresponds to the upper bound being approximately 3.93 times the lower bound on the HR scale.

8.1.3. Simulation for CRM

Several simulations were performed to fine-tune the CRM performance and to study operating characteristics of the chosen "best" CRM design. Below is a brief description of the simulation setup and key findings. Competing designs were evaluated against 6 different plausible scenarios of dose-toxicity profile varying in steepness of dose-DLT curve and location of the true MTD within the studied dose range. These scenarios are summarized in Table 6.

Table 6. Probability of DLT as a Function of Dose

	Dose-Toxicity Curve Scenario					
Dose	**Sc. 1: MTD= 50-flat**	**Sc. 2: MTD= 50-steep**	**Sc. 3: MTD= 150-flat**	**Sc. 4: MTD= 150-steep**	**Sc. 5: MTD= 600-flat**	**Sc. 6: MTD= 600-steep**
25 mg/QD	**0.25**	**0.25**	**0.10**	**0.10**	**0.05**	**0**
50 mg/QD	**0.30**	**0.30**	**0.20**	**0.20**	**0.07**	**0**
100 mg/QD	**0.40**	**0.60**	**0.25**	**0.25**	**0.10**	**0**
150 mg/QD	**0.50**	**0.80**	**0.30**	**0.30**	**0.12**	**0**
200 mg/QD	**0.60**	**0.85**	**0.40**	**0.60**	**0.15**	**0**
275 mg/QD	**0.70**	**0.9**	**0.50**	**0.80**	**0.17**	**0**
350 mg/QD	**0.80**	**0.92**	**0.60**	**0.90**	**0.20**	**0**
450 mg/QD	**0.90**	**0.95**	**0.80**	**0.98**	**0.22**	**0.10**
600 mg/QD	**0.98**	**0.98**	**0.98**	**0.98**	**0.25**	**0.30**

For each of the competing designs (ie, CRM design variant), the following operating characteristics were assessed, by scenario, to further quantify the trade-off between precision of MTD estimation and design cost:

- Probability to select MTD.
- Design cost:

  Average Sample Size;

  Average Number of DLTs;

  Average Proportion of DLTs.

These operating characteristics are summarized in Table 7 for the final design selected based on 1000 trials simulated.

Table 7. Operating Charateristics of the CRM in Phase 1

	MTD Dose Selection Decision (Probability, %)											
Scenarios	**25 mg/QD**	**50 mg/QD**	**100 mg/QD**	**150 mg/QD**	**200 mg/QD**	**275 mg/QD**	**350 mg/QD**	**450 mg/QD**	**600 mg/QD**	**Average Size**	**Average Num DLTs**	**Average DLTs (%)**
MTD 50 flat	26.09	30.8	9.32	1.14	0.1	0.03	0.04	0	0	15.7	5.03	38.8
MTD 50 steep	33.25	34.97	1.12	0	0	0	0	0	0	14.9	4.8	38.8
MTD 150 flat	10.36	29.07	24.38	12.78	5.85	4.36	3.41	0.42	0.09	24.4	6.3	27.1
MTD 150 steep	10.2	29.59	34.74	13.15	2.22	0.54	0.09	0	0	23.5	6.1	27.2
MTD 600 flat	0.97	2.85	3.31	1.98	2.11	4.17	6.83	11.33	65.48	34.3	5.4	16.2
MTD 600 steep	0	0	0	0	0	0.02	0.12	0.36	99.5	36	3.8	10.5

8.1.4. Statistical Methods for Different Types of Endpoints

Standard summary statistics will be used for description of different types of variables:

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- Time-to-event: Kaplan-Meier estimate of survivor function, median time to event, Brookmeyer-Crowley confidence interval for median time to event, probability of event by a particular time point, log(−log) method with back transformation for confidence interval of estimated probability of event by a given time point;

- Categorical: count and percentage of each category, confidence interval of the percentage based on normal approximation (unless specified otherwise).

Summaries of efficacy, PK CCI endpoints will be provided for dose level in Phase 1 and by treatment arm in all other cohorts. Summaries of other endpoints (demographics, safety, study conduct, etc.) will be provided for dose level in Phase 1 unless stated otherwise and by treatment arm in all other cohorts.

Listings for derived data in summaries will be provided. Listings of raw data will be provided as well.

8.2. Statistical Analyses

Data will be presented by Phase and Cohort within each Phase separately. Refer to Section 5 for definitions of analysis sets.

8.2.1. Analysis of Efficacy Endpoints

8.2.1.1. Phase 1

Analysis Set: Safety

In the Phase 1 portion of the study anti-tumor activity is a secondary objective.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor response at each visit, and best overall response.

