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

Compound:	PF-06747775
Compound Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	Non-IND Amendment
European Clinical Trials Database (EudraCT) Number:	N/A
Universal Trial Number:	N/A
Protocol Number:	B7971001
Phase:	Phase 1 / 2

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	24 December 2014	N/A
Amendment 1	19 March 2015	The Food and Drug Administration (FDA) requested changes clarifying conditions for continuing investigational therapy after Response Evaluation Criteria in Solid Tumors (RECIST) progression. Additional clarification of pharmacokinetic (PK) timepoints options (For sites closed on weekends follow the Schedule of Activities [SOA] regarding the addition of PK timepoints. Note that the PK sample at 192 hrs., if collected, should be prior to dose on Day 1). Grammatical and typographic corrections for increased clarity. Due to a recent update to the Pfizer Protocol template, Sections 8 (Adverse Event [AE] Reporting) and 15.1 (Communication of Results by Pfizer) were revised accordingly. Due to the number of dosing cohorts, the number of patients to be enrolled in the dose escalation portion of Phase 1 will be increased in size from 30 patients to 36 patients in order to align with the statistical design. Exclusion criteria text added to Concomitant Treatment section. In Japan, after completion of Cycle 1, patients will be asked to sign an additional consent document for confirmation of the patient's willingness to continue participation in this study before starting Cycle 2. Update to Appendix 3: AE Management Guidelines - Keratoconjunctivtis Guideline per FDA request. Version updated from DRAFT dated 11 March 2015 to FINAL dated 19 March 2015 after confirmation from FDA.

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		Per FDA comments on 19 March 2015, patients taking strong P-glycoprotein inhibitors are excluded from the study. Patients are also to avoid the use of the drugs that are strong P-gp inhibitors during the study. P-gp abbreviation added to the list.
Amendment 2	02 October 2015	Abbreviation list updated. Table of Content updated to reflect table number changes. Grammatical and typographic corrections for increased clarity. Schedule of Activities (SOAs) were tabled sequentially to provide better flow. References and links to these tables were updated throughout the entire protocol. Wording changes within some of the footnotes were added for clarity and accuracy. Footnotes were updated in Phase 1 Table 1: • Footnote 4 – baseline signs and symptoms including grade will be captured on the Medical History case report form (CRF) not the Adverse Event CRF (and other tables were this footnote applies). • Footnote 14 – 15 unstained formalin-fixed, paraffin-embedded (FFPE) sections (vs 10). Contact Sponsor for lesser amounts of tissue. (also referenced in section 7.3). • Footnote 29 – added: Blood samples for 4-β-hydroxycholesterol /cholesterol analysis: Three (3) mL of blood will be collected in lithium heparin tubes for the analysis of 4-β-hydroxycholesterol and cholesterol as outlined in Table 2 through Table 6. Table 3 and 4 – final footnote added providing guidance post the completion of the drug-drug interaction(DDI) sub studies:

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		• Following completion of the sub-study, patients will continue on once daily dosing of PF-06747775 at the Recommend Phase 2 Dose (RP2D). Starting on Cycle 2 Day 1, following the pre-dose PK draw, patients who have completed the sub-study will continue to complete study assessments as outlined in Table 1 (Phase 1 Schedule of Activities), without additional scheduled PK or 4-ß hydroxycholesterol /cholesterol assessments. Statistical Design changed from Bayesian Model Averaging (BMA)-Continuous Reassessment Method (CRM) to CRM due to the limitations of the BMA-CRM on dose skipping and availability of valid software for BMA-CRM – see Section 9.2 reference 19. Sections 3.3 to 3.5.3 were updated to reflect similar changes made to the SOA tables for the maximum tolerated dose (MTD) and DDI sub-studies (added clarity and accuracy). Inclusion Criterion 3 was amended to denote that the measurable lesion must not have been previously irradiated. Inclusion Criterion 4 was amended to request 15 unstained sections (vs 10 sections) but if a lesser amount of tissue is available, contact the Sponsor. Exclusion Criterion 1 was amended as follows: Previously diagnosed brain metastases, unless the patient has completed the treatment that is clinically indicated, if any, and has recovered from the acute effects of any treatment that was delivered prior to study registration, have discontinued corticosteroid treatment for these metastases prior to registration and are neurologically stable.

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		Exclusion Criterion 4 was amended to add clarity to the timeframe around discontinuation of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Patients must discontinue for a minimum of: • 2 days prior to registration for erlotinib or afatinib, or 3 days for gefitinib if they will be part of the lead-in single dose PF-06747775 PK study (Phase 1 Dose Escalation Single and Multiple dose PK and electrocardiogram (ECG) Assessments; Phase 1 Sildenafil at MTD and Japan PK sub-studies) Please contact the Sponsor for direction for any other EGFR TKI. • 5 half-lives, or 5 days, (whichever is longer), prior to registration if they will be starting on continuous PF-06747775 dosing directly (Phase 1 PK sub-studies at RP2D except Japan). Section 5.3 – added a notation that drugs used for the DDI and MTD studies will be supplied by the study site personnel (not the sponsor). Section 5.4 was amended for accuracy and clarity: PF-06747775 will be administered once daily (QD) on a continuous basis at approximately the same time each day, with the exception of the single dose lead-in period for those patients participating in the Phase 1 dose escalation cohorts. PF-06747775 is to be taken with a breakfast of 200-300 calories with 240 mL (8 ounces) of water. Food and liquids other than water are allowed 2 hours after dose. For PK sub-studies administration instructions may vary (see Section 3.5.1, 3.5.2, and 3.5.3). Following completion of PK sub-study (if applicable), patients will continue on once daily dosing of PF-06747775 as described above. Section 7 was amended to add the following language similar to that added to the footnotes for the DDI sub-studies:

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		• Patients participating in any of the PK sub-studies, including the sildenafil sub-study (MTD expansion cohort), the food effect/rifampin DDI sub-study, or the antacid effect/itraconazole DDI sub-study, will complete PK assessments as outlined in the SOA (See Table 3, Table 4, or Table 5). Upon completion of the sub-study portion, no additional scheduled PK or 4-β-hydroxycholesterol/cholesterol assessments are required, and patients will continue to complete all other study assessments as outlined in Table 1 (Phase 1 Schedule of Activities),with the exceptions noted on the relevant SOA footnotes. Section 7.3 was amended to added clarifying language.
Amendment 3	20 September 2016	The original Phase 2 portion of the study (open-label, multi-center, single-arm study of PF-06747775 at the RP2D for assessment of antitumor activity in patients with advanced EGFRm [del 19 or L858R] non-small cell lung cancer [NSCLC] with T790M [del 19 and T790M or L858R and T790M]) was revised extensively. Instead of the original Phase 2 study design, the protocol was amended to include sequential evaluation of the RP2D in 3 different clinical scenarios following completion of Phase 1 portion of the study. These scenarios are as follows: • 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

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		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 in previously-treated patients with EGFRm NSCLC with a secondary T790M mutation (del 19 and T790M or L858R and T790M). • Additionally, the Japan-specific protocol requirements were updated to enable this amended protocol to be opened for enrollment in Japan. PK assessments were updated to upcoming patient cohorts and additional assessments were added for Japan-only sites. • Several sections of the protocol were modified as a result of the study design change. A high-level summary of the major changes made by section are as follows: • Abbreviations list updated. • Protocol Summary updated. • Schedule of Activites (SOA) updated. • New SOA Tables 8 through 13 added. • Section 1, Introduction, updated. • Background information on combination agents (palbociclib and avelumab) added. • Rationale for combination starting doses and benefit-risk assessment for evaluation of the combinations added. • Section 2, Study Objectives and Endpoints, modified to include objectives and endpoints specific to the revised study design.

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		• Section 3, Study Design, modified to include details specific to the revised study design.
		
		• Section 4, Patient Selection, modified to include details specific to the revised study design.
		
		  • Entry criteria modified for new Cohorts. In addition, Inclusion Criterion 2 was modified to allow for enrollment of patients with EGFR mutation status determined by plasma sample.
		
		  • Dietary restriction guidelines added.
		
		• Section 5, Study Treatments, updated.
		
		  • Screen failure guidelines added.
		
		  • Treatment allocation methods updated.
		
		  • Drug supplies (preparation and dispensing, administration, food requirements, dose modifications) updated to include details for combination agents.
		
		  • Allowed concomitant treatments updated.
		
		• Section 6, Study Procedures, updated with details specific to revision of entry criterion allowing enrollment of patients based on EGFR mutation status determined by plasma sample.
		
		• Section 7, Assessments, updated with details specific to revised study design.
		
		• Section 9, Data Analysis/Statistical Methods, updated with details specific to revised study design.
		
		• Section 16, References, updated.

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		• Appendices updated to include: • List of Drugs Known to Predispose to Torsade de Pointes (Appendix 5). • Immune-related Response Criteria Derived from RECIST 1.1 (irRECIST) (Appendix 6). • Detailed Dose Escalation/De-Escalation Scheme for mTPI Design Based on 30% Toxicity Rate (Appendix 7).
Amendment 4-for Japan Only	19 Dec 2016	• Added a Japanese patient-only Lead-In Cohort (LIC) to investigate the safety, tolerability and PK of PF-06747775 in Japanese patients (Appendix 8) per requirement from PMDA. • Deleted the table; Japan Only: Single-Agent PF-06747775 in Previously Untreated EGFR Mutant NSCLC: Phase 2 Cohort 1 SCHEDULE OF ACTIVITIES per requirement from PMDA. • Corrected typographical errors and made minor updates to the text for clarity throughout the document.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

ABBREVIATIONS

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Ab	Antibody
ACRIN	American College of Radiology Imaging Network
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
AE	Adverse event
A/G	Albumin/globulin
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AUC	Area under the curve
AUC_{inf}	Area under the curve from zero to infinite time
AUC_{tau}	Area under the curve at steady state
AV	Atrioventricular
BA	Bioavailability
BBS	Biospecimen banking system
BCS	Biopharmaceutics classification system
BICR	Blinded Independent Central Review
BID	Twice daily
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
C	Cycle
cfDNA	Cell-free DNA
C_{eff}	Efficacious concentration
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum concentration
CNS	Central Nervous System
CPK	Creatinine phosphokinase
CRF	Case report form
CR	Complete response
CRA	Cytokine release assay

Abbreviation	Term
CRM	Continual Reassessment Method
CSA	Clinical study agreement
CCI [redacted]	[redacted]
CSF	Colony stimulating factor
CSR	Clinical study report
CT	Computed tomography
CTA	Clinical trial application
CTC	Common Toxicology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA 4	Cytotoxic T lymphocyte-associated antigen 4
C_{trough}	Concentration at steady state
CV	Coefficient of variation
CYP	Cytochrome P450
D	Day
DAI	Dosage and administration instructions
DCR	Disease control rate
DDI	Drug-drug interaction
del 19	Exon 19 deletion
DL	Dose level
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DU	Dispensible unit
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure during pregnancy
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
eg	For example
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor- mutant
ER	Estrogen receptor
EU	European Union Drug
EudraCT	European Union Drug Regulating Authorities Clinical Trials
Fc	Fragment crystalline
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle stimulating syndrome
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase

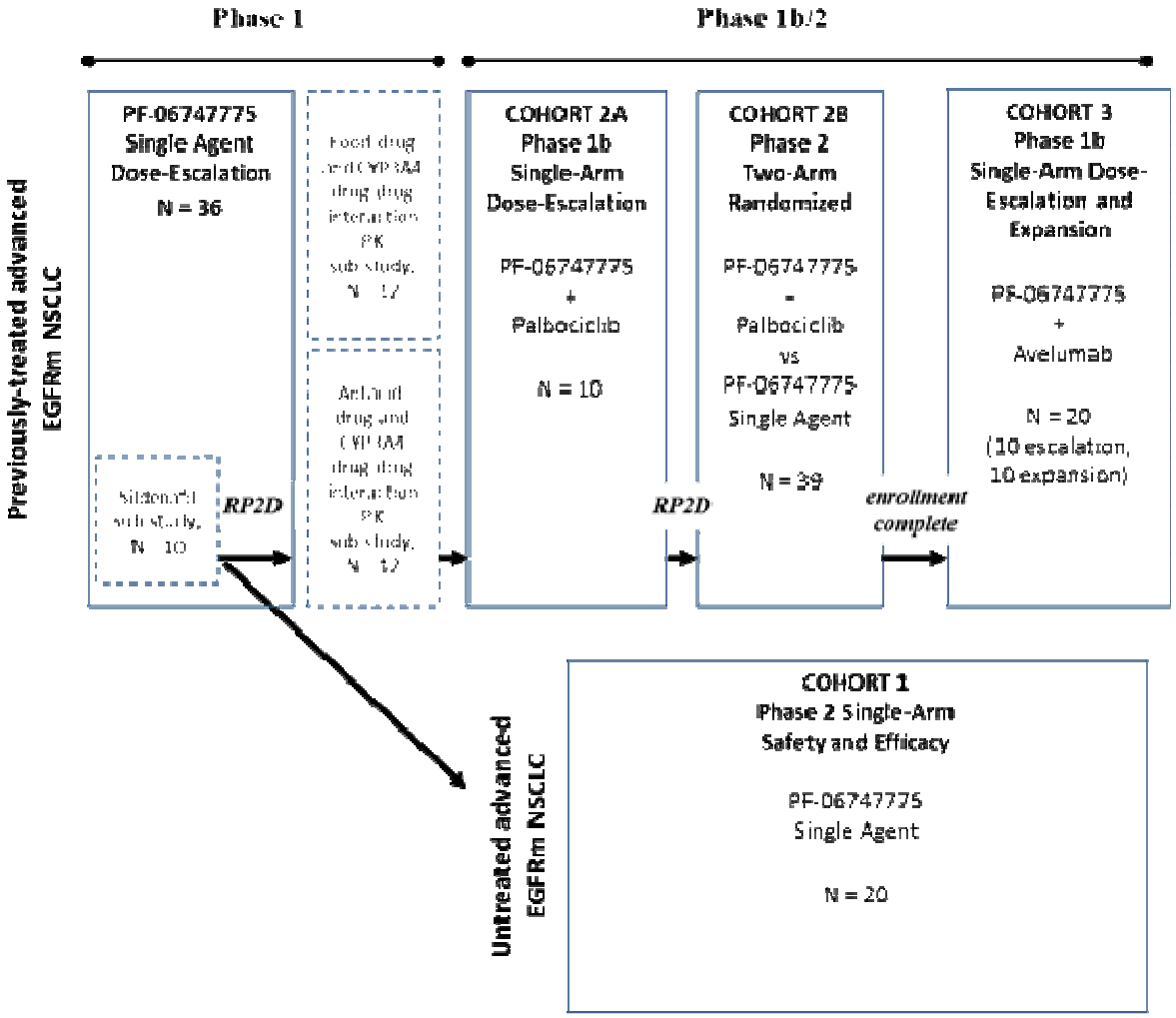
Abbreviation	Term
GI	Gastrointestinal
gm	Grams
GMP	Good Manufacturing Practice
GSTM1	Glutathione S-transferase Mu 1
G-CSF	Granulocyte-colony stimulating factor
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HDPE	High density polyethylene
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HR	Heart rate
HR	Hormone receptor
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ID	Identification
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
IND	Investigational new drug
INR	International normalized ratio
IP	Investigational product
ir	Immune-related
irAE	Immune-related adverse event
IRB	Institutional review board
IRC	Internal review committee
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRR	Infusion-related reaction
IRT	Interactive response technology
IUD	Intrauterine device
IV	Intravenous
IVD	In vitro diagnostic (product)
L858R	Point mutation in exon 21
LFT	Liver function test
LIC	Lead-in cohort
LPD	Local product document
LSFV	Last subject first visit
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction

Abbreviation	Term
mAb	Monoclonal antibody
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
MUGA	Multigated acquisition scan
N/A	Not applicable
Nab	Neutralizing antibody
NCI	National Cancer Institute
NGS	Next-generation sequencing
NK	Natural killer
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NTI	Narrow therapeutic index
OBD	Optimal biological dose
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically-based pharmacokinetic modeling
PHA	Phytohemagglutinin
pT	Target probability
PCD	Primary completion date
CCI	[redacted]
PD	Progressive disease
PD-1	Programmed cell death protein-1
CCI	[redacted]
PD-L2	Programmed death ligand-2
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PO	By mouth (oral administration)
PPI	Proton pump inhibitor
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTEN	Phosphate and tensin homolog
PTT	Partial thromboplastin time
Q2W	Every 2 weeks
QD	Every day

Abbreviation	Term
QT	Time between the start of the Q wave and the end of the T wave
R	Ratio
R_{ac}	Observed accumulation ratio
R_{ss}	Steady state accumulation ratio
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumor
RGQ	Rotor-Gene Q 5plex
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
R-R interval	R-R interval (heart rate)
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Single dose
SD	Stable disease
SIB	Suicidal ideation and behavior
SOA	Schedule of Activities
SPC	Summary of product characteristics
SRSD	Single reference safety document
SRS	Stereotactic radiosurgery
STD_{10}	Severely toxic dose
SST	Serum separator tube
T	Time
$t_{1/2}$	Half-life
TBR	Tumor background ratio
TCR	Tissue cross reactivity
TdP	Torsade de Pointes
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
TLS	Tumor lysis syndrome
T_{max}	Maximum concentration
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
UPM	Unit probability mass
US	United States
USPI	United States package insert
UTN	Universal Trial Number
UV	Ultraviolet
UVB	Ultraviolet B light
v	Version
Vz/F	Volume of distribution

Abbreviation	Term
WBC	White blood cell count
WT	Wild type

STUDY SCHEMA*



* Approximate enrollment totals indicated.
EGFRm = epidermal growth factor receptor mutant; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; RP2D = Recommended Phase 2 Dose

PROTOCOL SUMMARY:

INDICATION

Advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations (exon 19 deletion [del 19] or point mutation in exon 21 [L858R]).