8.2.1.2. Phase 1b/2

8.2.1.2.1. Primary Analysis of Efficacy

8.2.1.2.1.1. Cohort 1 – PF-06747775 Single-Agent in Patients with Previously Untreated EGFRm NSCLC

Primary analyses in Phase 2 Cohort 1 portion of study is based on objective response rate (ORR) which is calculated as the proportion of patients with a confirmed complete response(CR) or partial response (PR) relative to the total number of response evaluable patients using the Response Evaluable Analysis Set. A Clopper- Pearson exact 2-sided 90% CI for objective response rate will be presented.

A table summarizing objective response will include the number of patients and percentage of patients for CR, PR, SD, PD, IND, and objective response (CR+PR), the 90% CI for the objective response rate. Categories of symptomatic deterioration (per the case report form for end of treatment subject summary) and early death (ie, death prior to the second on-study assessment) may be presented in the table.

A waterfall plot will be presented for maximum percent change in tumor size (sum of diameters) from baseline, with best overall response identified.

Sensitivity analysis for ORR will be performed based on safety analyses set.

8.2.1.2.1.2. Cohort 2B – PF-06747775 Plus Palbociclib vs PF-06747775 Alone (Randomized)

The primary endpoint of PFS will be analysed and displayed graphically for each arm separately using the Kaplan-Meier method on the Full Analysis Set. The hazard ratio and its 2-sided 90% CI will be estimated. The median event time and 2-sided 90% CI using the Brookmeyer-Crowley method will be provided for each arm separately. Estimated probability of remaining progression-free at 6 months and its 2-sided 90% CI, using log-log transformation and back-transformation will be provided for each arm as well.

8.2.1.2.2. Secondary Analysis of Efficacy

Analysis Set: Safety Analysis Set unless specified otherwise

8.2.1.2.2.1. Phase 1

In the Phase 1 portion of the study anti-tumor activity is a secondary objective.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor response at each visit, and best overall response using Safety Analysis Set.

8.2.1.2.2.2. Phase 2 Cohort 1

DOR in responding patients will be characterized in terms of the median based on Kaplan - Meier estimates) among all responding patients. Their 90% confidence interval will also be computed.

PFS in the Safety Analysis Set will be characterized in terms of the median and 2-sided 90% confidence interval and the estimated probability of remaining progression-free at 6 months (based on Kaplan- Meier estimates), a 2-sided 90% confidence interval for the log(-log(6-month PFS probability)) will be calculated based on a normal approximation and then back transformed.

OS in the Safety Analysis set will be characterized in terms of the median and 2-sided 90% confidence interval and the estimated probability of being alive at 24 months (based on Kaplan-Meier estimates), a 2-sided 90% confidence interval for the log(-log(2-year survival probability)) will be calculated based on a normal approximation and then back transformed.

8.2.1.2.2.3. Phase 2 Cohort 2A

In the Cohort 2A portion of the study anti-tumor activity is a secondary objective.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor response at each visit, best overall response, PFS, and OS, using Safety Analysis Set.

8.2.1.2.2.4. Phase 2 Cohort 2B

The point estimate and 90% Clopper- Pearson exact 2-sided CI of the proportion of patients with ORR will be summarized by treatment arm using the Response Evaluable Analysis Set. A Pearson χ_2 test will be used to compare ORR between the two treatment arms. The point estimate and the 2-sided 90% confidence interval for the difference in ORR will be presented.

DOR in responding patients and OS in the Full Analysis Set will be analysed and displayed graphically for each treatment arm using the Kaplan-Meier method and the median and 2-sided 90% confidence interval will be provided for each endpoint as well as the hazard ratio and 2-sided 90% confidence interval for OS. The estimate of survival probabilities at 24 months and its 2-sided 90% CI (using log-log transformation and back-transformation) will be provided for each arm separately for OS.

8.2.1.2.2.5. Phase 2 Cohort 3

The median event time and corresponding 2-sided 90% CI will be provided for PFS, DOR and OS in the RP2D expansion cohort for responding patients (DOR) and the Safety Analysis Set (PFS and OS) . The estimated probability of remaining progression-free at 6 month and its 2-sided 90% CI (using log-log transformation and back-transformation) will be provided for PFS. The estimate of survival probability at 24 month and 90% CI (using log-log transformation and back-transformation) will be provided for OS.

The point estimate and 2-sided 90% exact CI of the proportion of patients with ORR (confirmed and unconfirmed) will be summarized using the Response Evauable and Safety Analysis Sets.

For DOR, the number of CR and PR patients may be small and thereby limit use of the Kaplan-Meier method to provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

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8.2.2. Analysis of Safety Endpoints

8.2.2.1. Analysis of Primary Endpoint for Phase 1, Phase 1b Cohort 2A, and Cohort 3

Analysis set: Per Protocol

Dose Limiting Toxicity (DLT) is the primary endpoint of Phase1 and Phase1b Cohort 2A and Cohort 3 of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the protocol. Adverse Events constituting DLTs will be listed per dose level.