BACKGROUND AND RATIONALE

Epidermal growth factor receptor -mutant (EGFRm) NSCLC accounts for approximately 20% of NSCLC, representing a conservative estimate of 100,000 to 200,000 newly diagnosed cases per year globally. Two frequent and mutually exclusive primary mutations, EGFR L858R and EGFR del 19, together accounting for approximately 85% of all cases, are oncogenic drivers, and are strong predictive biomarkers of response to EGFR tyrosine kinase inhibitors (TKIs). First-line treatment of EGFRm NSCLC patients with currently approved EGFR TKIs provides excellent response rates and disease control for 11 to 14 months, but patients invariably become resistant to these therapies and their disease progresses. For patients with resistant tumors, approximately 60% harbor a second mutation in the EGFR kinase domain (T790M), concurrently with the primary activating mutation. Thus, in efforts to discover and develop improved EGFR TKIs, these double-mutant EGFR variants, L858R/T790M and del 19/T790M, are key drug development targets in addressing resistance, and sparing wild type (WT) EGFR is essential in preventing dose-limiting toxicity (DLT).

PF-06747775 is a molecularly-targeted, rationally-designed, third generation EGFR TKI. In recombinant enzyme assays and cellular assays, PF-06747775 is a highly potent and irreversible inhibitor against the EGFR double-mutants (L858R/T790M and del 19/T790M) and single-mutants (L858R and del 19) and a weak inhibitor of WT EGFR. This inhibitory potency on mutant targets is paralleled by subsequent inhibition of the EGFR downstream signaling axis, induction of apoptosis, and viable cell decline. In xenograft mouse models, PF-06747775 demonstrates tumor growth inhibition and regression at well-tolerated doses in disease-relevant models driven by EGFR double- and single-mutants. The antitumor efficacy of PF-06747775 is dose-dependent and shows a strong correlation with pharmacodynamic (PD) inhibition of EGFR phosphorylation, inhibition of EGFR-mediated downstream signaling, and induction of apoptosis. Using multiple in vitro approaches to assess non-target kinase selectivity, PF-06747775 demonstrates the potential for high kinase selectivity, with only 7 out of 273 (3%) tested non-target kinases showing the potential for inhibition by PF-06747775 at pharmacologically-relevant concentrations.

Additionally, the compound has a preclinical safety profile which suggests that PF-06747775 can achieve an adequate therapeutic index based on the predicted efficacious concentration (C_{eff}) in patients.

There remains an unmet medical need to develop EGFR TKI agents that effectively target both the single activating mutations of del 19 and L858R, and the secondary resistance mutation T790M, while sparing WT EGFR. Drugs active against the resistance mutation will enable molecularly-targeted therapy with a more favorable toxicity profile than the

current standard of cytotoxic chemotherapy platinum-based doublets. Furthermore, by having a wide margin of selectivity favoring the EGFR mutants versus WT EGFR, PF-06747775 is likely to be positioned to improve patient outcomes from an efficacy and safety perspective.

Palbociclib is a first-in-class CDK4/6 inhibitor conditionally approved in the United States (US) for use in combination with letrozole or fulvestrant for advanced estrogen-receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer. By inhibiting CDK4/6 and subsequently downstream signaling through Rb protein that controls the cell cycle, palbociclib prevents actively proliferating cells from completing the cell division cycle, resulting in an arrest of tumor growth. EGFR TKIs inhibit phosphorylation of EGFR, thereby inhibiting downstream cell signaling through the EGFR axis including AKT, MEK/ERK, and transcription of cell cycle related genes such as cyclin D1 and E2F target genes, resulting in the induction of apoptosis and inhibition of proliferation in EGFR-dependent tumor cells. It is hypothesized that combination of the EGFR TKI PF-06747775 with palbociclib in EGFRm NSCLC could further impede tumor growth with increased efficacy over the EGFR TKI alone. This potential increased efficacy may reflect better inhibition of cell cycle progression with the combination.

In vitro and in vivo assessment of the combination of PF-06747775 and palbociclib showed increased efficacy over PF-06747775 alone in NSCLC models representing the first-line EGFRm and second-line T790M-resistant patient populations. Mechanistic studies suggest the combination effect predominantly relies on the addition of the pro-apoptotic effect of PF-06747775 plus the anti-proliferative effect of both agents. These studies support clinical testing of the PF-06747775 palbociclib combination for increased clinical benefit in EGFRm NSCLC

Separately, recent evidence has shown that tumors require suppression of the host immune system for continued growth and spread.

The development of agents targeting the interaction of programmed cell death protein-1 (PD-1) and its ligands has shown promise in the treatment of various cancers including NSCLC. Substantial clinical activity was observed with anti-PD-1 antibodies nivolumab and pembrolizumab, with an objective response rate of 15% and 20%, respectively, and long duration of response in unselected heavily pretreated NSCLC patients.

Although immune checkpoint inhibitors, including avelumab, are demonstrating promising activity in a variety of tumor types, there continues to be a need for new therapies. Tumor-directed therapies such as chemotherapy and targeted agents improve tumor antigenicity by inducing cell death, providing the basis for potential synergy with immune checkpoint inhibitors.

Recent studies in genetically-engineered mouse models demonstrate that EGFR mutations promote tumorigenesis not only by stimulating tumor cell proliferation, but also by suppressing antitumor immunity, in part by upregulating PD-1 on tumor-infiltrating T cells through a non-cell-autonomous mechanism.

Tagrisso® (osimertinib) is a third generation EGFR TKI with a similar activity profile to PF-06747775, along with numerous differences between the compounds. Tagrisso combined with the anti-programmed death ligand-1 (PD-L1) durvalumab was tested in patients with advanced EGFRm NSCLC in the Phase 1b TATTON study and the Phase 3 CAURAL study. While promising tumor responses were seen with the combination, it was too early to tell if the combination response was any different from single agent Tagrisso, and both studies revealed an increased incidence of interstitial lung disease (ILD). The TATTON study preliminary results indicated a 38% rate of ILD including 5 cases of Grade 3/4 in severity. Enrollment was suspended and both trials were put on hold in order to further assess the risk associated with the combination. It is not known currently what causes increased risk of ILD but causality due to the interaction of Tagrisso and durvalumab cannot be ruled out.

Tagrisso has been approved for single agent use and carries a warning and precaution on the label for ILD/pneumonitis, occurring in 3.3% of patients. In clinical testing of PF-06747775 to date, no ILD/pneumonitis adverse events (AE) have been observed.

Compared with anti-PD-1 antibodies that target T cells, avelumab is an anti-PD-L1 antibody that targets tumor cells. Avelumab is expected to have fewer side effects, including a lower risk of autoimmune related safety issues, as blockade of PD-L1 leaves the programmed death ligand-2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance. The anti-PD-1 antibodies pembrolizumab and nivolumab do carry a low risk of immune-related (ir) pneumonitis, with overall incidence of <3%. Hence the combination of PF-06747775 plus avelumab in patients with EGFRm NSCLC has the potential to differentiate from other EGFR TKI / anti-PD-1/-L1 combinations via an improved safety profile, especially clinically significant lung injury.

STUDY OBJECTIVES AND ENDPOINTS

This study has separate primary and secondary objectives and endpoints for the Phase 1 and each of the subsequent sections of the study.

Objectives

Phase 1

Primary Objective

- To evaluate safety and tolerability at increasing dose levels of PF-06747775 as a single agent in order to estimate the maximum tolerated dose (MTD) and the recommended Phase 2 dose (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.

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 pharmacokinetic (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 Cytochrome P450 3A4 (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 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 EGFRm NSCLC tumors;
- To evaluate tumor tissue biomarkers including, but not limited to, EGFR mutation by next generation sequencing.

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Phase 1b/2

Primary Objectives

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).

Cohort 2A –PF-06747775 plus Palbociclib: Dose Finding

- To evaluate safety and tolerability and establish 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).

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).

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 EGFRm NSCLC with a secondary T790M mutation (del 19 and T790M or L858 R and T790M).

Secondary Objectives

- To assess duration of response (DOR) and overall survival (OS) probability at 24 months (all Cohorts);
- To assess progression-free survival (PFS) (Cohorts 1, 2A, and 3);
- To further characterize the 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 single-agent patients) 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 single-agent patients) and in combination with palbociclib (Cohort 2A and 2B) and avelumab (Cohort 3);
- To assess in tumor and plasma the presence/absence of EGFR mutations (All Cohorts);
- To assess the immunogenicity of avelumab when given in combination with PF-06747775 (Cohort 3).

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- [redacted]
- [redacted]
- [redacted]

Japanese Patient-Only Lead In Cohort:

- To evaluate the safety and tolerability of PF-06747775 when given as a single agent in Japanese patients (RP2D tolerability cohort)
- To characterize single dose and steady state PK profiles of single agent PF-06747775 in Japanese patients (RP2D tolerability cohort and PK cohort)

Endpoints

Phase 1

Primary Endpoint

- Cycle 1 DLT.

Secondary Endpoints

- Overall safety profile of PF-06747775 characterized by type, incidence, severity, seriousness, and relationship to study therapy of AE (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03);
- Laboratory abnormalities;

- QT and R-R interval (R-R interval heart rate) for QTc effects of PF-06747775 when given as a single agent
- Plasma area under the curve from zero to infinite time (AUC_{inf}), maximum concentration observed after dose administration (C_{max}), half life ($t_{1/2}$), apparent clearance (CL/F), and volume of distribution (Vz/F) of PF-06747775 as a single agent after single dose;
- Pre-dose concentration at steady state (C_{trough}), area under the curve at steady state (AUC_{tau}), CL/F, observed accumulation ratio (R_{ac}), and steady state accumulation ratio (R_{ss}) of PF-06747775 as a single agent after multiple doses;
- Plasma AUC_{inf}, C_{max}, and CL/F of sildenafil alone and in combination with steady state plasma concentrations of PF-06747775;
- Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D under fed and overnight fasted conditions;
- Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and after esomeprazole treatment;
- Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and after itraconazole treatment;
- Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and after rifampin treatment;
- EGFR mutations in tumor and plasma;
- Objective response (OR), confirmed and unconfirmed, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for those patients with measurable disease.

Phase 1b/2

Primary Endpoints

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

- Confirmed OR, per RECISTv 1.1.

Cohort 2A - PF-06747775 Plus Palbociclib: Dose Finding

- Cycle 2 DLT.

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

- PFS.

Cohort 3 - PF-06747775 Plus Avelumab: Dose Finding

- Cycle 1 DLT.

Secondary Endpoints

- PFS (Cohort 1, Cohort 2A, Cohort 3);
- ORR (Cohort 2A, Cohort 2B, Cohort 3);
- DOR (All Cohorts);
- OS probability at 24 months (All Cohorts);
- Overall safety profile characterized by type, incidence, severity, seriousness, and relationship to study therapy of adverse events (NCI CTCAE v4.03);
- Laboratory abnormalities (All Cohorts);
- PK parameters of PF-06747775 following single and multiple doses as data permit when given as a single agent (Cohort 1 and Cohort 2B single-agent patients);
- PK parameters of PF-06747775 following multiple doses as data permit when given in combination with palbociclib and avelumab (Cohort 2 and Cohort 3);
- PK parameters of palbociclib and avelumab when given in combination with PF-06747775 as data permit (Cohort 2 and Cohort 3);
- QT and RR for QTc effects of PF-06747775 when given as a single agent (Cohort 1 and Cohort 2B single-agent patients) and in combination with palbociclib (Cohort 2) and avelumab (Cohort 3);
- EGFR mutations in tumor and plasma (All Cohorts);
- Avelumab serum anti-drug antibodies (ADA; neutralizing antibodies) (Cohort 3).

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Endpoint for Japanese Patient-Only Lead In Cohort

- Cycle 1 DLT (RP2D tolerability cohort);
- Overall safety profile of PF-06747775 characterized by type, incidence, severity, seriousness, and relationship to study therapy of AE (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03);
- Laboratory abnormalities;
- PK parameters of PF-06747775 following single and multiple doses as data permit when given as a single agent (RP2D tolerability cohort and PK cohort).

STUDY DESIGN

Study Overview

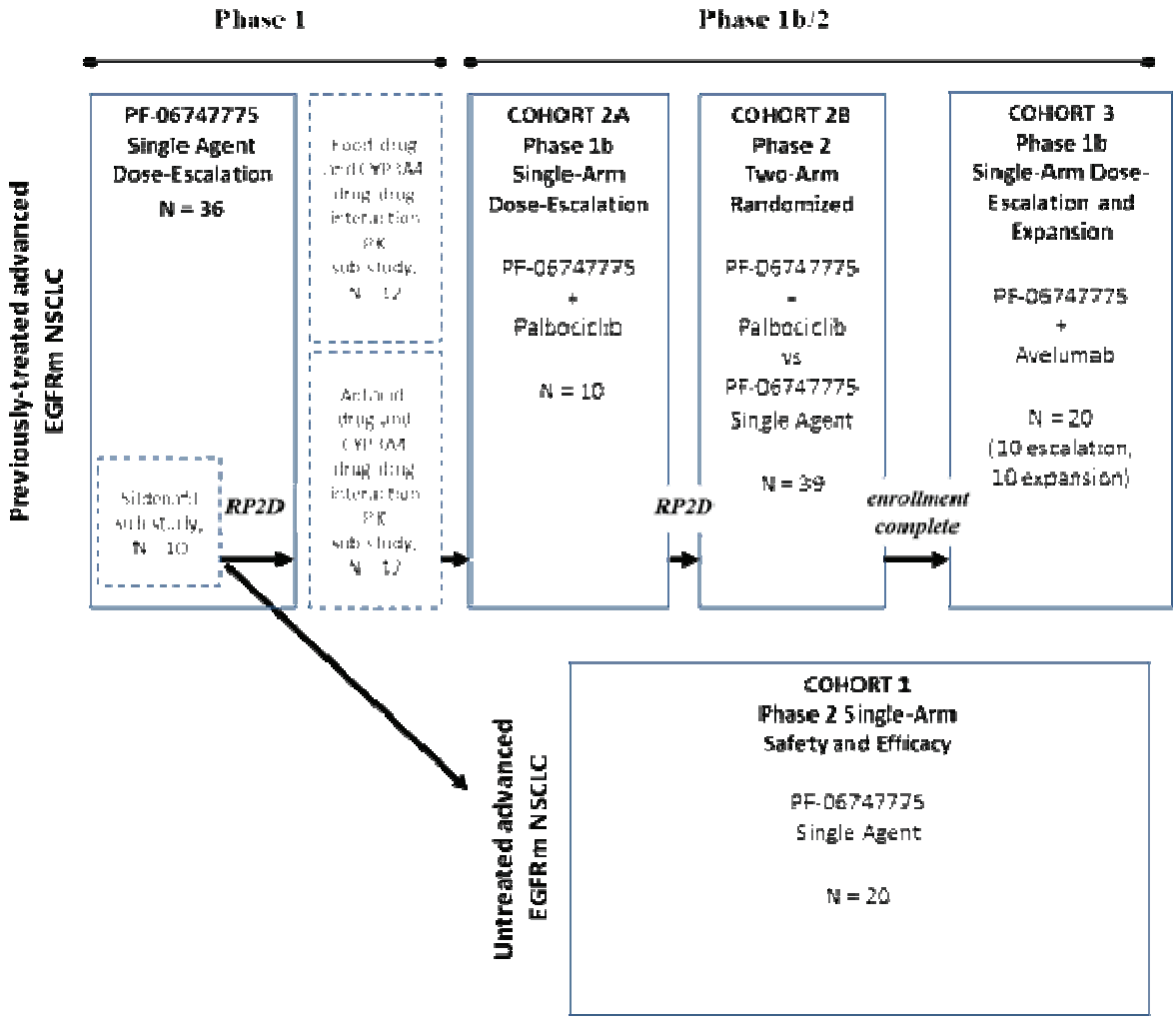
This is a Phase 1/2 study of PF-06747775 as a single agent and in combination with other cancer treatments in patients with advanced EGFRm NSCLC. The overall clinical study consists of a Phase 1 single agent dose-escalation and expansion part to determine the RP2D of PF-06747775 single agent in patients 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 in 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 (Cohort 2A) and Table 17 (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 modified toxicity probability interval (mTPI) design as described in Section 3.1.3.1 (Cohort 2A) and Section 3.1.4 (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) CCI [redacted]

Figure 1. Study B7971001 Study Schema*



* Approximate enrollment totals indicated.
EGFRm = epidermal growth factor receptor mutant; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; RP2D = Recommended Phase 2 Dose

The status of the EGFR mutations will be determined in all patients using tumor or plasma samples obtained at study entry. Patients providing tumor samples will be enrolled based on a local EGFR mutation test that includes the QIAGEN Therascreen® EGFR RGQ PCR Kit, Roche cobas® EGFR mutation kit, or a Sponsor-approved laboratory developed test that is

validated in a Clinical Laboratory Improvement Amendments (CLIA) laboratory. Patients providing plasma samples will be enrolled based on a local EGFR mutation test that includes the QIAGEN Therascreen EGFR Plasma RGQ kit, Roche cobas® EGFR mutation test v2 (US-in vitro diagnostic product [IVD]), Sysmex Inostic's OncoBEAM™ EGFR test, or a Sponsor-approved laboratory developed test that is validated in a CLIA laboratory, which will then be retrospectively confirmed by a validated cell-free DNA (cfDNA) test as determined by the Sponsor. All patients — ie, in both Phase 1 and Phase 2 parts of the study — will have their tumor's EGFR mutation status confirmed by the central lab test using FDA-approved QIAGEN Therascreen EGFR RGQ PCR kit (tumor-based) or a validated cfDNA test as determined by the Sponsor (plasma-based). The tissue samples may also be tested retrospectively using the Thermo Fisher Scientific Oncomine Next Generation Sequencing (NGS) cancer panel, which detects exon 19 deletions, exon 20 insertions, T790M mutations, and exon 21 (L858R) substitution mutations.

Study design details specific to Phase 1 are provided in Section 3.1.1. Study design details specific to Cohorts 1, 2, and 3 are provided in Section 3.1.2, Section 3.1.3, and Section 3.1.4, respectively.

All patients (regardless of Phase or Cohort) will be allowed to continue therapy until disease progression or intolerable toxicity, withdrawal of consent, termination of the study by the Sponsor, or death. Treatment continuation beyond objective disease progression is acceptable if the Investigator deems the patient to have ongoing clinical benefit. Treatment on PF-06747775 alone is also permitted if the combination is intolerable, but no patients may continue on trial on palbociclib or avelumab as single agents. Antitumor activity will be determined based on Investigator assessment. Individual patients' imaging will be prospectively collected for potential follow-up assessment by Blinded Independent Central Review (BICR).

For all patients who have a RECIST response, confirmation of the response is required at least 4 weeks after initial assessment of response.

Phase 1

The Phase 1 part of this study is an open label, multi-center, multiple dose, non-randomized, safety, PK, [redacted], 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 MTD based on cumulative data on DLTs in the first cycle of treatment.

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

- A sildenafil sub-study (PF-06747775 will be assessed for CYP3A4 induction/inhibition, utilizing sildenafil as the CYP3A4 substrate);

- A food-drug and a CYP3A4 drug-drug interaction (DDI) PK sub-study (CYP3A4 induction interaction with rifampin);

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

Phase 2 Cohort 1

Upon determination of the RP2D of PF-06747775 single agent, 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 in previously untreated patients with advanced EGFRm (del 19 or L858R, with or without T790M) NSCLC.

Phase 1b/2 Cohort 2

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[redacted] 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). Both Cohort 2A and Cohort 2B will enroll patients with previously-treated advanced EGFRm NSCLC (del 19 and T790M or L858R and T790M).

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

Dose finding will follow mTPI method with adjustments using DLT rate.

Phase 2 Cohort 2B will be initiated once the RP2D of the PF-06747775 and palbociclib combination is determined. Approximately 39 patients will be randomized in a 2:1 ratio to receive either PF-06747775 plus palbocicib combination or PF-06747775 single agent.

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

Cohort 3

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, PK[redacted] of the RP2D of PF-06747775 administered PO QD in combination with avelumab administered intravenously (IV) every 2 weeks (Q2W) in previously-treated patients with advanced EGFRm NSCLC (del 19 and T790M or L858R and T790M).

The starting dose level (DL1) for the Cohort 3 combination is PF-06747775 200 mg PO QD and avelumab 10 mg/kg IV Q2W in 28-day (4-week) cycles.

Dose finding will follow the mTPI design. Once RP2D of PF-06747775 in combination with avelumab is determined, the Dose Expansion Phase will be opened. In Cohort 3, a total of approximately 20 patients will be enrolled to assess the safety, PK, [redacted] of the combination.

The Schedule of Activities (SOA) Tables outline the study treatments including separate SOA for each phase/group of the study and for the Phase 1 PK sub-studies.

Japanese Patient-Only Lead In Cohort

This study will include a Japanese patient lead in cohort (LIC) to evaluate the safety, tolerability and PK of PF-06747775 in Japanese patients with advanced EGFRm NSCLC at RP2D (PF-06747775 200 mg) when given as a single agent. This Japanese LIC will consists of 2 cohorts; RP2D tolerability cohort and PK cohort. The RP2D tolerability cohort will be enrolled first. Up to 3 patients will be enrolled and treated at RP2D. If no DLT is observed, no additional patients will be enrolled in this cohort. If a DLT is observed in 1 of the initial 3 treated patients, then 3 additional patients will be enrolled and treated. Following 1 cycle (21 days) of treatment, a safety review will be performed by Japanese investigators and the Sponsor to determine whether the emerging data from this cohort will support inclusion of patients at Japanese sites in Phase 2 (Cohort 1) and Phase 1b/2 (Cohort 2A, 2B and 3). After tolerability in Japanese patients has been confirmed in the RP2D tolerability cohort, an additional PK cohort will be initiated. In the second PK cohort, 3 patients will be enrolled and they will receive 100 mg single dose followed by once daily continuous dosing at the RP2D. In both cohorts, blood samples will be collected for PK assessment (See Appendix 8).

SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) tables provide an overview of the protocol visits and procedures. Refer to the Assessments section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

The SOA Tables has been organized by Study Phase and Cohort. Further, the schedules of activities for PK and electrocardiogram (ECG) assessments have been added outside of the primary SOAs for clarity.

Table 1. PHASE 1 SCHEDULE OF ACTIVITIES

Phase 1								
		Lead-in PK	CYCLE 1 (21 days)		CYCLE 2 (21 days)	CYCLE ≥3 (21 days)	End of Treatment[26]	Follow-up[27]
Visit Identifier	**Screening[2]**	**(Day -8)**	**Day 1[1]**	**Day 11**	**Day 1**	**Day 1**		
Visit Window	**≤28 days from registration**	**±3**	**±1**	**±4**	**±2**	**±2**	**±3**	+7
Informed consent[3]	X							
Tumor history	X							
Medical history	X							
Physical examination	X		X		X	X		
Baseline signs and symptoms[4]			X					
Height	X							
Weight	X		X		X	X		
Vital signs[5]	X	X	X	X	X	X	X	X
Performance status (ECOG)[6]	X		X	X	X	X	X	X
Laboratory								
Hematology[7]	X		(X)		X	X	X	
Blood Chemistry[8]	X		(X)		X	X	X	
Coagulation[9]	X		(X)				X	
Urinalysis[10]	X		(X)				X	
Pregnancy test[11]	X		X		X	X	X	
(12-lead) ECG [12]	X	See Table 2						
Registration and Treatment								
Registration[13]		X						
PF-06747775[14]		X	Once daily, PO, continuous					
Tumor assessments								
CT or MRI imaging[15]	X					X every other cycle (every 6 weeks) +/- 7 days	X	

Phase 1								
		Lead-in PK	CYCLE 1 (21 days)		CYCLE 2 (21 days)	CYCLE ≥3 (21 days)	End of Treatment[26]	Follow-up[27]
Visit Identifier	**Screening[2]**	**(Day -8)**	**Day 1[1]**	**Day 11**	**Day 1**	**Day 1**		
Visit Window	**≤28 days from registration**	**±3**	**±1**	**±4**	**±2**	**±2**	**±3**	+7
Other clinical assessments								
Adverse Events[16]		X	X	X	X	X	X	X
Concomitant treatments and non-drug supportive interventions[17]	X		X	X	X	X	X	X
Other samplings								
[redacted] CCI	[redacted]						[redacted]	
Pharmacokinetics								
Sildenafil sub-study[19]	See Table 3							
PF-06747775 single and multiple dose pharmacokinetics[20]	See Table 2							
Food Effect sub-study[21]	See Table 4							
Antacid effect sub-study[22]	See Table 5							
CYP3A4 sub-studies[23]	See Table 4 and Table 5							
[redacted] CCI	[redacted]							
[redacted] CCI	[redacted]							
Plasma samples for mutation analysis[28]	X					X (Every 3 cycles)	X	
Blood samples for 4-β-hydroxycholesterol / cholesterol analysis[29]	See Table 2 through Table 5							

Abbreviation: CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

Footnotes

1. Day relative to start of study treatment (Day 1).
2. **Screening:** to be obtained within 28 days prior to registration.
3. **Informed Consent:** must be obtained prior to undergoing any study specific procedures unless considered standard of care.

4. **Baseline Signs & Symptoms:** patients will be asked about any signs and symptoms experienced within the past 14 days of registration. Baseline signs and symptoms (including NCI CTCAE grade if applicable) will be recorded on the Medical History case report form (CRF) page.
5. **Vital Signs:** vital signs include blood pressure (BP) and heart rate (HR).
6. **Performance status:** use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
7. **Hematology:** See Section 7.1.4 for specific required tests. No need to repeat on Cycle 1 Day 1 (C1D1) if screening assessment performed within 7 days prior to that date.
8. **Blood Chemistry:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
9. **Coagulation:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date.
10. **Urinalysis:** See Section 7.1.4 for specific required tests. Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
11. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, ie. who do not fit the definition of "female patients who are not of childbearing potential" in inclusion criterion 13, a pregnancy test, with sensitivity of at least 25 mIU/mL, and assayed in a certified laboratory, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
12. **Triplicate 12-lead ECG:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QT interval corrected by Fridericia's formula (QTcF interval). When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed in the dose escalation cohorts at screening, pre-dose and 2 hrs. post dose on Day -8, pre-dose and 2 hrs. post dose on Day 11 of Cycle 1, and pre-dose on Days 1 of Cycles 2 to 4. The 2 hrs. post dose ECG assessment is intended to target C_{max}, this time point may be re-assessed as data emerge. See Table 2 **for detailed information.**
13. Registration: "randomization" patient number and dose level allocation operated by Pfizer Inc. Registration will be within 2 days prior to the Day -8 single dose lead-in as appropriate. (see Section 5.2).
14. **Study Treatment**: PF-06747775 will be taken with a breakfast of 200-300 calories in the morning every day at approximately the same time. More information is provided under Study Treatments section.
15. **CT or MRI Tumor Assessments:** Baseline tumor assessments should be within 28 days of first dose of treatment. Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans. Minimally, chest, liver and adrenals must be imaged. Brain scans are required at baseline and every assessment if intra-cerebral disease is present; if no intra-cerebral disease is found at baseline, then brain imaging is only required on study if clinically indicated. Bone scans will be performed at baseline if clinically indicated and on-study as appropriate to follow disease. Tumor assessment should be completed every 6 weeks (2 cycles) and repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. For all patients with RECIST measurable disease who have a RECIST response, confirmation of the response is required at least 4 weeks after initial assessment of response.

16. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version *4.0.* Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
17. **Concomitant Treatments:** all concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF.

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19. **Sildenafil sub-study (Phase 1 only at RP2D):** Sildenafil (SDF) sub-study will be performed at the MTD (expansion cohort) of Phase 1. **See** Table 3 **for detailed information**.
20. **PF-06747775 single dose and multiple dose pharmacokinetics:** serial blood samples will be collected after single and multiple doses (steady state) of PF-06747775 to characterize their pharmacokinetic behavior in the dose escalation. Patients participating in any of the PK sub-studies will not be part of this assessment. **See** Table 2 **for detailed information**.
21. **Food effect sub-study (Phase 1 only at RP2D):** in a subset of patients (12) enrolled at the PF-06747775 RP2D, a PK sub-study characterizing the potential effect that a high fat high calorie meal could have on the absorption of PF-06747775 will be performed prior to the starting of the Phase 2 portion. Each patient will serve as their own control in which PF-06747775 will be administered in the morning under either "fed" or "overnight fasted" (≥10 hrs.) conditions. The testing order for fed versus fasted conditions will be as follows: the first 6 patients to participate in this sub-study will be tested under fed followed by fasted conditions, the next 6 patients will be tested under fasted followed by fed conditions. Patients participating in the food effect sub-study will also participate in the rifampin DDI sub-study that will follow as a fixed sequence design. **See** Table 4 **for detailed information**.
22. **Antacid effect sub-study (Phase 1 only at RP2D):** in a subset of patients (12) enrolled at the PF-06747775 RP2D, a PK sub-study characterizing the potential effect that acid reducing agents could have on the absorption of PF-06747775 treatment will be performed prior to the starting of the Phase 2 portion. Each patient will serve as their own control in a fixed sequence. PF-06747775 treatment will be administered once daily in the morning under fasted conditions followed by 4 consecutive days of PF-06747775 QD + esomeprazole (antacid). In the morning of the fifth day of antacid treatment, PK blood samples will be collected for a 24 hr. period. Patients participating in the antacid effect sub-study will also participate in the itraconazole DDI sub-study (fixed sequence). See Table 5 for detailed information.

23. **CYP3A4 sub-studies (Phase 1 only at RP2D)**: in a subset (12) of patients enrolled at the RP2D, two PK sub-studies characterizing the potential effect that CYP3A4 inhibitors and inducers could have on the exposure of PF-06747775 treatment will be performed prior to the starting of the Phase 2 portion. Each patient will serve as their own control in a fixed sequence. PF-06747775 treatment will be administered in combination with either itraconazole (inhibitor) or rifampin (inducer) after either the antacid effect or food effect sub-study has been performed. Itraconazole or rifampin will be given for 5 or 12 consecutive days in combination with PF-06747775. In the morning of the fifth or twelfth day of either CYP3A4 inhibitor or inducer treatment, PK blood samples will be collected for a 24 hr. period. **See Table 4 and Table 5 for detailed information.**

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26. **End of Treatment visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
27. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
28. **Plasma Samples for Mutation Analysis**: Two, 10 mL blood draws in K_2EDTA tubes will be collected at screening, every three cycles and at End of Treatment and processed for plasma according to the Study Manual to be used for mutation analysis, including, but not necessarily limited to, the EGFR gene.
29. Blood samples for 4-β-hydroxycholesterol /cholesterol analysis: Three (3) mL of blood will be collected in lithium heparin tubes for the analysis of 4-β-hydroxycholesterol and cholesterol as outlined in Table 2 through Table 5.

Table 2. Phase 1 Single and Multiple Dose PK and ECG Assessments for Phase 1 Dose Escalation Cohorts.

Patients Participating in any of the PK Sub-Studies will not be Part of this Assessment.

Visit Identifier	Lead-in Day -8 (± 3)						Cycle 1 Day-7	Cycle 1 Day -6	Cycle 1 Day -5 / -4*	Cycle 1 Day -3* / -2*	Cycle 1 Day -1* / 1*	Cycle 1 Day 1 - 10	Cycle 1 Day 11 (± 4)							Cycle 1 Day 12		Cycle 1 Day 13 - 21	Cycles 2 - 4 Day 1
Hours Post Dose	0[a]	1	2	4	6	8	24	48	72/96*	120*/ 144*	168*/ 192*		Pre-dose[b]	0[a]	1	2	4	6	8	Pre-dose[b]	0[a]	0[a]	Pre-dose[b]
PF-06747775 Dose[c]	X											X		X							X	X	
PK blood sampling[d]		X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X			X
12-lead ECG[e]	X		X										X			X							X
4-β-hydroxy-cholesterol/ cholesterol[f]	X																			X			X

a. **0 hrs. Dose time:** dose time of PF-06747775 that triggers the defined post dose sample collection times.

b. **Pre-dose sample collection:** before study treatment dose.

c. **PF-06747775 dose:** PF-06747775 dose will be given in the morning with a breakfast of 200-300 calories, at approximately the same time once daily in 21 day cycles. Food is allowed 2 hrs. after dose.

d. **PK blood sampling for PF-06747775 analysis:** On Day -8, 4 mL of blood in K_2EDTA tubes will be collected as shown above for single dose PK analysis. On Day 11 of Cycle 1, 4 mL of blood in K_2EDTA tubes will be collected as shown above for multiple dose PK analysis. On Day 1 of Cycles 2 to 4, 4 mL of blood in K_2EDTA tubes will be collected prior to PF-06747775 dose (pre-dose) for steady state PK analysis.

e. **Triplicate 12-lead ECG:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed at pre-dose and 2 hrs. post dose on Day -8, pre-dose and 2 hrs. post dose on Day 11 of Cycle 1, and pre-dose on Days 1 of Cycles 2 to 4. The 2 hrs. post dose ECG assessment is intended to target C_{max}, this time point may be re-assessed as data emerge.

f. Blood sampling for 4-β-hydroxycholesterol and cholesterol analysis: 3 mL blood collected in Lithium heparin tubes pre-dose.

* In order to accommodate weekends, only 3 of these 5 timepoints (Day -4, Day -3, Day -2, Day -1, Day 1) should be collected. This pertains to all sites. The PK sample at 192 hrs, if collected, should be prior to dose on Day 1.

Abbreviations: PK = pharmacokinetic.

Table 3. Phase 1 Sildenafil Sub-Study (Phase 1 only at MTD Expansion Cohort).