8.2.2.2. Analysis of Secondary Safety Endpoint

Analysis: Safety

All safety reports will be separated by Phase and Cohort. Safety data in Phase 1, Cohort 2A, and Cohort 3 will be reported by dose level or treatment arm, and total. Safety data in Cohort 2B will be reported by treatment arm.

Summary of Adverse Events

AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients who experienced any AE, 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).

Deaths will be summarized by time period (on-treatment vs. during follow-up) and cause of death. Deaths that occurred within 28 days after the last dose of study medication are defined as on-treatment deaths. Death data will also be listed.

For all safety analyses, only descriptive methods will be used without any formal statistical test.

Treatment-emergent adverse events (all causality and treatment related) including:

- number of patients evaluable for AEs;
- total number of AEs (counting each unique preferred term across all patients);
- total number of SAEs (counting each unique preferred term across all patients);
- number of patients with AEs;
- number of patients with SAEs;
- number of patients with Grade 3 or Grade 4 AEs;
- number of patients with Grade 5 AEs;
- number of patients who discontinued due to AEs (per the AE CRF page);

- number of patients with dose decreases due to AEs (per the AE CRF page);
- number of patients with dose delays due to AEs (per the AE CRF page).

The following summaries will be presented for all-causality and treatment-related treatment emergent AEs, or treatment- emergent irAEs and IRR (Cohort 3 only) separately.

The number and percentage of patients with treatment-emergent AEs will be summarized by MedDRA system organ class, preferred term, and maximum CTCAE grade for all cycles combined for each dose level. The total for all grades will be included as the last column.

The number and percentage of patients with treatment-emergent AEs will be summarized by MedDRA preferred term and maximum CTCAE grade in descending order of frequency (based on total frequency for all grades) for all cycles combined for each dose level. The total for all grades will be included as the last column.

The number and percentage of patients with treatment-emergent SAEs will be summarized by MedDRA system organ class, preferred term, and maximum CTCAE grade for all cycles combined for each dose level. The total for all grades will be included as the last column.

The number and percentage of patients with treatment-emergent AEs of Grade 3-5 will be summarized by MedDRA preferred term and maximum CTCAE grade in descending order of frequency (based on total frequency for all grades) for all cycles combined for each dose level. The total for all grades will be included as the last column.

Laboratory Tests

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay. The analyses will summarize laboratory tests both on the entire treatment period and by cycle (Cycle 1, Cycle 2, and Cycles beyond 2). For laboratory tests without CTC grade definitions, results will be categorized as normal, abnormal or not done.

- **Hematology –** Descriptive statistics will be provided for each test result and for change from baseline by visit. Baseline is defined as the last evaluation prior to the first dose of study drug. Hematology results will be graded according to the NCI CTCAE Version 4.03. A summary of maximum CTCAE grade as well as shift summary of baseline grade by maximum CTCAE grade, cycle, and dose will be presented. Patients who developed a grade 3 or greater toxicity will also be listed.
- **Biochemistry -** Descriptive statistics will be provided for each parameter result and for change from baseline by visit. Baseline is defined as the last evaluation prior to the first dose of study drug. Biochemistry results will be graded according to the NCI CTCAE version 4.03. A summary of maximum CTCAE grade as well as shift summary of baseline grade by maximum CTCAE grade, cycle, and dose will be presented. Patients who developed a grade 3 or greater toxicity will also be listed.
- **Urine** - Urinalysis data will be listed for each subject.

- **Other Laboratory Tests** – Individual patient test results will be listed.

ECG

Triplicate ECGs will be performed (approximately 2 minutes apart) before vital signs or any type of blood draws at indicated visits per Schedule of Activities table in the protocol. If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at the time of the event.

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data based on independent cardiologist central reading data. ECG data recorded on CRF by principal investigator will be listed only. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates.

QT measurements corrected by heart rate (QTc) will be used for the data analysis and interpretation. In addition to commonly used techniques including Bazzett's (QTcB) and Fridericia's (QTcF) methods, a study-specific correction method will be evaluated (QTcS) for the QTc evaluable patients. QTcF is planned to be the primary analysis method for the secondary QT endpoint. If QTcF cannot sufficiently correct for the heart rate, the most appropriate correction method that eliminates any QT vs. RR relationship may be chosen after reviewing the data.

Analysis of QTc

Changes in QTc (QTcB, QTcF, and/or QTcS) from baseline to steady state will be summarized by dose and by treatment arm (PF-06747775 alone, or in combination with palbociclib or avelumab), using descriptive statistics and categorical analysis by nominal time point. The primary correction factor will be QTcF. If QTcF cannot sufficiently correct for the heart rate, the most appropriate correction method that eliminates any QT vs. RR relationship may be chosen after reviewing the data.

For Phase 1, Day 11 of Cycle 1 and Day 1 of Cycles 2-4 will be used to characterize the potential effect of PF-06747775 on the QT interval. The baseline for Phase 1 is defined as the ECGs recorded on Day -8 pre-dose.