Visit Identifier	Lead-in Day -8 (± 3)								Cycle 1 Day -7	Cycle 1 Day 1 - 10	Cycle 1 Day 11 (± 4)								Cycle 1 Day 12	Cycle 1 Days 12 - 21
Hours Post Dose	0[a]	0.5	1	2	3	4	6	8	24	0[a]	Pre-dose[b]	0[a]	0.5	1	2	3	4	6	8	Pre-dose[b]	0[a]
Sildenafil dose[c]	X											X									
PF-06747775 Dose[d]										X		X									X
PK blood sampling[e]		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	
4-β-hydroxy-cholesterol/ cholesterol[f]	X										X										

a. **0 hrs. Dose time:** dose time of sildenafil or PF-06747775 that triggers the defined post dose sample collection times.

b. **Pre-dose sample collection:** before study treatment dose.

c. **Sildenafil dose:** a single 25 mg dose of sildenafil will be given in the morning at approximately the same time on Day -8 and on Day 11 of Cycle 1 following a ≥10 hr. overnight fast; food is allowed 2 hrs. after dose. On Day 11 of Cycle 1, PF-06747775 will be given together with sildenafil (see Section 3.5.1).

d. **PF-06747775 dose:** PF-06747775 at the MTD dose will be given in the morning, with a breakfast of 200-300 calories, at approximately the same time once daily in 21 day cycles. On Day 11 of Cycle 1, PF-06747775 will be given in the morning with sildenafil following a ≥10 hr. overnight fast. Food is allowed 2 hrs. after dose.

e. **PK blood sampling for PF-06747775 and sildenafil analysis:** On Day -8, 4 mL of blood in K2EDTA tubes will be collected for PK analysis. On Day 11, a PK blood sample will be collected prior to the dose of sildenafil + PF-06747775 (pre-dose). After sildenafil and PF-06747775 dose, 4 mL of blood in K2EDTA tubes will be collected as shown above for PK analysis.

f. Blood sampling for 4-β-hydroxycholesterol and cholesterol analysis: 3 mL blood collected in Lithium heparin tubes pre-dose.

Following completion of sub-study, patients will continue on once daily dosing of PF-06747775 at the MTD. Starting on Cycle 2 Day 1, patients who have completed the sub-study will continue to complete study assessments as outlined in Table 1 (Phase 1 Schedule of Activities), without any additional scheduled PK or 4-β-hydroxycholesterol /cholesterol assessments.
Abbreviation: PK = pharmacokinetic.

Table 4. Phase 1 Food Effect and Rifampin DDI Sub-Studies (Phase 1 only at the RP2D).

Visit Identifier	Cycle 1 Day 8 (fasted-fed & fed-fasted)							Cycle 1 Day 9 (fasted-fed & fed-fasted)							Cycle 1 Day 10	Cycle 1 Day 10 - 20		Cycle 1 Day 21							Cycle 2 Day 1
Hours Post Dose	Pre-dose[a]	0[b]	1	2	4	6	8	Pre-dose[a]	0[b]	1	2	4	6	8	Pre-dose[a]	-2	0[b]	-2	Pre-dose[a]	0[b]	1	2	4	6	8	Pre-dose[a]
PF-06747775 dose[c]		X							X								X[d]			X						
Rifampin Dose[d]																X[d]		X[d]								
PK blood sampling[e]	X		X	X	X	X	X	X		X	X	X	X	X	X				X		X	X	X	X	X	X
4-β-hydroxy-cholesterol/ Cholesterol[f]	X																		X							

a. **Pre-dose sample collection:** before study treatment dose.

b. **0 hrs. Dose time:** dose time of PF-06747775 that triggers the defined post dose sample collection times.

c. **PF-06747775 dose:** PF-06747775 at the RP2D will be given in the morning, starting on Cycle 1 Day 1, with a breakfast of 200-300 calories (see Section 3.5.2), at approximately the same time once a day in 21 day cycles. On Days 8 and 9 of Cycle 1, following ≥10 hr overnight fast, PF-06747775 will be given either while fasting or with a high-fat, high-calorie meal. The testing order for fasted versus fed conditions will be as follows: the first 6 patients to participate in this sub-study will be tested under fasted followed by fed conditions, the next 6 patients will be tested under fed followed by fasted conditions. Food is allowed 4 hrs. after dose in both fasted and fed conditions. A fixed sequence with rifampin treatment will happen after the fasted/fed portions have been completed.

d. **Rifampin dose:** On Days 10 to 20 of Cycle 1, a 600 mg dose of rifampin will be given to patients at approximately the same time in the morning 2 hours prior to breakfast. On Day 21 of Cycle 1, following ≥10 hr overnight fast, a pre-dose sample should be collected followed by rifampin + PF-06747775 treatment. Food is allowed 4 hrs. after dose.

e. **PK blood sampling for PF-06747775 analysis:** On Day 8 of Cycle 1, 4 mL PK blood samples in K2EDTA tubes will be collected pre and post dose as shown above. On Day 9 of Cycle 1, 4 mL PK blood sample in K2EDTA tubes will be collected pre and post dose as shown above. On day 21 of Cycle 1, 4 mL PK blood sample in K2EDTA tubes will be collected pre and post dose as shown above.

f. Blood sampling for 4-β-hydroxycholesterol and cholesterol analysis: 3 mL blood collected in Lithium heparin tubes pre-dose.

Following completion of the sub-study, patients will continue on once daily dosing of PF-06747775 at the R2PD. Starting on Cycle 2 Day 1, following the pre-dose PK draw, patients who have completed the sub-study will continue to complete study assessments as outlined in Table 1 (Phase 1 Schedule of Activities), without additional scheduled PK or 4-β-hydroxycholesterol /cholesterol assessments.
Abbreviations: PK = pharmacokinetic.

Table 5. Phase 1 Antacid Effect and Itraconazole DDI Sub-Studies (Phase 1 only at the RP2D).

Visit Identifier	**Cycle 1 Day 8**							**Cycle 1 Day 9**			**Cycle 1 Day 10 - 12**		**Cycle 1 Day 13 (antacid)**							**Cycle 1 Day 14**		**Cycle 1 Day 15 - 16**	**Cycle 1 Day 17 - 20**	**Cycle 1 Day 21**							**Cycle 2 Day 1**
Hours Post Dose	Pre-dose[a]	0[b]	1	2	4	6	8	-2	Pre-dose[a]	0[b]	-2	0[b]	-2	Pre-dose[a]	0[b]	1	2	4	6	8	Pre-dose[a]	0[b]	0[b]	0[b]	-3	Pre-dose[a]	0[b]	1	2	4	6	8	Pre-dose[a]
PF-06747775 dose[c]		X								X		X			X							X	X	X			X					
Esomeprazole dose[d]								X			X		X																			
Itraconazole dose[e]																								X	X							
PK blood sampling[f]	X		X	X	X	X	X		X					X		X	X	X	X	X	X					X		X	X	X	X	X
4-β-hydroxy-cholesterol/ Cholesterol[g]	X																									X						

a. **Pre-dose sample:** before study treatment dose.
b. **0 hrs. Dose time:** dose time of PF-06747775 that triggers the defined post dose sample collection times.
c. **PF-06747775 dose:** PF-06747775 at the RP2D will be given in the morning, starting on Cycle 1 Day 1, with a breakfast of 200-300 calories (see Section 3.5.3), at approximately the same time once a day in 21 day cycles. Each patient will serve as their own control in a fixed sequence. A washout period of 3 days prior to dosing itraconazole is required to restore the pH of the stomach (C1 D14 - 16). During this washout period, PF-06747775 will be given daily in the morning with a breakfast of 200-300 calories. Food is allowed 2 hrs. after dose. A minimum of 12 patients (PK evaluable) are required for this study.
d. **Esomeprazole dose**: on Days 9-12 of Cycle 1, a 40 mg dose of esomeprazole (antacid) will be given to patients 2 hrs. prior to breakfast and PF-06747775. On Day 13 of Cycle 1, patients will take 40 mg of esomeprazole at home without food (fasted) prior to arriving at the clinic, then a PK blood sample will be collected prior to dose (pre-dose), then patients will receive PF-06747775 with a breakfast of 200-300 calories, approximately 2 hrs. after esomeprazole dose. Food is allowed 2 hrs. after dose of PF-06747775.
e. **Itraconazole dose:** On days 17 to 20 of Cycle 1, a 200 mg dose of itraconazole + PF-06747775 should be given with a breakfast of 200-300 calories in the morning at approximately the same time of the day. On day 21 of Cycle 1, 3 hrs. prior to the administration of PF-06747775 treatment, 200 mg of itraconazole should be taken at home without food (fasted) prior to arriving at the clinic, then a pre-dose PK blood sample will be collected approximately 3 hrs. post itraconazole dose, followed by PF-06747775 treatment with a breakfast of 200-300 calories. Food is allowed 2 hrs. after dose.
f. **PK Blood sampling for PF-06747775 analysis:** On Day 8 of Cycle 1, a 4 mL PK blood sample in K_2EDTA tubes will be collected prior to dose (pre-dose) then patients will receive PF-06747775 treatment, and 4 mL PK blood samples in K_2EDTA tubes will be collected as shown above. On Day 13 of Cycle 1, a 4 mL PK blood sample in K_2EDTA tubes will be collected prior to dose (pre-dose, 2 hrs. after esomeprazole administration) then patients will receive PF-06747775, and 4 mL PK blood sample in K_2EDTA tubes will be collected as shown above. On Day 21 of Cycle 1, a 4 mL PK blood sample in K_2EDTA tubes will be collected prior to dose of PF-06747775 (pre-dose, 3 hrs. after itraconazole administration) then patients will receive PF-06747775, and 4 mL PK blood samples in K_2EDTA tubes will be collected as shown above.
Blood sampling for 4-β-hydroxycholesterol and cholesterol analysis: 3 mL blood collected in Lithium heparin tubes pre-dose.

Following completion of sub-study, patients will continue on once daily dosing of PF-06747775 at the R2PD. Starting on Cycle 2 Day 1, following the pre-dose PK draw, patients who have completed the sub-study will continue to complete study assessments as outlined in Table 1 (Phase 1 Schedule of Activities), without additional scheduled PK or 4-β-hydroxycholesterol /cholesterol assessments.

Abbreviations: PK = pharmacokinetic.

Table 6. Single-Agent PF-06747775 in Previously-Untreated EGFRm NSCLC: Phase 2 Cohort 1 SCHEDULE OF ACTIVITIES

	Phase 2							
		LEAD-IN PK	CYCLE 1 (21 days)		CYCLE 2 (21 days)	CYCLES ≥3 (21 days)	End of Treatment[23]	Follow- up[24]
Visit Identifier	**Screening[2]**	**Day -4**	**Day 1[0]**	**Day 11**	**Day 1**	**Day 1**		
Visit Window	**≤28 days from registration**		**±1**	**±4**	**±2**	**±2**	**±3**	**+7**
Informed consent[3]	X							
Tumor history	X							
Medical history	X							
Physical examination	X		(X)		X	X		
Baseline signs and symptoms[4]			X					
Height	X							
Weight	X		X		X	X		
Vital signs[5]	X		X	X	X	X	X	X
Performance status (ECOG)[6]	X		X	X	X	X	X	X
Contraception check[7]	X		(X)		X	X	X	
Laboratory								
Hematology[8]	X		(X)		X	X	X	
Blood Chemistry[9]	X		(X)		X	X	X	
Coagulation[10]	X		(X)				X	
Urinalysis[11]	X		(X)				X	
Pregnancy test[12]	X		X		X	X	X	
12-Lead ECG[13]	X	X (See Table 7)	See Table 7				X	
Registration and Treatment								
Registration[14]		X						
PF-06747775[15]		X	Once daily PO continuous					
Tumor assessments								
CT or MRI imaging[16]	X					X and every other cycle (every 6 weeks) +/- 7 days	X	
Other clinical assessments								
Adverse Events[17]			X	X	X	X	X	X
Concomitant treatments and non-drug supportive interventions[18]	X		X		X	X	X	X

	Phase 2							
		LEAD-IN PK	CYCLE 1 (21 days)		CYCLE 2 (21 days)	CYCLES ≥3 (21 days)	End of Treatment[23]	Follow- up[24]
Visit Identifier	**Screening[2]**	**Day -4**	**Day 1[0]**	**Day 11**	**Day 1**	**Day 1**		
Visit Window	**≤28 days from registration**		**±1**	**±4**	**±2**	**±2**	**±3**	+7
Other samplings								
[redacted] CCI	[redacted]						[redacted]	
Pharmacokinetics[20]		X (See Table 7)	See Table 7					
[redacted] CCI	[redacted]							
Genotyping sample[22]	X							
Plasma Samples for Mutation Analysis[25]	X					Cycle 5 only	X	
[redacted] CCI	[redacted]					[redacted]	[redacted]	
Survival[27]								X

Abbreviation: →= ongoing/continuous event; AEs = adverse events; C = cycle; CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

Footnotes

1. Day relative to start of study treatment (Day 1).
2. **Screening:** to be obtained within 28 days prior to registration.
3. **Informed Consent:** must be obtained prior to undergoing any study specific procedures unless considered standard of care.
4. **Baseline Signs & Symptoms:** patients will be asked about any signs and symptoms experienced within the past 14 days of registration. Baseline signs and symptoms (including NCI CTCAE grade, if applicable) will be recorded on the Medical History case report form (CRF) page.
5. **Vital signs:** vital signs include blood pressure (BP) and heart rate (HR). Vital signs will be taken and recorded during the site clinic visit.
6. **Performance status:** use Eastern Cooperative Oncology Cohort (ECOG) – see Appendix 2.
7. **Contraception Check:** Male patients who are able to father children, and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly, and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
8. **Hematology:** See Section 7.1.4 for specific required tests. No need to repeat on Cycle 1 Day 1 (C1D1) if baseline assessment performed within *7* days prior to that date.
9. **Blood Chemistry:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within *7* days prior to that date.
10. **Coagulation:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within *7* days prior to that date.

11. **Urinalysis:** See Section 7.1.4 for specific required tests. Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
12. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, ie, who do not fit the definition of "female patients who are not of childbearing potential" in inclusion criterion 13, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory>, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
13. **Triplicate 12-Lead ECGs:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed according to the schedule outlined in Table 7.
14. Registration: Patients will be enrolled according to a computer generated pseudo-random code. Randomization numbers will be assigned by a central web-based randomization system operated by Pfizer Inc.
15. **Study Treatment**: The recommended Phase 2 Dose (RP2D) of PF-06747775 will be given with a breakfast of 200-300 calories in the morning every day at approximately the same time once daily in 21 day cycles.
16. **CT or MRI Tumor Assessments: Baseline assessments must be within 28 days of first study treatment.** Tumor assessments will include all known or suspected disease sites. Tumor response will be assessed per RECIST v1.1. Imaging may include chest, abdomen and pelvis CT or MRI scans. Minimally, chest, liver and adrenals must be imaged. Brain scans are required at baseline and every assessment if intra-cerebral disease is present; if no intra-cerebral disease is found at baseline, then brain imaging is only required on study if clinically indicated. Bone scans will be performed at baseline if clinically indicated and on-study as appropriate to follow disease. For all patients with RECIST measurable disease who have a RECIST response, confirmation of the response is required at least 4 weeks after initial assessment of response. Tumor assessment should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. For patients that have discontinued the treatment period due to reasons other than disease progression: Tumor assessments must continue until documented progression of disease by investigator. Patients who discontinue treatment without PD should continue to have tumor assessments performed every 6 weeks until PD is confirmed by investigator regardless of subsequent anti-cancer treatments.
17. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version *4.0*. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.
18. **Concomitant Treatments:** all concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF.

CCI [redacted]

20. **PK Sampling:** serial blood samples will be collected after single and multiple doses of PF-06747775 to characterize PK behavior. See Table 7 for more detailed information**.** CCI [redacted]

CCI [redacted]

22. Genotyping sample: A 4 mL blood in K_2 edetic acid (ethylenediaminetetraacetic acid, EDTA) optimized for DNA analysis will be collected at the baseline visit for genotyping analysis.
23. **End of Treatment visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
24. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. For patients that have discontinued the treatment period due to reasons other than disease progression: Tumor assessments will continue to be performed every 6 weeks during long term follow up until documented disease progression, start of a new anti-cancer treatment, death or lost to follow-up (whichever occurs first). All patients will be followed for at least 24 months after initial dose of last patient treated.
25. **Plasma Samples for Mutation analysis**: Two, 10 mL blood specimens will be collected at screening, Cycle 5 Day 1, and at End of Treatment and processed for plasma preparation according to the Study Manual and will be used for mutation analysis, including, but possibly not limited to, the EGFR gene.

CCI [redacted]

27. **Survival:** Will be performed every 2 months for up to 24 months after PD or new anti-cancer therapy has commenced (telephone contact is acceptable).

Table 7. SINGLE-AGENT PF-06747775: Cohort 1 Phase 2 PK and ECG Assessments

Visit Identifier	Lead-in									Cycle 1								Cycles 2 - 4
Day	-4						-3	-2	-1	1 (± 1)		Day 11 (± 4)					12	1 (± 2)
Hours Post Dose	0[a]	1	2	4	6	8	24	48	72	96[f] (Pre-Dose[b])	0[a]	Pre-Dose[b]	1	2	4	6	24 (Pre-Dose[b])	Pre-Dose[b]
PF-06747775 Dose[c]	X										X	Once daily PO continuous, with breakfast						
PK blood sampling[d]		X	X	X	X	X	X	X	X	X[b]		X	X	X	X	X	X[b]	X[b]
12-Lead ECG[e]	X		X									X		X		X		X

a. **0 hrs. Dose time:** dose time of PF-06747775 triggers the defined post dose sample collection times.

b. **Pre-dose sample collection:** before study treatment dose.

c. **PF-06747775 dose:** PF-06747775 dose will be given in the morning with a breakfast of 200-300 calories, at approximately the same time once daily in 21 day cycles starting continuous dosing on Cycle 1 Day 1. On days in which pre-dose ECG or PK assessments are conducted, dosing should occur in clinic with breakfast after pre-dose ECGs are completed and pre-dose PK samples are drawn. Food is allowed 2 hrs. after dose.

d. **PK blood sampling for PF-06747775 analysis:** On Day -4, 4 mL of blood in K_2EDTA tubes will be collected as shown above for single dose PK analysis. On Day 1 of Cycle 1, (96 hr post lead-in dose) a PK sample will be taken before dose of PF-06747775 (the start of continuous daily dosing). On Day 11 of Cycle 1, 4 mL of blood in K_2EDTA tubes will be collected as shown above for multiple dose PK analysis. On Day 1 of Cycles 2 - 4, 4 mL of blood in K_2EDTA tubes will be collected prior to PF 06747775 dose (pre-dose) for steady state PK analysis.

e. **Triplicate 12-Lead ECG:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed at pre-dose and 2 hrs. post dose on Day -4, pre-dose and 2 hrs. and 6 hrs. post dose on Day 11 of Cycle 1, and pre-dose on Days 1 of Cycles 2 - 4. The 2 hrs. post dose ECG assessment is intended to target C_{max}, this time point may be re-assessed as data emerge.

f. If the -1 day window is utilized for the Cycle 1 Day 1 visit, then the 72 hrs. PK blood draw should occur prior to the dose of PF-06747775, which starts the once daily continuous dosing; in this case the 96 hrs. PK blood draw will not be completed.