For Phase 1b/2, Day 11 (Cohort 1) or Day 15 (Cohort 2A, 2B, and 3) of Cycle 1 and Day 1 of Cycles 2-3 (Cohort 3) or 2-4 (Cohort 1, 2A, and 2B) will be used to characterize the potential effect of PF-06747775 on the QT interval. The baseline for Phase 1b/2 is defined as the ECGs recorded on Day -4 (Cohort 1) or Day 1 (Cohort 2A, 2B, and 3) pre-dose.

A random effect model with the nominal time point as a fixed effect and the patients as a random effect will be used to estimate the mean change in QTc from baseline at each post-baseline nominal time point by dose and by treatment. The 2-sided 90% CI for the changes from baseline in QTc (equivalent to the boundaries of upper one-sided 90% confidence intervals) will be provided at each post-baseline nominal time point.

Mean QTcF change and 90% CI from baseline will be presented along with the mean and 90% CI plasma concentrations of PF-06747775 by dose, by treatment, and by nominal time point in a summary table.

Summary and Categorical Analysis of ECG

For the ECGs assessments the following directions should be followed by the ECG central Laboratory:

- Review of ECGs from a particular patient should be performed by a single reader.
- Pre-specification of the lead for internal measurements.
- Baseline and on-treatment ECGs should be based on the same lead.

All ECGs obtained during the study will be evaluated for safety. ECGs recorded on Day -8 (Phase 1), Day -4 (Phase 1b/2 Cohort 1) or Day 1 (Phase 1b/2 Cohort 2A, 2B, and 3) pre-dose will be used as baseline. For Phase 1 the QTc baseline-adjusted on Day 11 of Cycle 1 and Day 1 of Cycles 2-4 will be used to characterize the potential effect of PF-06747775 on the QT interval. For Phase 1b/2, the QTc baseline-adjusted on Day 11 (Cohort 1) or Day 15 (Cohort 2A, 2B, and 3) of Cycle 1 and Day 1 of Cycles 2-3 (Cohort 3) or 2-4 (Cohort 1, 2A, and 2B) will be used to characterize the potential effect of PF-06747775 on the QT interval.

For Phase 1, figures of Mean Corrected Change from Baseline in QTcF Intervals vs. Time by Cycle 1 Day 11 and Day 1 of Cycles 2-4 will be presented.

For Phase 1b/2 Cohort 1, figures of Mean Corrected Change from Baseline in QTcF Intervals vs. Time by Cycle 1 Day 11 and Day 1 of Cycles 2-4 will be presented.

For Phase 1b/2 Cohort 2A and 2B, figures of Mean Corrected Change from Baseline in QTcF Intervals vs. Time by Cycle 1 Day 15 and Day 1 of Cycles 2-4 will be presented.

For Phase 1b/2 Cohort 3, figures of Mean Corrected Change from Baseline in QTcF Intervals vs. Time by Cycle 1 Day 15 and Day 1 of Cycles 2-3 will be presented.

All figures listed above may also be presented by dose of study treatment(s).

The triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates.

For all patients in the safety analysis population, individual change in QTc (QTcB, QTcF, QTcS) will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

For all patients in the safety analysis population, categorical analysis of the QTcF/QTcB data will be conducted and summarized as follows:

- The number and percentage of patients with maximum increase from baseline in QTcF/QTcB (<30, 30- 60, and ≥60 ms).
- The number and percentage of patients with maximum post-dose QTcF/QTcB (<450, 450-<480, 480- <500, and ≥500 ms).
- PR changes from baseline ≥25% and absolute values over >200 ms.
- QRS changes from baseline ≥25% and absolute values over >110 ms.
- Number and percentage of individuals with abnormal ECG findings.
- Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, eg, palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.

The ECG analyses described above for the safety population will be repeated separately for the QTc evaluable population.

- The following analyses will be provided for the QTcB, QTcF, QTcS, QRS, PR, RR-derived HR, systolic blood pressure, and diastolic blood pressure: absolute parameter with 2-sided 90% confidence intervals, and baseline-adjusted parameter with 2-sided 90% confidence intervals.
- Provide categorical analyses of outliers for the QTc, QRS, PR, and RR-derived heart rate. For outlier thresholds use QTc>450, 480, & 500 ms, QTc increase from baseline >30 ms & 60 ms, QRS>110 ms, PR>200 & 220 ms, HR <50, 40, & 30 bpm and HR>90 bpm.

Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate), by dose and by treatment. *Individual QT` (all evaluated corrections) intervals will be listed by 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 corrected QT value and changes from baseline in corrected QT after treatment by dose,* treatment, *and time point. For each patient, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT value.*

Shift tables by dose and by treatment/cohort *will be provided for baseline vs worst on treatment corrected QT (one or more correction method will be used) using Maximum CTC AE 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 (including frequency and percentage). These tables may also be provided by dose, and with several treatments/cohorts and doses combined. *The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.*

8.2.3. Baseline Characteristics

Analysis Set: Full

Patient characteristics such as age, gender, height, weight, ethnicity, diagnosis, performance status, and medical history at study entry will be summarized in frequency tables, and descriptive statistics will be provided for quantitative variables.

8.2.4. Analysis of Pharmacokinetics

8.2.4.1. Population Pharmacokinetic Analysis or PK/PD Modeling

Data may be pooled with other study results and/or explored further in a standalone PK/PD report.

8.2.4.1.1. Derivation of Pharmacokinetic Parameters Prior to Analysis

Pharmacokinetic parameters for PF-06747775 will be derived from plasma PF-06747775 concentration-time data as described in the following table.

PF-06747775 PK parameters for either single or multiple doses from the multiple sub-studies/cohorts may be reported together by dose or as dose-normalized parameters, in addition to reporting by cohort or treatment.

Table 8. PK Parameters to be Determined for PF-06747775

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
AUC_{24}	Area under the plasma concentration-time profile from time zero to 24 hours	Linear/Log trapezoidal method
AUC_{tau}	Area under the plasma concentration-time profile from time zero to time tau, the dosing interval, where tau = 24 hours	Linear/Log trapezoidal method
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence

Parameter	Definition	Method of Determination
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
C_{trough}	Predose concentration during multiple dosing	Observed directly from data
CL/F[a]	Apparent clearance	Dose / AUC_{inf} for single dose Dose / AUCτ for steady state
V_z/F[a]	Apparent volume of distribution	Dose / (AUC_{inf} · k_{el}) for single dose Dose / (AUCτ ·kel) for steady state
R_{ac}	Observed accumulation ratio	Steady state AUC_{tau} / Single dose AUC_{24}
R_{ss}[a]	Steady state accumulation ratio	Steady state AUC_{tau} / Single dose AUC_{inf}
AUC_{last}(dn)	Dose-normalized AUC_{last}	AUC_{last} / Dose
AUC_{inf}(dn)[a]	Dose-normalized AUC_{inf}	AUC_{inf} / Dose
AUC_{tau}(dn)	Dose-normalized AUC_{tau}	AUC_{tau} / Dose
AUC_{24}(dn)	Dose-normalized AUC_{24}	AUC_{24} / Dose
C_{max}(dn)	Dose-normalized C_{max}	C_{max} / Dose
C_{trough}(dn)	Dose-normalized C_{trough}	C_{trough} / Dose

[a]If data permit

Pharmacokinetic parameters for sildenafil will be derived from plasma sildenafil concentration-time data as described in the following table.

Table 9. PK Parameters to be Determined for Sildenafil

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	AUC_{last} + (C_{last}*/k_{el}), where C_{last}* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
CL/F[a]	Apparent clearance	Dose / AUC_{inf}

[a]If data permit

Cohort 2A and 2B: Pharmacokinetic parameters for palbociclib will be derived from plasma palbociclib concentration-time data as described in the following table (Table 10).

Table 10. PK Parameters to be Determined for Palbociclib

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{tau} [a]	Area under the plasma concentration-time profile from time zero to time tau, the dosing interval, where tau = 24 hours	Linear/Log trapezoidal method
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
C_{trough}	Predose concentration during multiple dosing	Observed directly from data
$AUC_{last}(dn)$ [b]	Dose-normalized AUC_{last}	AUC_{last} / Dose
$AUC_{tau}(dn)$ [a,b]	Dose-normalized AUC_{tau}	AUC_{tau} / Dose
$C_{max}(dn)$ [b]	Dose-normalized C_{max}	C_{max} / Dose
$C_{trough}(dn)$ [b]	Dose-normalized C_{trough}	C_{trough} / Dose

[a] If data permit; [b] To be determined only if more than one palbociclib dose is assigned and utilized in combination treatment.

For avelumab, end-of-infusion peak (C_{max}) and pre-dose concentration (C_{trough}) will be reported from serum avelumab concentration-time data.

8.2.4.2. PF-06747775 Single-Dose and Steady State PK Analysis

The single dose and steady-state PK parameters will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by treatment/cohort, dose, cycle and day, for both Phase 1 and Phase 1b/2, as data permit. This applies to the single dose and/or steady state PK collected for PF-06747775 in cohorts in the Phase 1 dose escalation, the Phase 1 MTD expansion sildenafil sub-study, and the Phase 2 single agent PF-06747775 in previously untreated patients (Cohort 1).

The single dose and steady-state PF-06747775 plasma concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by treatment/cohort, dose, cycle, day, and nominal time.