Abbreviations: PK = pharmacokinetic; PO = by mouth; QTcF = QT interval corrected by Fridericia's formula.

Table 8. PF-06747775 + Palbociclib: Cohort 2A and Cohort 2B SCHEDULE OF ACTIVITIES

Visit Identifier	**Screening**[2]	**Treatment Phase (1 Cycle = 21 days)**			**End of Treatment**[24]	**Post-Treatment Follow-up**[25]
		CYCLES 1 and 2		**CYCLES ≥3**		
Study Day:	**≤28 days from registration**	**Day 1**[1]	**Day 15**	**Day 1**		
Visit Time Window:		**±2 days (except Cycle 1)**	**±2 days**	**±3 days**	**±3 days**	**+7 days**
Informed Consent[3]	X					
Tumor History[4]	X					
Medical History	X					
Physical Examination[5]	X	X	X	X	X	
Baseline Signs and Symptoms[6]		X				
Height	X					
Weight	X	X		X		
Vital Signs[7]	X	X	X	X	X	
ECOG Performance Status[8]	X	X		X	X	
Contraception Check[9]	X	X		X	X	
Laboratory						
Hematology[10]	X	(X)	X	X	X	
Blood Chemistry[10]	X	(X)	X	X		
Coagulation[10]	X	(X)	X	X		
Urinalysis[10]	X	(X)		X	X	
Pregnancy Test[11]	X	X		X	X	
12-Lead ECG[12]	X	See Table 9 and Table 10				
Registration and Treatment						
Registration[13]		X				
PF-06747775[14]		Once daily, PO continuous				
Palbociclib[14]		Once daily, PO continuous				
Tumor Assessments						
CT or MRI imaging[15]	X			X, then every other cycle (Q6W) ±7 days	X	
Other Clinical Assessments						
Adverse Events[16]		Monitored and Recorded Continuously				
Concomitant treatments and non-drug supportive interventions[17]		X	X	X	X	X

Visit Identifier	Screening[2]	Treatment Phase (1 Cycle = 21 days)			End of Treatment[24]	Post-Treatment Follow-up[25]
		CYCLES 1 and 2		CYCLES ≥3		
Study Day:	**≤28 days from registration**	**Day 1[1]**	**Day 15**	**Day 1**		
Visit Time Window:		**±2 days (except Cycle 1)**	**±2 days**	**±3 days**	**±3 days**	**+7 days**
Special Laboratory Studies						
PF-06747775 and Palbociclib Pharmacokinetics[18]		See Table 9 and Table 10				
Banked Biospecimens[19]	X					
Genotyping sample[21]	X					
Tumor Tissue Specimen[21]	X (Mandatory)				X (optional)	
Plasma Samples for Mutation Analysis[22]	X			X (C5 only)	X	
[redacted] CCI	[redacted]			[redacted]	[redacted]	
Survival[26]						X

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PO = by mouth (oral administration); Q6W = every 6 weeks; MRI = magnetic resonance imaging; MTD=Maximum Tolerated Dose; TK=Thymidine Kinase.

1. Day relative to start of study treatment (Day 1).
2. **Screening:** to be obtained within 28 days prior to registration.
3. **Informed Consent:** must be obtained prior to undergoing any study specific procedures unless considered standard of care.
4. **Tumor History:** To include information on prior anticancer treatments.
5. **Physical Examination:** A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at Screening. Symptom directed physical examinations, blood pressure and pulse rate assessment will be performed at all other timepoints.
6. **Baseline Signs/Symptoms:** patients will be asked about any signs and symptoms experienced within the past 14 days of registration. Baseline signs and symptoms (including NCI CTCAE grade, if applicable) will be recorded on the Medical History case report form (CRF) page.
7. **Vital signs:** vital signs include blood pressure (BP) and heart rate (HR). Vital signs will be taken and recorded during the site clinic visit.
8. **ECOG Performance Status:** see Appendix 2.
9. **Contraception Check:** Male patients who are able to father children, and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly, and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

10. **Hematology, Coagulation, Blood Chemistry, and Urinalysis:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within *7* days prior to that date. For urinalysis, dipstick is acceptable; microscopic analysis to be performed if dipstick is abnormal. Additional blood tests should be performed where needed for the purpose of evaluating potential DLTs or other adverse events. In particular, if a patient has Grade 3 neutropenia, a complete blood count (CBC) should be performed with greater frequency as clinically indicated.
11. **Pregnancy Test:** For female patients of childbearing potential, ie, who do not fit the definition of "female patients who are not of childbearing potential" in inclusion criterion 13, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory>, will be performed on two occasions prior to starting study therapy once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
12. **Triplicate 12-Lead ECG:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed according to the schedule outlined in Table 9 and Table 10.
13. **Registration:** A patient is considered enrolled when all screening procedures have been completed, the patient has satisfied the requirements of all inclusion/exclusion criteria, and the completed registration form has been approved by the Sponsor. Allocation of patients to treatment groups will proceed through the use of an Interactive Response Technology (IRT) system. For Cohort 2B , patients will be enrolled in a 2:1 ratio to either PF-06747775 in combination with palbociclib or PF-06747775 single agent.
14. **Study Treatment:** PF-06747775 and palbociclib will be taken at the same time along with a breakfast of 200-300 calories at approximately the same time each morning. On visits in which patients undergo pre-dose PK collection, study treatments should be taken in clinic after any pre-dose assessments are completed. More information is provided in Section 5.4.3.
15. **CT or MRI Tumor Assessments: Baseline assessments must be within 28 days of first study treatment.** Tumor assessments will include all known or suspected disease sites. Tumor response will be assessed per RECIST v1.1. Imaging may include chest, abdomen and pelvis CT or MRI scans. Minimally, chest, liver and adrenals must be imaged. Brain scans are required at baseline and every assessment if intra-cerebral disease is present; if no intra-cerebral disease is found at baseline, then brain imaging is only required on study if clinically indicated. Bone scans will be performed at baseline if clinically indicated and on-study as appropriate to follow disease. For all patients with RECIST measurable disease who have a RECIST response, confirmation of the response is required at least 4 weeks after initial assessment of response. Tumor assessment should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. For patients that have discontinued the treatment period due to reasons other than disease progression: Tumor assessments must continue until documented progression of disease by investigator. Patients who discontinue treatment without PD should continue to have tumor assessments performed every 6 weeks until PD is confirmed by investigator regardless of subsequent anti-cancer treatments.

16. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version *4.0*. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
17. **Concomitant Treatments:** all concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF.
18. **Blood Sample for Pharmacokinetics: Cohort 2A:** Blood samples will be collected after multiple doses of PF-06747775 and palbociclib to characterize their pharmacokinetic behavior according to the assessments outlined in Table 9. **Cohort 2B:** Blood samples will be collected after multiple doses (steady state) of PF-06747775 and palbociclib to characterize their pharmacokinetic behavior according to the assessments outlined in Table 10. CCI [redacted]
19. **Banked Biospecimen:** Unless prohibited by local regulations, a blood specimen (Prep D1: 4 mL K2 EDTA whole blood collection optimized for DNA analysis will be collect at screening.え
20. Genotyping sample: A 4 mL blood in K_2 edetic acid (ethylenediaminetetraacetic acid, EDTA) optimized for DNA analysis will be collected at the baseline visit for genotyping analysis.
21. **Tumor Tissue Specimen:** A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be provided that is of sufficient size to allow, if possible, for sectioning of fifteen (15) 5-micron tissue sections. If an FFPE tumor tissue block cannot be provided, sites should try to provide fifteen (15) unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. If archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample must be obtained in accord with local institutional practice for tumor biopsies. Archived or de novo tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Acquisition of the mandatory tumor tissue and submission to the Sponsor-designated Central Laboratory (see Study Manual) can be completed outside the 28-day screening window, but is required for enrollment. Please ensure the newest available specimen is submitted (eg, if a patient had a biopsy post-EGFR TKI progression, that sample should be submitted. If the T790M presence was diagnosed by plasma samples only, then the initial diagnostic biopsy may be submitted to fulfill the tissue specimen collection requirement. An optional de novo (ie, fresh biopsy) tumor sample will be collected at End of Treatment if a patient discontinues due to disease progression. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate.
22. **Plasma Samples for Mutation analysis**: Two, 10 mL blood specimen will be collected at screening, Cycle 5 Day 1, and at End of Treatment and processed for plasma preparation according to the Study Manual and will be used for mutation analysis, including, but possibly not limited to, the EGFR gene.

CCI [redacted]

24. **End of Treatment Visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).

25. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. For patients that have discontinued the treatment period due to reasons other than disease progression: Tumor assessments will continue to be performed every 6 weeks during long term follow up until documented disease progression, start of a new anti-cancer treatment, death or lost to follow-up (whichever occurs first). All patients will be followed for at least 24 months after initial dose of last patient treated.
26. **Survival:** Will be performed every 2 months for up to 24 months after PD or new anti-cancer therapy has commenced (telephone contact is acceptable).

Table 9. PF-06747775 + Palbociclib: Cohort 2A (Phase 1b) – PK and ECG Assessments

Visit Identifier	**Cycle 1**								**Cycle 2**			**Cycles 3 – 4**
Day	**1**		**15 (± 2)**					**16**	**1 (± 2)**	**15 (± 2)**		**1 (± 3)**
Hours Post Dose	Pre-Dose[b]	0[a]	Pre-Dose[b]	1	2	4	6	24 (Pre-Dose[b])	Pre-Dose[b]	Pre-Dose[b]	2	Pre-Dose[b]
Palbociclib Dose[c]		X	Once daily PO continuous, with breakfast									
PF-06747775 Dose[d]		X	Once daily PO continuous, with breakfast									
PK blood sampling (PF-06747775 and palbociclib)[e]			X	X	X	X	X	X	X	X	X	X
12-Lead ECG[f]	X		X		X		X		X	X	X	X

a. **0 hrs.** Dose time: dose time of PF-06747775 and palbociclib triggers the defined post dose sample collection times.

b. **Pre-dose sample collection:** before dose of PF-06747775 and palbociclib.

c. **Palbociclib dose:** palbociclib dose will be given in the morning along with PF-06747775 and breakfast, at approximately the same time once daily in 21 day cycles. On Day 15 of Cycle 1 and Cycle 2, both PF-06747775 and palbociclib will be given in clinic with breakfast after pre-dose ECG is completed and pre-dose PK blood samples have been drawn, then post-dose samples will be collected as above. See Section 5.4.3.2 for more details.

d. **PF-06747775 dose:** PF 06747775 dose will be given in the morning, with a breakfast of 200-300 calories, at approximately the same time once daily in 21 day cycles. On Day 15 of Cycle 1 and Cycle 2, both PF-06747775 and palbociclib will be given in clinic with breakfast after pre-dose ECG is completed and pre-dose PK blood samples have been drawn, then post-dose samples will be collected as above. Food is allowed 2 hrs. after dose.

e. **PK blood sampling for PF-06747775 and palbociclib analysis:** On Cycle 1 Day 15, 4 mL of blood in K2EDTA tubes will be collected for PK analysis of both PF-06747775 and palbociclib at each time shown above. On Cycle 1 Day 16, a PK blood sample will be collected prior to the dose of PF-06747775 and palbociclib (pre-dose). On Day 1 of Cycles 2 – 4, pre-dose PK samples will be collected, and on Day 15 of Cycle 2 PK blood samples will be collected pre-dose and 2 hrs. post-dose. In the event a patient is only receiving one agent, please contact Sponsor for further direction on PK blood draws.

f. **Triplicate 12-Lead ECG:** At each time point, three consecutive 12 lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed at pre-dose on Day 1 of Cycle 1; at pre-dose and 2 and 6 hours post dose on Day 15 of Cycle 1; at pre-dose and 2 hours post dose on Day 15 of Cycle 2; and pre-dose on Days 1 of Cycles 2 - 4. The 2-hour. post-dose ECG assessment is intended to target Cmax of PF-06747775; this time point may be re-assessed as data emerge.

Abbreviations: PK = pharmacokinetic; PO = by mouth; QTcF = QT interval corrected by Fridericia's formula.

Table 10. PF-06747775 + Palbociclib: Cohort 2B (Phase 2) – PK and ECG Assessments

Visit Identifier	Cycle 1				Cycles 2 - 4	
Day	1		15 (± 2)		1 (± 3)	
Hours Post Dose	Pre-dose[b]	0[a]	Pre-dose[b]	2	Pre-dose[b]	2
Palbociclib Dose (patients randomized to combination only)[c]		X	Once daily PO continuous, with breakfast			
PF-06747775 Dose[d] (all patients)		X	Once daily PO continuous, with breakfast			
PK blood sampling for palbociclib (patients randomized to combination only)[e]			X	X	X	X
PK blood sampling for PF-06747775[f] (all patients)			X	X	X	X
12-Lead ECG (all patients)[g]	X		X	X	X	X

a. **0 hrs. Dose time:** dose time of PF-06747775 and palbociclib (if applicable) that triggers the defined post dose sample collection times.

b. **Pre-dose sample collection:** before dose of PF-06747775 and palbociclib (if applicable).

c. **Palbociclib dose (patients randomized to combination only):** palbociclib dose will be given in the morning along with PF-06747775 and breakfast, at approximately the same time once daily in 21 day cycles. On Day 15 of Cycle 1 and Day 1 of Cycles 2 - 4, both PF-06747775 and palbociclib will be given in clinic with breakfast after pre-dose ECG is completed and pre-dose PK blood samples have been drawn. See Section 5.4.3.2 for more details.

d. **PF-06747775 dose (all patients):** PF-06747775 dose will be given in the morning, with a breakfast of 200 - 300 calories, at approximately the same time once a day in 21 day cycles. On Day 15 of Cycle 1 and Day 1 of Cycles 2 - 4, PF-06747775 and palbociclib (if applicable) will be given in clinic with breakfast after pre-dose ECG is completed and pre-dose PK blood samples have been drawn. Food is allowed 2 hrs. after dose.

e. **PK blood sampling for palbociclib analysis (patients randomized to combination only):** On Day 15 of Cycle 1 and Day 1 of Cycles 2 - 4, a 4 mL PK blood sample in K_2EDTA tubes will be collected prior to dose of PF 06747775 and palbociclib (pre-dose) for PK analysis of both PF-06747775 and palbociclib, then patients will receive PF-06747775 and palbociclib treatment and then at 2 hrs. post dose another 4 mL PK blood sample will be collected.. In the event a patient is only receiving one agent, please contact Sponsor for further direction on PK blood draws.

f. **PK blood sampling for PF-06747775 analysis (all patients):** On Day 15 of Cycle 1 and Day 1 of Cycles 2 - 4, a 4 mL PK blood sample in K2EDTA tubes will be collected prior to dose (pre-dose) for PK analysis of PF-06747775 and palbociclib (if applicable), then patients will receive PF-06747775 treatment and then at 2 hrs. post dose another 4 mL PK blood sample will be collected.

g. **12-Lead ECG (all patients):** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed at pre-dose on Cycle 1 Day 1, and at pre-dose and 2 hrs. post dose on Day 15 of Cycle 1 and Day 1 of Cycles 2 - 4. The 2 hrs. post dose ECG assessment is intended to target C_{max} of PF-06747775; this time point may be re-assessed as data emerge.

Abbreviation: PK = pharmacokinetic; PO = by mouth; QTcF = QT interval corrected by Fridericia's formula.