Dose-normalized parameters as data permit for single dose (AUC_{inf}, AUC_{last}, and C_{max}) and steady-state (AUC_{tau} and C_{max}) will be plotted against dose (using a logarithmic scale) by cycle and day (nominal visit time). 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. Plots of dose-normalized parameters may also be presented together across multiple treatment/cohorts (ie, from Phase 1 dose escalation, DDI sub-study, combination with another agent, etc.).

Trough concentrations (pre-dose 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.

Individual patient and median profiles of the single dose and steady-state concentration-time data will be plotted by treatment, dose, cycle, and day, using actual times for individual patients and nominal times for median profiles. Median profiles will be presented on both linear-linear and log-linear scales, paged by treatment, cycle and day with all doses on the same plot. Individual patient profiles will be presented on linear-linear and log-linear scales, paged by treatment, cycle, day, and dose with all subjects on the same plot. Only data for days with intensive PK sampling will be presented in these plots (ie, days with only a single pre-dose PK sample will not be included). Plots of median profiles may also be presented together across multiple treatments/cohorts (ie, from Phase 1 dose escalation, DDI sub-study, combination with another agent, etc.) either by PF-06747775 dose assigned, or using dose-normalized plasma concentrations.

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8.2.4.3.2. Itraconazole and Antacid Sub-Study

The treatment selected for further development will be evaluated for the effect that an acid reducing agent, esomeprazole, a proton pump inhibitor, as well as a strong CYP3A4 inhibitor, itraconazole, may have on PF-06747775 exposure. For the esomeprazole effect, natural log transformed AUC_{tau} and C_{max} values will be analyzed using a mixed effects model with treatment (fasted and esomeprazole) as fixed effect and patient as a random effect. For the itraconazole effect natural log transformed $AUC_{tau}(dn)$ and $C_{max}(dn)$ values will be analyzed using a mixed effects model with treatment (fasted, and itraconazole) as fixed effect and patient as a random effect.

Esomeprazole Drug-Drug Interaction: Estimates of the adjusted mean differences (with esomeprazole - fasted) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratios of adjusted geometric means (with esomeprazole/fasted) and 90% confidence intervals for the ratios.

Itraconazole Drug-Drug Interaction: Estimates of the adjusted mean differences (with itraconazole - fasted) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratios of adjusted geometric means (with itraconazole/fasted) and 90% confidence intervals for the ratios.

8.2.4.4. Sildenafil Sub-study: MTD Expansion Cohort

Sildenafil PK:

Sildenafil PK parameters for this sub-study will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by treatment. Sildenafil *AUC_{inf} and C_{max} values will be plotted by treatment (with and without PF-06747775) using box-and-whisker plots.* Sildenafil parameter descriptive summary and box-and-whisker plots may also be presented by the PF-06747775 dose assigned.

The main purpose of this sub-study is to appropriately estimate the potential CYP3A4 inhibitory ability of PF-06747775. Natural log transformed AUC_{inf} and C_{max} values for sildenafil will be analyzed using a mixed effects model with treatment as fixed effect and patient as random effect to estimate the effect of steady-state PF-06747775 on sildenafil exposure. Estimates of the adjusted mean differences (with and without PF-06747775) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratios of adjusted geometric means (with/without PF-06747775) and 90% confidence intervals for the ratios. Estimates of mean differences and confidence intervals may be also reported by the PF-06747775 dose assigned.

Plasma sildenafil concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by treatment and nominal time. Sildenafil concentration summaries may also be reported by the PF-06747775 dose assigned.

Individual patient and median profiles of the sildenafil concentration-time data will be plotted by treatment, using actual times for individual patients and nominal times for median profiles. Median profiles will be presented on both linear-linear and log-linear scales with both treatments on the same plot. Individual patient profiles will be presented on linear-linear and log-linear scales, paged by treatment with all subjects on the same plot. Median and individual sildenafil profiles may also be presented by the PF-06747775 dose assigned.

PF-06747775 PK:

PF-06747775 parameters at steady-state (assessed on Cycle 1 Day 11) will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) and presented as described above in Section 8.2.4.2 Plasma PF-06747775 concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by nominal time. Individual and median concentration-time profiles may be presented as well.

If more than one dose level of PF-06747775 was assigned and utilized in the MTD expansion sub-study, then PF-064747775 PK parameters and concentration-time plots will be presented by dose, and dose-normalized parameters will also be reported. Individual and median concentration-time profiles may also be generated for dose-normalized plasma concentrations.

8.2.4.5. Phase 2 Single Agent PF-06747775 in Previously Untreated Disease (Cohort 1)

The single dose and steady-state PK parameters for PF-06747775 will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by cycle and day, as described above in Section 8.2.4.2. Single dose parameters will be assessed on Day -4 of the lead in period and steady-state parameters will be assessed on Day 11 of Cycle 1. Single dose and steady-state plasma PF-06747775 concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by cycle, day, and nominal time.

Individual and median concentration-time profiles following single and multiple-dose may be presented as well as described in Section 8.2.4.2.

Trough concentrations (pre-dose concentrations) may be plotted using a box-and-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.

8.2.4.6. Phase 1b Single Arm Combination with Palbociclib (Cohort 2A)

PF-06747775 PK:

PF-06747775 PK parameters at steady-state will be summarized descriptively(n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by cycle and day, as described above in Steady-state parameters will be assessed on Day 15 of Cycle 1. Plasma PF-06747775 concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by cycle, day, and nominal time.

Individual and median concentration-time profiles following multiple-dose may be presented as described in Section 8.2.4.2.

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

If more than one dose level of palbociclib was used in this dose-finding cohort, PF-06747775 PK parameters, plasma concentrations, and figures may also be presented by dose of palbociclib assigned. Box-and-whisker plots for PF-06747775 C_{max} and AUC_{tau} at each dose of palbociclib may be generated also.

Palbociclib PK:

Palbociclib steady-state PK parameters will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose (if applicable), cycle, and day. Steady-state parameters will be assessed on Day 15 of Cycle 1.

The steady state palbociclib concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose (if applicable), cycle, day, and nominal time.

The trough concentrations (pre-dose concentrations) for palbociclib will be plotted using a box-and-whisker plot by cycle and day within cycle in order to assess the attainment of steady state. Individual and median concentration-time profiles following multiple-dose (using the methods described above in Section 8.2.4.2. for PF-06747775) may be presented as well.

If more than one dose level of palbociclib was used in this cohort, then palbociclib PK parameters, plasma concentrations, and figures may be presented by dose, and dose-normalized parameters may be presented as well. Box-and-whisker plots for palbociclib C_{max} and AUC_{tau} or AUC_{last} at each dose may be generated also.

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APPENDICES

Appendix 1. Programming Specifications for AE analyses

a. Time to AE onset

- **Definition**

  Time to AE onset (days) will be calculated as first *AE start date – first dose date* +1. The definition and calculations are similar for time to Grade 3/4 AE onset.

  AE start date

  The Date of Onset for the first occurrence of the AE based on the Log AE CRF page.

  First dose date

  The date of the starting dose: Cycle 1 Day 1

b. Duration of AE

- **Definition**

  Duration of AE (days) is defined as the cumulative duration across episodes of the AE where duration for each episode is calculated as *AE end date – AE start date* +1 excluding any overlap. Duration of AE is defined for subjects with the AE.

  AE start date

  The Date of Onset based on the Log AE CRF page.

  AE end date

  The Date Resolved based on the Log AE CRF page.

- **Censoring**

  AE resolution is considered an event (censoring variable=1). If a subject has an AE that was ongoing (does not have to be the last AE) at the time of analysis, the time is censored (censoring variable=0) at the last available on treatment visit date. Subjects who die prior to resolution of the AE will be censored at the *date of death*. If the date of death is the same as the date of the resolution of the AE, the subject will be censored at that date (ie, resolution will not be considered an event) only if the AE is the AE that resulted in death.

  Date of death

  Death date is based on the Notice of Death CRF page.

- **Clustered Events**

  For clustered events, a patient could have multiple events in the cluster which may overlap. In this case, AE duration will be summed across all events in the cluster accounting for the overlap (ie, overlapping periods between events in the same cluster are not double-counted). Lags between events in the same cluster are not included in the duration.

  The following scenarios provide examples of the calculation for 2 events in the same cluster. The extension to 3 or more events of the same cluster is similar.

  - **TWO EVENTS OF THE SAME CLUSTER WHERE ONE EVENT COMPLETELY CONTAINS THE OTHER EVENT**

    event 1 [----------]
    startdate1 enddate1
    event 2 [----------]
    startdate2 enddate2

    duration = enddate1-startdate1+1

  - **CERTAIN PORTIONS OF TWO EVENTS IN THE SAME CLUSTER OVERLAP**

    event 1 [----------]
    startdate1 enddate1
    event 2 [----------]
    startdate2 enddate2

    duration = enddate2-startdate1+1

  - **TWO EVENTS OF THE SAME CLUSTER ARE CONTIGUOUS TO EACH OTHER**

    event 1 [----------]
    startdate1 enddate1
    event 2 [----------]
    startdate2 enddate2

    duration = enddate2-startdate1+1

  - **TWO EVENTS OF THE SAME CLUSTER ARE NON-OVERLAPPING**

    event 1 [----------]
    startdate1 enddate1
    event 2 [----------]
    startdate2 enddate2

    duration = (enddate1-startdate1+1) + (enddate2-startdate2+1)

Appendix 2. STUDY SPECIFIC INFORMATION FOR EFFICACY

- **Baseline**: is defined as the last observation prior to the first dose or randomization (Cohort 2B) of study treatment.