Table 11. PF-06747775 + Avelumab: Cohort 3 (Phase 1b) SCHEDULE OF ACTIVITIES

Visit Identifier	Screening[2]	Treatment Phase (1 Cycle = 28 days)				Post-Treatment		
		CYCLES 1-2		CYCLES ≥3				
Study Day	**≤28 days from registration**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**End of Treatment/ Withdrawal[32]**	**30-day Follow-up[33]**	**90-Day Follow-up Telephone Contact[33]**
Visit Time Window (days):[1]		**±2 days (except Cycle 1)**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**
Informed Consent[3]	X							
Tumor History History[4]	X							
Medical History	X							
Physical Examination[5]	X	X		X		X		
Baseline Signs and Symptoms[6]		X						
Height	X							
Weight	X	X		X	X	X		
Vital signs[7]	X	X	X	X	X	X		
ECOG Performance Status[8]	X	X		X		X		
Contraception Check[9]	X	X		X		X		
Laboratory								
Hematology[10]	X	(X)	X	X	X	X		
Blood Chemistry[10]	X	(X)	X	X	X	X		
Coagulation[10]	X	(X)	X	X	X	X		
Urinalysis[10]	X	(X)				X		
Thyroid Function Test and ACTH[11]	X	X		X (then every 2 cycles)		X	X	
ANA, ANCA, RF	X	If clinically indicated						
HBV, HCV testing	X							
Pregnancy test[12]	X	X		X		X		
12-Lead ECG[13]	X	See Table 12				X		
Registration and Treatment								
Registration[14]		X						
Administration of PF-06747775[15]		Once daily PO continuous, with breakfast						
Administration of avelumab[15]		X	X	X	X			

Visit Identifier	Screening[2]	Treatment Phase (1 Cycle = 28 days)				Post-Treatment		
		CYCLES 1-2		CYCLES ≥3				
Study Day	**≤28 days from registration**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**End of Treatment/ Withdrawal[32]**	**30-day Follow-up[33]**	**90-Day Follow-up Telephone Contact[33]**
Visit Time Window (days):[1]		**±2 days (except Cycle 1)**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**
Tumor assessments								
CT or MRI imaging[16]	X			X, then every other cycle (Q8W) ±7 days		X		
Other Clinical Assessments								
Adverse Events[17]		X						
Concomitant treatments and non-drug supportive interventions[18]		X						
Special Laboratory Studies								
PF-06747775 Phamacokinetics[19]		See Table 12						
Avelumab Pharmacokinetics[20]		See Table 12 (Up to Cycle 3, then every 3 cycles thereafter)						
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Visit Identifier	Screening[2]	Treatment Phase (1 Cycle = 28 days)				Post-Treatment		
		CYCLES 1-2		CYCLES ≥3				
Study Day	**≤28 days from registration**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**End of Treatment/ Withdrawal[32]**	**30-day Follow-up[33]**	**90-Day Follow-up Telephone Contact[33]**
Visit Time Window (days):[1]		**±2 days (except Cycle 1)**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±3 days**	**±7 days**
Whole Blood Biospecimen for TCR Sequencing[29]	X	X		X (Cycles 3, 4, 7, and 10)		X	X	
Whole Blood for Target Occupancy[30]		X (Cycle 1 Day 1, Cycle 1 Day 2, Cycle 2 Day 1)		X (Cycles 3, 4, 7, and 10)		X		
Blood for avelumab ADA (Immunogenicity) Testing[31]		See Table 12 (Up to Cycle 3, then every 3 cycles thereafter)				X	X	
Survival[34]								X

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PO = by mouth (oral administration); Q8W = every 8 weeks; MRI = magnetic resonance imaging; MTD=Maximum Tolerated Dose; TK=Thymidine Kinase.

1. **Visit Time Windows:** Day is relative to start of PF-06747775 and avelumab study treatment (Day 1). If avelumab is delayed, the cycle start is relative to PF-06747775. A cycle length is 4 weeks (28 days).
2. **Screening:** to be obtained within 28 days prior to registration.
3. **Informed Consent:** must be obtained prior to undergoing any study specific procedures unless considered standard of care.
4. **Tumor History:** To include information on prior anticancer treatments.
5. **Physical Examination:** A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at Screening. Symptom directed physical examinations, blood pressure and pulse rate assessment will be performed at all other timepoints.
6. **Baseline Signs/Symptoms:** patients will be asked about any signs and symptoms experienced within the past 14 days of registration. Baseline signs and symptoms (including NCI CTCAE grade, if applicable) will be recorded on the Medical History case report form (CRF) page.
7. **Vital Signs**: vital signs include blood pressure (BP) and heart rate (HR). Vital signs will be taken and recorded during the site clinic visit.
8. **ECOG Performance Status:** See Appendix 2.
9. **Contraception Check:** Male patients who are able to father children, and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly, and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

10. **Hematology, Coagulation, Blood Chemistry, and Urinalysis:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within *7* days prior to that date. For urinalysis, dipstick is acceptable; microscopic analysis to be performed if dipstick is abnormal. Additional blood tests should be performed where needed for the purpose of evaluating potential DLTs or other adverse events. In particular, if a patient has Grade 3 neutropenia, a complete blood count (CBC) should be performed as clinically indicated.
11. **Thyroid Function Tests:** Free T4, TSH, and ACTH will be performed at Screening, Day 1, and then every 8 weeks thereafter during the Treatment Phase, and at the End of Treatment and 30-day Follow-up visits after last administration of study treatment unless performed in the prior 8 weeks.
12. **Pregnancy Test:** For female patients of childbearing potential, ie, who do not fit the definition of "female patients who are not of childbearing potential" in inclusion criterion 13, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory>, will be performed on two occasions prior to starting study therapy once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
13. **Triplicate 12-Lead ECG:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QT interval corrected by Fridericia's formula (QTcF interval). When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed at screening and according to Table 12.
14. **Registration:** A patient is considered enrolled when all screening procedures have been completed, the patient has satisfied the requirements of all inclusion/exclusion criteria, and the completed registration form has been approved by the Sponsor. Allocation of patients to treatment groups will proceed through the use of an Interactive Response Technology (IRT) system.
15. **Study Treatment:** PF-06747775 will be taken with a breakfast of 200-300 calories in the morning every day at approximately the same time in 28-day cycles. Avelumab will be given as a 1-hour infusion every 2 weeks. On visits in which patients undergo pre-dose PK collection, study treatments should be taken in clinic after any pre-dose assessments are completed. More information is provided in Section 5.4.3.
16. **CT or MRI Tumor Assessments: Baseline assessments must be within 28 days of first study treatment.** Tumor assessments will include all known or suspected disease sites. Tumor response will be assessed per RECIST v1.1. Imaging may include chest, abdomen and pelvis CT or MRI scans. Minimally, chest, liver and adrenals must be imaged. Brain scans are required at baseline and every assessment if intra-cerebral disease is present; if no intra-cerebral disease is found at baseline, then brain imaging is only required on study if clinically indicated. Bone scans will be performed at baseline if clinically indicated and on-study as appropriate to follow disease. For all patients with RECIST measurable disease who have a RECIST response, confirmation of the response is required at least 4 weeks after initial assessment of response. Tumor assessment should be repeated at the End of Treatment visit if more than 8 weeks have passed since the last evaluation. For patients that have discontinued the treatment period due to reasons other than disease progression: Tumor assessments should continue to be performed every 8 weeks during long term follow up until documented disease progression, start of a new anti-cancer treatment, death or lost to follow-up.
17. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version *4.0*. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events

occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

18. **Concomitant Treatments:** all concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF.
19. **Blood Sample for PF-06747775 Pharmacokinetics:** Blood samples to characterize the pharmacokinetic behavior of PF-06747775 will be collected according to Table 12. CCI
20. **Blood Sample for Avelumab Pharmacokinetics**: Pre-dose PK samples for avelumab must be taken before administration of PF-06747775 and avelumab and will be collected according to Table 12 until Cycle 3, then every 3 cycles thereafter.

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32. **End of Treatment:** Obtain these assessments if not completed in the prior week, except for tumor assessments, which need not be repeated if performed within the prior 8 weeks. Patients continuing to experience treatment-related toxicity at this point following discontinuation of treatment will continue to be followed every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
33. **Safety Follow-up after Last Dose:** To occur Day 30 ±3 after the last study treatment administration or until the time of initiation of a new systemic anticancer treatment. The Day 90 Follow-up visit will be conducted as a phone call. If any concern arises, the patient will be called in for a follow-up visit within 5 calendar days for appropriate assessments (as per the investigator's medical judgment).
34. **Survival:** Will be performed every 2 months for up to 24 months after PD or new anti-cancer therapy has commenced (telephone contact is acceptable).

Table 12. PF-06747775 + Avelumab: Cohort 3 (Phase 1b) – PK and ECG Assessments

Visit Identifier	Cycle 1						Cycles 2 - 3		
Day	1			15 (±2)			1 (±2)		
Hours Post Dose	Pre-dose[b]	0[a]	1 (EOI)[c]	Pre-dose[b]	0[a]	1 (EOI) c	Pre-dose[b]	0[a]	1 (EOI)[c]
Avelumab Administration[d]		X			X			X	
PF-06747775 Dose[e]		X	Once daily PO continuous, with breakfast						
PK blood sampling for avelumab [f]	X		X	X		X	X		X
PK blood sampling for PF-06747775[g]				X			X		
12-lead ECG[h]	X			X			X		X (Cycle 2 only)
ADA blood sampling[i]	X			X			X		

a. **0 hrs. Dose time:** Dose time of PF-06747775 triggers the defined post dose sample collection times. Avelumab infusion should begin as soon as possible thereafter.

b. **Pre-dose sample collection:** Prior to the dose of PF-06747775 and avelumab administration.

c. **End of Infusion (EOI) PK sample:** The 1 hour PK sample for avelumab should be within 30 minutes of the end of infusion (EOI) of avelumab, drawn from the arm opposite (contralateral) from that arm which is receiving avelumab infusion.

d. **Avelumab administration:** Avelumab will be given as a 1-hour infusion every 2 weeks in 28 day cycles (as described in Section 5.4.3.3), after pre-dose ECG is completed and pre-dose PK and ADA blood samples have been drawn.

e. **PF-06747775 dose:** PF-06747775 will be given in the morning, with a breakfast of 200 - 300 calories, at approximately the same time once a day in 28 day cycles starting on Cycle 1 Day 1. On days of avelumab infusion, PF-06747775 will be given in clinic with breakfast after any required pre-dose ECG is completed and any required pre-dose PK blood samples have been drawn. Food is allowed 2 hrs. after dose.

f. **PK blood sampling for avelumab analysis:** A 3.5 mL PK blood sample in a Serum Separator Tube (SST) for avelumab will be collected at pre-dose and at EOI of avelumab on Cycle 1 Day 1, on Day 15 of Cycle 1, and on Day 1 of Cycles 2 – 3. After Cycle 3, pre-dose PK samples will be collected every 3 cycles thereafter. See Table 11 for more details. For EOI samples, blood should be drawn from the arm opposite (contralateral) from that arm which is receiving avelumab infusion. In the event a patient is only receiving one agent, please contact Sponsor for further direction on PK blood draws.

g. **PK blood sampling for PF-06747775 analysis:** A 4 mL PK blood sample in K_2EDTA tubes will be collected at pre-dose on Day 15 of Cycle 1 and Day 1 of Cycle 2 – 3. In the event a patient is only receiving one agent, please contact Sponsor for further direction on PK blood draws.

h. **Triplicate 12-Lead ECG:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed at pre-dose on Day 1 of Cycle 1, Day 15 of Cycle 1, Day 1 of Cycles 2 – 3, and at EOI on Day 1 of Cycle 2.

i. **Anti-drug antibodies for avelumab:** A 3.5 mL sample of blood will be drawn into a Serum Separator Tube (SST) to assess anti-avelumab antibodies prior to avelumab administration (pre-dose) on Cycle 1 Day 1 and Day 15, and on Day 1 of Cycles 2 – 3, then every 3 cycles thereafter. Additional samples for ADAs will be collected 30 days after the end of therapy. All samples that are positive for ADA may also undergo characterization for neutralizing antibodies (Nab).

Abbreviation: ADA=anti-drug antibodies; EOI=end of infusion of avelumab; Nab=neutralizing antibodies; PK = pharmacokinetic; PO = by mouth; QTcF = QT interval corrected by Fridericia's formula; SST=serum separator tube.

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APPENDICES

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06747775 is a highly selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) with strong activity against the EGFR mutants (EGFRm), including EGFR double-mutants (L858R/T790M and del 19/T790M) and the EGFR single-mutants (L858R and del 19). There remains an unmet medical need to develop EGFR TKI agents that effectively target both the single activating mutations of del 19 and L858R, and the secondary resistance mutation T790M, while sparing wild type (WT) EGFR. Drugs active against the resistance mutation will enable molecularly-targeted therapy with a more favorable toxicity profile than the current standard of cytotoxic chemotherapy platinum-based doublets.

The purpose of this Phase 1/2 study is to explore the safety and antitumor activity of PF-06747775 as single agent and in combination with palbociclib (PD-0332991) or avelumab (MSB00010718C) in patients with advanced EGFRm (del 19 or L858R ± T790M) non-small lung cancer (NSCLC).

1.2. Background and Rationale

1.2.1. Non-Small Cell Lung Cancer

EGFRm NSCLC accounts for approximately 20% of NSCLC, representing a conservative estimate of 100,000 to 200,000 newly diagnosed cases per year globally. Two frequent and mutually exclusive primary mutations, EGFR L858R and EGFR del 19, together account for approximately 85% of all EGFRm cases.[1] These somatic EGFR mutants are oncogenic drivers and are strong predictive biomarkers of response to EGFR TKIs, such as erlotinib, gefitinib, afatinib, and dacomitinib. All of these EGFR TKIs are dose-limited by their potency on WT EGFR. Inhibition of WT EGFR drives toxicities in epithelia where WT EGFR functions in normal adult physiology.[2,3] EGFR TKI first-line treatment of EGFRm NSCLC patients provides excellent response rates and disease control for 11 to 14 months, but patients invariably become resistant to these therapies and their disease progresses. For patients with resistant tumors, approximately 60% harbor a second mutation in the EGFR kinase domain (T790M) concurrently with the primary activating mutation[4] that renders the receptor insensitive to inhibition by the EGFR TKIs, thus restoring constitutive signaling through the EGFR axis. Hence, in efforts to discover and develop improved EGFR TKIs, these double-mutant EGFR variants, L858R/T790M and del 19/T790M, are key targets in addressing resistance, and sparing WT EGFR is essential in preventing dose-limiting toxicities (DLTs).

Further complexity identified from clinical observations and nonclinical studies has shown the resistant tumor is not simply a homogeneous T790M double-mutant-driven condition. In nonclinical studies, resistant tumor cells appeared to harbor both single- and double-mutant EGFR alleles in different ratios, and either single- or double-mutant EGFR may provide oncogenic signaling.[5] In addition, resistant tumors appeared to contain a heterogeneous mix of tumor cells, with some cells containing only single-mutant alleles admixed with other cells containing both single- and double-mutant alleles. Clinical observations supporting this

phenomenon found that continuing initial EGFR TKI upon development of tumor resistance provides significant clinical benefit over stopping initial EGFR TKI upon development of EGFR TKI resistance.[6,7,8] It is currently recommended that EGFRm NSCLC patients remain on EGFR TKI therapy even after developing resistance.[9] To provide the most effective disease control in these patients, it is hypothesized that inhibition of both the double-mutants and the single-mutants is required. PF-06747775 was discovered and optimized to meet this profile.

1.2.2. PF-06747775

PF-06747775 is a molecularly-targeted, rationally-designed, third generation EGFR TKI. PF-06747775 shows highly potent cellular activity (inhibition of EGFR phosphorylation in patient-derived NSCLC cell models) against double-mutants L858R/T790M and del 19/T790M and single-mutants L858R and del 19, and is a weak inhibitor of WT EGFR. Therefore, WT EGFR-driven PF-06747775 toxicity is anticipated to be very limited with strong efficacy against the mutant targets.

In vivo assays employing single- and double-mutant target driven tumor models were used to build a quantitative understanding of target modulation and anti-tumor activity as a function of plasma exposure of PF-06747775. The efficacious concentration (C_{eff}) providing tumor stasis was determined based on multiple in vivo models and was in close agreement between the models as 58 to 139 nM free plasma concentration.

The compound has a preclinical safety profile (Section 1.2.2.2) which suggests that PF-06747775 can achieve a good therapeutic index based on the predicted C_{eff} in patients.

These data suggest that PF-06747775 will have more than adequate potency and exposure to produce anti-tumor responses in patients with EGFRm NSCLC, which remains an unmet medical need.

1.2.2.1. PF-06747775 Nonclinical Pharmacokinetic Data

The non-clinical pharmacokinetics (PK) of PF-06747775 were characterized by moderate to high plasma clearances in mice (53 mL/min/kg) and rats (48 mL/min/kg), and low to moderate clearances in dogs (11.6 mL/min/kg). The volume of distribution was characterized as low to moderate in rats (0.66 L/kg), dogs (0.94 L/kg) and mice (1.48 L/kg). Rapid absorption was observed in all nonclinical species (0.25-1 h).

Using Day 1 toxicokinetic data from the 1-month definitive toxicity studies of PF-06747775, the T_{max} occurred at 0.5 hours in rats at all doses (≤60 mg/kg) and corresponded with mean plasma unbound C_{max} of 983 ng/mL at 60 mg/kg. On Day 1 in the 1-month toxicity studies in dogs, T_{max} was observed to range from 1.44 to 4.0 hours post dose across all doses (≤90 mg/kg) in dogs. The T_{max} appeared delayed at 90 mg/kg relative to lower doses, and corresponded with mean plasma unbound C_{max} of 836 ng/mL. According to rat brain penetration studies conducted at 10 mg/kg PF-06747775 administered by mouth (PO), PF-06747775 does not distribute into the brain, as evidenced by a mean free brain to plasma C_{max} ratio of 0.017 or 1.7%.

1.2.2.2. PF-06747775 Nonclinical Safety Data

PF-06747775 was administered once daily by oral gavage to rats and dogs in toxicity studies up to 1 month in duration. After 1 month of PF-06747775 administration, the severely toxic dose (STD_{10}) in rats was 60 mg/kg/day (unbound Day 25 AUC_{24} of 6310 ng•h/mL); a highest non-severely toxic dose (HNSTD) was not identified in dogs at doses ≥15 mg/kg/day (unbound Day 27 AUC_{24} of 2580 ng•h/mL). The primary target organs identified in rats and/or dogs included the gastrointestinal system, skin, eye, and kidney. The potential for reversibility of all target organ toxicities was established following a 1-month non-dosing period. In genetic toxicology tests, PF-06747775 was not mutagenic or clastogenic, but was aneugenic in vitro. PF-06747775 is also a potential phototoxicant based on ultraviolet (UV) B-absorbing properties.

1.2.2.2.1. Gastrointestinal System

Effects on the gastrointestinal system were dose-limiting in rats and dogs. Repeat-dose oral administration of PF-06747775 at ≥100 mg/kg/day and ≥60 mg/kg/day in rats and dogs, respectively, led to decreased body weight and unscheduled euthanasia. Histopathological examination of these non-tolerated doses revealed gastrointestinal lesions extending from the esophagus to the colon of rats, and from the tongue to the colon of dogs. The lesions impacted the epithelial and/or mucosal layers and ranged from minimal atrophy to erosions/ulcers. In the esophagus and nonglandular stomach of rats, the atrophy was characterized by thinning of the stratified squamous epithelium and a less dense keratin layer. In the glandular stomach, mucosal atrophy was primarily in the pyloric region and was characterized by mucosal thinning with attenuation and loss of epithelium. In rats at 500 mg/kg/day (after 9 days of dosing) and ≥30 mg/kg/day (after 29 days of dosing), there were erosions/ulcers in the glandular stomach mucosa accompanied by lower glucose and potassium compared with baseline values. Erosions/ulcers may have been a response to mucosal atrophy, but decreased food consumption may have also contributed[10,11] at 500 mg/kg/day. Nonadverse mucosal congestion in the glandular stomach and cecum of rats at 60 mg/kg/day was also identified. Similar findings in dogs consisted of minimal to moderate erosion/ulceration of the tongue, minimal to moderate erosions in the esophagus with minimal atrophy of esophageal epithelium, minimal to moderate duodenal crypt dilatation with minimal to mild mucosal atrophy and/or erosions, and minimal to mild crypt dilatation in the jejunum, colon, ileum, and cecum. In the duodenum and ileum, mucosal atrophy was characterized by epithelial attenuation, loss, and villar blunting. In the cecum and colon, mucosal atrophy was characterized by epithelial attenuation and loss and collapse of surrounding stroma with a slight increase in mononuclear inflammatory cells.

Soft feces were noted in rats at ≥60 mg/kg/day, and the most common gastrointestinal observation in dogs at ≥15 mg/kg/day was a non-dose related incidence of abnormal (soft, mucoid, watery, and/or red-tinged) feces at all dose levels lasting up to 27 days during the dosing phase. Body weight loss and poor condition of dogs at ≥60 mg/kg/day correlated with decreased serum creatinine compared with baseline. Emesis was also sporadically noted in dogs (1 to 5 days of study) with increased incidence (3 to 4 /group) when compared with controls (1 to 2 /group) for females at 60 mg/kg/day and males ≥60 mg/kg/day.

Microscopic findings which did not fully recover in rats included erosion/ulcer of the glandular stomach, and epithelial atrophy of the non-glandular stomach at 60 mg/kg/day, and epithelial atrophy of the cecum at 30 mg/kg/day in rats. After a 1-month recovery phase, there was recovery of all clinical observations, body weight and food consumption changes, and histology findings at 60 mg/kg/day in dogs.

There were no effects on the liver after repeated dosing of PF-06747775 in nonclinical toxicity studies in rats and dogs up to 1-month in duration.

1.2.2.2.2. Skin

Effects on the skin were dose-limiting in dogs after repeat oral dosing. The severity of observations including lameness, footpad lesions and/or swelling after repeat-dose oral administration of PF-06747775 at ≥15 mg/kg/day in dogs led to unscheduled euthanasia. Skin lesions/discoloration (red-tinged) were noted on the forepaw, hindpaw, forelimb, hindlimb, head, eyelid, ear, abdomen, scrotum, tail tip, and/or cervical, thoracic and inguinal regions. While lesions were occasionally noted in association with skin discoloration, there was no clear correlation. Skin lesions and discoloration generally occurred later in the study with onset between Days 11 and 23, most often persisting for several days post cessation of dose administration or until euthanasia (up to 15 days). Skin crusting on the scrotum was noted with or without skin discoloration or lesions in 1 to 2 males/group with onset between Days 22-28 persisting for 1-7 days. Hair loss from the eyelid, forepaw, and/or hindpaw was noted with low incidence (1 to 2/group) in association with red-tinged skin in dogs. In the 14_day study in rats, there was microscopic epidermal atrophy at ≥100 mg/kg/day. In the 1-month study in rats, skin hair granulomas which corresponded to the in-life observations of swollen lips or muzzles and skin lesions at 60 mg/kg/day, and granulomatous inflammation in the Harderian gland at ≥30 mg/kg/day were due to foreign body reactions from epithelial atrophy (ie, atrophic hair follicle epithelium and Harderian gland acinar epithelium). Nonadverse findings in the skin of rats included hair loss in multiple regions at ≥10 mg/kg/day, tissue swelling (lips, muzzle, and/or anus) at ≥30 mg/kg/day, and skin lesions (muzzle, cervical or dorsal thoracic regions), adnexal atrophy, and crusting of the skin at 60 mg/kg/day. PF-06747775-related microscopic findings that did not recover included nonadverse adnexa atrophy of the skin and increased mononuclear cell infiltrate in the Harderian gland at 60 mg/kg/day.

1.2.2.2.3. Eye

Ocular effects were dose-limiting in the 14-day exploratory toxicity study in dogs; the female dog at 120 mg/kg/day was euthanized on Day 9 due to progressing eye findings of conjunctival hyperemia (moderate to severe), corneal edema with mucus/discharge, excessive lacrimation, constricted pupil/miosis, sclera congestion, swollen and partially closed eyelids, which evolved to central corneal ulceration. In order to attenuate the progression of the ocular observations in the 1-month definitive toxicity study in dogs, a lubricant was prophylactically, topically administered to the eyes of all dogs in the study starting on Day 1. As a result, no dogs were euthanized early due to ocular lesions in the 1-month study. However, adverse ocular findings were still present at all dose levels (≥15 mg/kg/day). From the animals available for ophthalmologic examination at the

conclusion of the dosing phase, multifocal or diffuse cornea opacities consistent with corneal edema[21,22] were observed at ≥15 mg/kg/day, often associated with observations of partially closed eyes and/or microscopic findings of minimal to marked atrophy of the corneal epithelium in both sexes. Additionally, a dull appearance of the eye was noted during ophthalmologic examination of some dogs suggesting alterations in the precorneal tear film. This was consistent with observations of meibomian gland inflammation noted in the eyelids of animals that had observations of swollen and/or discolored eyelids and changes in the cornea itself. Changes in eyelids and tear film as well as corneal atrophy have previously been associated with EGFR inhibition.[12] It is notable that the corneal epithelial atrophy was less severe in animals that survived the dosing phase compared to animals that were euthanized early. Similar ocular observations and microscopic findings were also seen in rats at doses ≥60 mg/kg/day. Multifocal corneal opacities and rough corneal surfaces correlating to corneal epithelial atrophy and corneal ulcers/erosions were seen at ≥30 mg/kg/day. At the end of the recovery phase, findings of corneal opacities in rats and dogs had resolved; however, corneal neovascularization (a further progression of the corneal findings) had developed in one rat at 60 mg/kg/day.

1.2.2.2.4. Kidney

Kidney findings were only observed at non-tolerated doses (≥100 mg/kg/day) in the 14-day exploratory toxicity study in rats. At ≥100 mg/kg/day in rats, there was PF-06747775-related tubular basophilia. At 500 mg/kg/day there was papillary necrosis and dilatation of tubules. Tubular basophilia and tubular dilatation were both bilateral and were associated with macroscopic observations of abnormal kidney color (mottled) in 1/5 rats at 500 mg/kg/day. The kidney findings were associated with clinical pathology increases in blood urea nitrogen (BUN) and/or creatinine. There were no kidney findings in dogs at any dose in studies up to 1 month in duration. These rodent-specific kidney effects are probably based on the pharmacology of PF-06747775 (ie, inhibition of EGFR).[13,14]

1.2.2.2.5. Lymphohematopoietic

Hematological effects that affected both myeloid and erythroid parameters were observed in rats and dogs administered PF-06747775; these changes were predominantly associated with inflammation or invasion of bacteria as a result of diminished integrity of the epithelial barrier in multiple tissues.

In rats, non-adverse differences in clinical pathology parameters, consistent with inflammatory changes noted microscopically in the skin, gastrointestinal tract and eye, were increased white blood cells, neutrophils, and lymphocytes in females at ≥30 mg/kg/day, and monocytes in males and females at ≥30 mg/kg/day, and decreased albumin in females at ≥30 mg/kg/day, albumin/globulin (A/G) ratio in females at 60 mg/kg/day, and potassium in males at ≥10 mg/kg/day. In dogs, erosions, ulcers and/or inflammation that occurred in multiple tissues including skin, tongue, esophagus, and/or duodenum at ≥15 mg/kg/day correlated with inflammatory changes (typically not dose responsive) that were present in the hematology, coagulation, and clinical chemistry parameters and were similar in magnitude in animals at scheduled and unscheduled euthanasia. In dogs at ≥15 mg/kg/day there were increases in monocytes, fibrinogen, and globulin with concurrent decreases in albumin and

often total protein indicating an inflammatory response. The decrease in albumin may also be partially attributed to protein loss associated with the ulceration/erosions of epithelial surfaces. In addition at ≥60 mg/kg/day, due to inflammation in multiple tissues, neutrophils, white blood cells, and platelet counts were increased. The inflammatory changes noted above led to non-dose responsive, non-progressive decreases in red cell mass parameters at ≥15 mg/kg/day due to suppression of the bone marrow production of red blood cells. None of these hematology, coagulation, or clinical chemistry effects was considered adverse based on the characteristics of these responses, which were secondary to the inflammatory changes present in the dogs.

Secondary non-adverse morphological changes occurred in the thymus, bone marrow, and lymph nodes at ≥15 mg/kg/day in dogs. There was mild lymphoid depletion in the thymus in a few male dogs consistent with corticosteroid-induced stress[15,16] that correlated with decreases in lymphocytes and eosinophils in individual animals. There was increased myeloid cellularity of the bone marrow secondary to the inflammation that correlated with higher leukocyte counts and fibrinogen. Also, there were increased lymphocytes in the cortex accompanied with increased plasma cells in the popliteal, mandibular, and/or iliac lymph nodes, reflecting secondary reactive and functional responses to inflamed drainage/regional areas of the skin and digestive system.

1.2.2.2.6. Cardiovascular

Cardiovascular effects were only observed in rats after a single dose. Oral administration of PF-06747775 at 20 mg/kg caused minimally higher systolic, diastolic, and mean blood pressure compared with vehicle control values. The higher blood pressure values persisted from 8 - 24 hours post dose and were highest from 20 - 24 hours post dose, which was disconnected from the observed time of maximum PF-06747775 plasma concentration (0.5 hours post dose). There were no cardiovascular effects (blood pressure, heart rate, or electrocardiogram [ECG] parameters) in dogs at single doses up to 30 mg/kg. There also were no effects on ECG parameters in dogs after repeat doses up to 90 mg/kg/day in the 1-month definitive toxicity study.

1.2.2.2.7. Other Findings

Other nonadverse PF-06747775-related anatomic and clinical pathology findings in rats included increased inflammatory cell infiltrates (secondary to epithelial atrophy and subsequent inflammation) in the prostate, mesenteric lymph nodes, and connective and adipose tissues[23] in several locations at ≥10 mg/kg/day, decreased secretory content in the prostate gland with lower prostate weights and higher adrenal gland weights at ≥30 mg/kg/day, lower epididymal weights in males and lower thymus weights in females at 60 mg/kg/day without microscopic correlates.

1.2.2.3. PF-06747775 Projection of Human Pharmacokinetics

In humans, PF-06747775 is predicted to be hepatically cleared (metabolized) and thus the parent drug is not believed to be excreted via the bile or kidney unchanged, based on in vivo studies in rat and dog. Scaling from hepatocytes and using population based physiologically-based pharmacokinetic (PBPK) modeling (SimCYP), PF-06747775 is predicted to have a

geometric mean plasma clearance of 0.7 mL/min/kg, a volume of distribution of 0.78 L/kg, a half-life of ~11 hours, and a geometric mean oral bioavailability of 83% at doses under 20 mg once a day. Based on data from RRCK cells, PF-06747775 is predicted to have good absorption (~88%) at the predicted efficacious dose.

PF-06747775 is indicated to be an efflux transporter substrate for both MDR1 and BCRP using in vitro transwell evaluations, with respective efflux ratios of 20.4 and 33.9. The efflux transporter substrate effect is predicted to have a small effect on systemic exposure at and above the predicted Ceff dose of 20 mg; however, the efflux transporter substrate status may impede brain penetration which is evidenced by rat brain penetration studies showing little, if any, brain exposure compared to systemic exposure.

PF-06747775 can potentially alter pharmacokinetics of other co-administered drugs that are hepatically eliminated via the CYP3A4 pathway evidenced by its ability to induce CYP3A4 mRNA levels in cyropreserved human hepatocytes in vitro. PF-06747775 is also thought to be cleared in the liver by a number of pathways: 1) CYP3A4 (62%), 2) intrinsic binding to glutathione, and 3) GSTM1-mediated glutathione conjugation.

1.2.2.4. PF-06747775 Nonclinical Pharmacology

PF-06747775 was studied in a variety of in vitro and in vivo model systems to determine its potencies at inhibiting different mutant EGFR variants, selectivity against non-target kinases, antitumor efficacy, pharmacokinetic/pharmacodynamic (PK/PD) relationships, and mechanism of action.

In recombinant enzyme and cellular assays, PF-06747775 is a highly potent and irreversible inhibitor against the EGFR double-mutants (L858R/T790M and del 19/T790M) and single-mutants (L858R and del 19) and a weak inhibitor of WT EGFR. This inhibitory potency on mutant targets is paralleled by subsequent inhibition of the EGFR downstream signaling axis (eg, inhibition of phosphorylation of AKT and ERK kinases) and induction of apoptosis. In xenograft mouse models, PF-06747775 demonstrates tumor growth inhibition and regression at well-tolerated doses in disease-relevant models driven by EGFR double- and single-mutants. The antitumor efficacy of PF-06747775 is dose-dependent and shows a strong correlation with pharmacodynamic inhibition of EGFR phosphorylation, inhibition of EGFR-mediated downstream signaling, and induction of apoptosis. Using multiple in vitro approaches to assess non-target kinase selectivity, PF-06747775 demonstrates the potential for high kinase selectivity, with only 7 out of 273 (3%) tested non-target kinases showing the potential for inhibition by PF-06747775 at pharmacologically-relevant concentrations. In order to quantitatively define plasma concentrations sufficient for efficacy (C_{eff}), a mathematical model was generated incorporating the plasma levels of PF-06747775, the associated inhibitory effects on EGFR phosphorylation, and the antitumor efficacy in xenograft models. Applying the mathematical model, the C_{eff} for PF-06747775 is 58 nM (24 ng/mL) in the H1975 L858R/T790M double-mutant model, and 119-139 nM (49-58 ng/mL) in the PC9 del 19 single-mutant model, when expressed as the average plasma concentration of unbound PF-06747775 to achieve tumor stasis. The results from all xenograft models employed are consistent with tumor stasis resulting from achieving an average of at least 60% to 80% PD inhibition of EGFR phosphorylation over the dosing interval.

1.2.3. Palbociclib

Palbociclib is a first-in-class CDK4/6 inhibitor conditionally approved in the United States (US) for use in combination with letrozole or fulvestrant for advanced estrogen-receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer. By inhibiting CDK4/6 and subsequently downstream signaling through Rb protein that controls the cell cycle, palbociclib prevents actively proliferating cells from completing the cell division cycle, resulting in an arrest of tumor growth. EGFR TKIs inhibit phosphorylation of EGFR, thereby inhibiting downstream cell signaling through the EGFR axis including AKT, MEK/ERK, and transcription of cell cycle related genes such as cyclin D1 and E2F target genes,[24] resulting in the induction of apoptosis and inhibition of proliferation in EGFR-dependent tumor cells. It is hypothesized that combination of the EGFR TKI PF-06747775 with palbociclib in EGFR-mutant NSCLC could further impede tumor growth with increased efficacy over the EGFR TKI alone. This potential increased efficacy may reflect better inhibition of cell cycle progression with the combination. In addition, palbociclib may arrest the growth of EGFR TKI-resistant cells present or acquired and attempting to get a foot hold for growth in the heterogeneous tumor when the predominant EGFR-sensitive cell population is challenged with an EGFR TKI.

1.2.3.1. Palbociclib Nonclinical Pharmacology Data

Palbociclib nonclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Single agent palbociclib has showed antiproliferative effects (selective G1 arrest) on Rb-positive cancer cells *in vitro* and *in vivo*[25] where palbociclib activity was associated with reduced Rb-phosphorylation and decreased expression of the cell proliferation marker Ki67.

Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific pRb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of pRb. The IC_{50} values for reduction of pRb phosphorylation at serine -780 and -795 in MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 μM, respectively. The IC_{50} values for reduction of pRb phosphorylation are similar to the IC_{50} values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to palbociclib (IC_{50} <150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. Sensitive cell lines in this panel represent mostly the luminal ER-positive subtype.[26]

Additional nonclinical studies were conducted with the objective to characterize the activity of combined PF-06747775 and palbociclib as compared to each single agent in both cell-based and in vivo assays using models of EGFR-mutant NSCLC.