- **Adequate Baseline:**

    - Baseline tumor evaluations must be performed within 4 weeks (28 days) prior to the first dose of study treatment or randomization (Cohort 2B);

    - Presence of target and/or non-target lesions at baseline) for solid tumors;

    - All lesions recorded at baseline must have an associated status recorded on the CRF;

    - Baseline lesions must be assessed with an acceptable method that includes: Conventional CT Scan, Spiral CT Scan, X-ray, MRI, Physical Exam, Bone Scan and Other. Note: If based on data review "unacceptable" methods (eg, ultrasound, etc) are noted under "Other", then this category will not be considered acceptable (on a case by case basis).

- **"On-treatment" period for safety:** is defined as the period from the date of the first dose until 28 days after the last dose of each patient.

- **Subsequent anti-tumor treatment:** include systemic anticancer therapy (other than study medication), radiation and surgical resection.

Appendix 3. DETERMINATION OF EFFICACY – SOLID TUMORS

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

Non-measurable disease

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

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

Normal sites

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

RECORDING TUMOR ASSESSMENTS

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

Target lesions

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

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

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

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

Non-target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target disease

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

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

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

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

- Indeterminate. Progression has not been documented, and

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

    or

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

    or

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

    or

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

Non-target disease

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

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

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

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

New Lesions

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

Supplemental Investigations

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

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

Subjective progression

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

Table 1. Objective Response Status at Each Evaluation

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

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

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

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

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

Appendix 4. Detailed Dose Escalation/De-Escalation Scheme for mTPI Design Based on 30% Toxicity Rate

DLTs at current dose level	Number of patients per dose level (cumulative)										
	1	2	3	4	5	6	7	8	9	10
0	NA	NA	E	E	E	E	E	E	E	E
1	D	**S**	**S**	**S**	**S**	E	E	E	E	E
2		DU	D	S	S	S	**S**	**S**	E	E
3			DU	DU	D	D	**S**	**S**	S	E
4				DU	DU	DU	DU	DU	DU	DU

E= escalate or if current dose level is DL1 stay on DL1; S= stay at current dose; D= de-escalate; DU = de-escalate and dose is unacceptable due to toxicity

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 -> remain at the same 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
  - 1-2 DLTs -> remain at the same dose
  - 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
  - 4-5 DLTs -> de-escalate and consider current dose as intolerable
- With 6 patients treated at current dose level

- 0-1 DLT -> escalate
- 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
  - 5-7 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
  - 4-8 DLTs -> de-escalate and consider currentdose as intolerable
- With 9 patients treated at current dose level
  - 0-2 DLT -> escalate
  - 3 DLTs -> remain at the same dose
  - 4-9 DLTs -> de-escalate and consider current dose as intolerable
  - With 10 patients treated at current dose level
  - 0-3 DLT -> escalate (MTD if highest dose)
  - 4-10 DLTs -> de-escalate and consider current dose as intolerable

Appendix 5. Treatment Exposure

PF-06747775 or Palbociclib:

The dose level is calculated as actual dose administered (mg/day). The duration of treatment (in weeks) during the study is defined as:

duration (weeks) = (last dose date – first dose date + 1)/7

The cumulative dose (mg) per patient in a time period is the sum of the actual dose levels that the patient received within that period (ie, total dose administered (mg)). In a week if all doses (eg, 2×5=10 mg/day) were received the cumulative dose would be 7×10 mg.

The dose intensity (DI) and the relative dose intensity (RDI) will be calculated for each patient during the study. The DI (mg/week) during the study is defined as

DI (mg/week) = [cumulative dose (mg)]/[duration (week)]

The RDI is defined as the ratio of the DI and planned dose and expressed in %

RDI (%) = 100 × [DI (mg/week]/[3xd (mg/week)]

where d is fixed at the start of treatment for a patient, which can be 7x200 for PF-06747775; 7x100, 7x75, or 7x50 for palbociclib; for PF-06747775 in Cohort 3, the denominator will [4 x d (mg/week)] as it will be 4 weeks per cycle.

Avelumab:

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

The duration of avelumab treatment (in weeks) during the study for a patient is defined as:

duration (weeks) = (last dose date –first dose date + 14)/7

The cumulative dose (mg/kg) of avelumab per patient in a time period is the sum of the actual dose levels that the patient received within that period (ie, total dose administered (mg) / weight (kg)).

Each cycle for avelumab is defined by a 4-week period with 1 infusion every 2 week. The dose intensity (DI) and the relative dose intensity (RDI) will be calculated for each patient across all cycles. The dose intensity (mg/kg/cycle) per cycle is defined as

DI (mg/kg/cycle) = Cumulative dose (mg/kg)/ [duration of therapy (in weeks)/4]

The relative dose intensity (RDI) is defined as the actual dose intensity divided by the planned dose per cycle and expressed in %.

RDI (%) = 100 × [DI (mg/kg/cycle)/2x10 (mg/kg/cycle)]