At the cellular level, study objectives were to address: 1) efficacy of combination versus single agents in long term viability assays where cell outgrowth depended on drug resistance; and 2) the mechanistic effects of combination versus single agent treatment using downstream signaling biomarker assays and cell cycle analysis.

At the in vivo level, study objectives were to address: 1) the in vivo anti-tumor efficacy of the combination compared to each single agent; and 2) the effect on body weight and any apparent clinical observations from combination versus single agent treatment in the in vivo efficacy studies as an indicator of safety.

In vitro and in vivo assessment of the combination of PF-06747775 and palbociclib showed increased efficacy over PF-06747775 alone in NSCLC models representing the first-line EGFRm and second-line T790M-resistant patient populations. Mechanistic studies suggest the combination effect predominantly relies on the addition of the pro-apoptotic effect of PF-06747775 plus the anti-proliferative effect of both agents. These studies support clinical testing of the PF-06747775 palbociclib combination for increased clinical benefit in EGFR-mutant NSCLC.[27]

1.2.3.2. Palbociclib Nonclinical Pharmacokinetic Data

In nonclinical species (rat, dog, and monkey), palbociclib exhibits low to moderate plasma clearance, large volume of distribution, and moderate oral bioavailability ranging from 23% to 56%. Plasma protein binding of palbociclib is moderate in mouse, rat, rabbit, dog, and human plasma. Radioequivalents were widely distributed to most rat tissues and fluids following an oral dose of [^{14}C]palbociclib, with radioactivity levels consistently greater than those observed in blood. In vitro, palbociclib is primarily metabolized by cytochrome P450 (CYP)3A and sulfotransferase (SULT) 2A1 enzymes. The major primary metabolic pathways for [^{14}C]palbociclib in rats and humans involved sulfonation and oxidation. In rats and dogs, [^{14}C]palbociclib was mainly eliminated via the feces; the high fecal elimination occurred via biliary excretion in rats. Palbociclib and its oxidative metabolite, PF-05089326, demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 enzyme activities and thus, showed low potential for CYP-mediated PK drug interactions. However, palbociclib and PF-05089326 caused time-dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities and may have the potential for PK drug interactions with compounds for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance. Palbociclib did not cause induction of CYP1A2, CYP2B6, CYP2C8, or CYP3A4 mRNA expression and/or enzyme activity in vitro in human hepatocytes; thus, the potential for palbociclib to induce these enzymes is considered to be low at clinically relevant concentrations. The potential for palbociclib to inhibit UGT enzymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was assessed and the likelihood of drug-drug interaction (DDI) at clinically relevant concentrations is considered low. In vitro, inhibition of efflux transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), hepatic uptake transporters (OATP1B1 and OATP1B3), hepatic efflux transporter (BSEP) and renal transporters (OAT1, OAT3 and OCT2) by palbociclib were assessed and determined to be unlikely at clinically relevant concentrations.

1.2.3.3. Palbociclib Human Pharmacokinetic Data

The PK of palbociclib is explained in detail in the palbociclib Investigator's Brochure (IB).[67] Palbociclib was shown to achieve steady-state concentrations following 8 days of once-daily (QD) dosing. The elimination half-life ($t_{1/2}$) ranges from 23.2 to 28.8 hours with a median time of maximum concentration (T_{max}) between 4 and 8 hours post-dose. Metabolism is the major route of elimination of palbociclib; excretion of unchanged [^{14}C] palbociclib in the feces and urine was 2.3% and 6.9% of dose, respectively. When single oral doses of midazolam were co-administered with multiple doses of palbociclib, weak time-dependent CYP3A4/5 inhibition mediated by palbociclib was observed. In vitro studies indicate that palbociclib is a substrate of CYP3A4. Based on data following coadministration of itraconazole and rifampin, the concurrent administration of strong CYP3A inhibitors and inducers with palbociclib should be avoided.

Given the shared metabolic pathway, namely CYP3A4, of PF-06747775 and palbociclib, the observed impact of palbociclib on the exposure of a sensitive CYP3A4 substrate (midazolam), and the current lack of clinical data on the ability of PF-06747775 to inhibit or induce the CYP3A4 enzyme, the impact of concomitant administration of each drug upon the exposure of the other is currently unknown. Serial PK data will be collected for each drug following multiple dosing.

1.2.3.4. Palbociclib Clinical Data

Palbociclib has been explored in multiple clinical trials in a variety of malignancies, as single agent and in combination therapy.

Two Phase 1 trials evaluated single agent administration of palbociclib to patients with Rb-positive cancers. One of these trials determined that the DLT was neutropenia and the maximum tolerated dose (MTD) was 125 mg once daily when administered for 21 of 28 days (3 weeks on/1 week off schedule).[28,] The most common non-hematologic adverse events (AEs) included fatigue, nausea, and diarrhea. The mean half-life of palbociclib was 26.9 hours. Patients were selected for Rb-positive cancers, based on immunohistochemistry (IHC) stain, defined as positive if staining intensity was 1+ or greater above background. Stable disease for ≥4 cycles (16 weeks) occurred in 27% of evaluable patients and in a number of tumor types (liposarcoma, testicular, renal, ovarian, breast, appendiceal, peritoneal, melanoma, thymoma and lung). Another Phase I trial of palbociclib using an alternative dosing plan (21 day cycles; 2 weeks on/1 week off schedule) observed a similar likelihood of disease control in a variety of tumor types.[29] These studies demonstrate that palbociclib has substantial activity in Rb-positive tumors.

A randomized Phase 2 trial was initiated to determine the overall safety and efficacy of palbociclib (125 mg) and letrozole (2.5 mg) versus letrozole in post-menopausal women with ER+ HER2-negative advanced breast cancer.[30] The objective response rate (ORR) was 45% for those women who received palbociclib plus letrozole versus 31% for those who received letrozole (statistically significant). Importantly, the median progression-free survival (PFS) was significantly different (26.2 versus 7.5 months) favoring the combination arm. The most common adverse drug reactions of any grade reported in patients in the palbociclib plus

letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. The most frequently reported serious adverse drug reaction in patients receiving palbociclib plus letrozole was diarrhea (2.4%).

Overall, neutropenia of any grade was reported in 62 (74.7%) patients in the combination arm, with Grade 3 neutropenia being reported in 40 (48.2%) patients, and Grade 4 neutropenia being reported in 5 (6.0%) patients.

In the combination arm, 56.6% of patients had a maximum grade of Grade 3 neutropenia and 4.8% of patients had a maximum grade of Grade 4 neutropenia based on laboratory data. The median time to first episode of neutropenia was 15 days for any grade, Grade ≥2, and Grade 4 neutropenia, and 28 days for Grade ≥3 neutropenia in the palbociclib plus letrozole arm. Median duration of Grade 3 or 4 neutropenia was 7 days. Most episodes of Grade ≥3 neutropenia were managed by dose reduction and/or dose delay or temporary discontinuation and did not require permanent discontinuation of study treatment or addition of supportive therapy. Grade 3-4 fatigue/asthenia, vomiting, diarrhea and peripheral neuropathy rates were 6%, 0%, 4% and 0% respectively.

Based on these data, the US Food and Drug Administration (FDA) approved palobociclib for the treatment of hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- Letrozole as initial endocrine based therapy in postmenopausal women, or
- Fulvestrant in women with disease progression following endocrine therapy.

The indication in combination with letrozole is approved under accelerated approval based on PFS. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Clinical data for single agent palbociclib in NSCLC, not selected for EGFRm, has demonstrated modest activity only.[66]

Additional information for palbocicib may be found in the single reference safety document (SRSD), which for this study is the Palbociclib Investigator's Brochure.[67]

1.2.4. Avelumab

Avelumab (MSB0010718C) is a fully human monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 isotype.

Programmed death ligand-1 (PD-L1) is expressed by a variety of human tumors, both by the tumor cells, as well as by the immune cells that are present in the tumor microenvironment.[31] High levels of PD-L1 expression have been found to be associated with disease progression, increased metastases, poor response to treatment, and decreased survival in a number of human cancers.[31] Importantly, anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of murine tumor models as monotherapy and has shown synergistic effect in the combination therapy setting.[32,33,34,35,36,37,38]

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed cell death protein-1 (PD-1). Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the programmed death ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.[39,40]

1.2.4.1. Avelumab Nonclincial Data

1.2.4.1.1. Nonclinical Pharmacology

The nonclinical pharmacology studies have shown that avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo.

Avelumab binds to human PD-L1 with a high affinity of 0.7 nM and not to any other B7 family proteins, and competitively blocks the interaction of PD-L1 with PD-1. The in vitro study results have shown that by binding to PD-L1, avelumab effectively enhances T cell activation as measured by interleukin (IL)-2 or interferon-gamma (IFN-γ) production. In addition, as a fully human IgG1 antibody, avelumab has the potential to trigger the antibody-dependent cell-mediated cytotoxicity (ADCC) against target cells expressing PD-L1.

As a monotherapy, avelumab has demonstrated anti-tumor activity against murine MC38 colon carcinoma tumors that are characterized by a high level of PD-L1 expression. A dose-dependent trend was observed, and 400 μg per dose (20 mg/kg, approximately) was identified as the optimally effective dose when given every third day for 3 total doses.

The in vivo anti-tumor effects were found to be primarily mediated by CD8+ T cells as evidenced by the observation that in vivo depletion of this cell type completely abrogated the anti-tumor efficacy of avelumab. The contribution of ADCC as a potential mechanism of anti-tumor activity was further demonstrated in vivo using a deglycosylated version of avelumab to abrogate fragment crystalline (Fc) receptor binding or via the systemic depletion of natural killer (NK) cells. In both settings, loss of in vivo ADCC potential significantly reduced the anti-tumor activity.

The combination of avelumab with commonly used cancer treatments, such as cytotoxic agents and radiation therapy, resulted in an improved anti-tumor activity. Chemotherapy with combination therapy (with folinic acid, 5-fluorouracil, and oxaliplatin [FOLFOX], and radiation therapy showed the better tumor growth inhibition. In particular, radiation therapy was found to be a highly synergistic combination with avelumab capable of causing complete regression of established tumors probably through generating anti-tumor immune memory.

Various immunomonitoring assays were incorporated into the in vivo studies. Treatment with avelumab resulted in a consistent increase in the percentage of CD8+PD-1+ T cells and an increased frequency of CD8+ T cells with an effector memory (TEM) phenotype as determined by flow cytometry. Furthermore, these changes correlated with the anti-tumor effect. Increases in tumor antigen-specific T cell responses, as measured by enzyme-linked

immunosorbent spot and pentamer immunoassays, were evident following treatment with avelumab and these responses were enhanced when combined with FOLFOX or radiation. Hence, increases in CD8+PD-1+ T cells, CD8+ TEM cells, and antigen-specific T cell responses, may be leveraged as PD biomarkers with translational relevance to the clinical setting.

1.2.4.1.2. Nonclinical Pharmacokinetics and Metabolism

As expected for a mAb binding to a cellular target, avelumab demonstrated pronounced non-linear PK characteristics in mice and monkeys in single dose studies at doses below 20 mg/kg, suggesting a combination of first order catabolic clearance and saturable target-mediated clearance. Toxicokinetic data from repeated dose toxicity studies in mice, rats, and monkeys indicated that the PK of avelumab was linear within the dose range of 20 to 140 mg/kg, suggesting that the target mediated clearance could be saturated when higher doses than 20 mg/kg are administered. Similar terminal half-lives ($t_{1/2}$) of approximately 60 to 70 hours were observed in toxicity studies in mice and monkeys.

A PK/PD study in C57BL/6 mice was used to correlate receptor occupancy data of avelumab in blood with drug concentrations. A plasma concentration of 58.5 µg/mL was calculated as required for 95% target occupancy in this model.

Avelumab is immunogenic in mice, rats, and monkeys with a lower incidence of anti-drug antibodies (ADAs) at higher doses. The latter is probably due to interference of free avelumab with the immunogenicity assay (drug interference). In animals, the generated ADAs seem to have the potential to increase the clearance of the avelumab. As the fully human avelumab represents a foreign protein to the immune system of animals, the observed immunogenicity of avelumab in rodents and non-human primates is not deemed predictive for an immune response to avelumab in humans.

1.2.4.1.3. Nonclinical Toxicology

The toxicological profile of avelumab was evaluated in repeat-dose toxicity studies of 4-week duration with once weekly Iv bolus injection/infusion of avelumab in mice, rats, and cynomolgus monkeys. A repeat-dose toxicity study with intermittent once weekly Iv infusion of avelumab over 13 weeks followed by an 8-week recovery period in cynomolgus monkeys was also conducted. In addition, in vitro cytokine release assays (CRA) in human and cynomolgus monkey whole blood and peripheral blood mononuclear cells (PBMCs) followed by an optimized CRA in phytohemagglutinin (PHA) pre-stimulated PBMCs from 16 human volunteers was completed. Tissue cross reactivity (TCR) studies in normal human and cynomolgus monkey tissues have also been was performed.

On the basis of the binding affinity data, the cynomolgus monkey and the mouse were selected as relevant species for the nonclinical safety testing of avelumab. Due to severe hypersensitivity reactions after repeated administration of avelumab in mice and the low binding affinity in rats, rodent species are not considered appropriate for nonclinical safety testing of avelumab and therefore, a single species approach (cynomolgus monkey only) is applied.

In cynomolgus monkeys neither in the pilot 4-week Iv repeat-dose toxicity study nor in the pivotal 13-week study, clinical signs of hypersensitivity have been seen after repeated treatment with avelumab at dose levels of 20, 60, and 140 mg/kg, respectively. For the pilot 4-week study as well as for the pivotal 13-week Iv repeat-dose toxicity study, a no observed adverse effect level (NOAEL) of 140 mg/kg for systemic toxicity was established.

Initial CRA in human and cynomolgus monkey whole blood and PBMCs revealed no clear-cut evidence for release of pro-inflammatory cytokines. However, a subsequent, optimized CRA demonstrated evidence of potential cytokine release in PHA pre-stimulated PBMCs.

1.2.4.2. Avelumab Human Pharmacokinetics

Avelumab PK and dose proportionality following the first 1-hour infusion have been characterized in 77 Caucasian patients treated in the dose escalation and expansion cohorts of Trial EMR 100070-001 by standard non-compartmental analysis. This analysis revealed that the exposure parameters of maximum concentration (C_{max}) and area under the concentration-time curve to the end of the dosing period (AUC_{τ}) increased in a dose proportionate fashion for the 10 and 20 mg/kg doses. The half-life of avelumab tended to increase with dose, likely due to target mediated disposition at lower doses (1 and 3 mg/kg), but terminal half-life of 10 mg/kg (102 ±28 hours) and 20 mg/kg (120 ± 42 hours) doses were similar, taking into account the PK variability. This likely indicates target mediated elimination does not increase at these two doses and target occupancy is very high.

Target occupancy on peripheral blood CD3+ T-cells was investigated in human blood in vitro by flow cytometry after spiking of whole blood samples from 8 healthy volunteers with avelumab over a concentration range of 0.003-10 μg/mL. Fifty percent (50%) receptor occupancy was observed at a drug concentration of 0.122 μg/mL ± 0.042 μg/mL with a plateau indicating at least 95% receptor occupancy reached in all blood samples at 1 μg/mL.

PK profiles obtained during the dose escalation phase of Trial EMR 100070-001 were utilized to investigate whether this concentration of at least 1 μg/mL was achieved throughout the dosing interval. The median ± standard deviation trough concentration (C_{trough}) at the end of the first cycle after administration of the 10 mg/kg dose is 21 ± 12 μg/mL (n=283). This median C_{trough} increases during the subsequent cycles to 25 ± 16 μg/mL (second cycle) (n=269), 27 ± 17 μg/mL (third cycle) (n=202), and remains between 27 and 36 μg/mL during the subsequent cycles (n=55–171).

1.2.4.3. Avelumab Clinical Experience

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in a wide variety of adult cancers, such as non-small cell lung cancer, gastric cancer, Merkel cell carcinoma, renal cell carcinoma, ovarian cancer, urothelial cancer, and Hodgkin's Lymphoma, as single agent or in combination with chemotherapy, tyrosine kinase inhibitors, or other immune-modulating agents.

As of 05 November 2015, more than 1300 patients have been treated with avelumab. The largest trial is study EMR100070-001, a Phase 1, open-label, multiple-ascending dose clinical study aimed to investigate the safety, tolerability, PK, biological activity, and clinical activity of avelumab in patients with metastatic or locally advanced solid tumors. Study EMR100070-001 consists of 2 parts, a dose-escalation phase and a dose-expansion phase, which is performed in selected tumor indications. Avelumab is administered intravenously (IV) at the assigned dose level as a 1-hour infusion once every 2 weeks (Q2W). The following dose levels have been investigated: 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg, and 20.0 mg/kg.

As of 05 November 2015, 53 patients were treated in the dose-escalation phase of study EMR 100070-001, with 4, 13, 15, and 21 patients treated with avelumab doses of 1, 3, 10, and 20 mg/kg, respectively. None of the patients treated with doses up to 10 mg/kg experienced DLT, and the 10 mg/kg dose of avelumab was thus considered a safe and well-tolerated dose for further investigation in the tumor type specific expansion cohorts. One DLT (a Grade 3 immune-related adverse event characterized by increased creatine kinase, myositis, and myocarditis) was observed in 1 patient at the dose of 20 mg/kg.

As of 05 November 2015, 1300 patients have been enrolled in the tumor type specific expansion cohorts of study EMR 100070-001 and treated with the recommended dose of 10 mg/kg avelumab Q2W. A summary of the safety data for the pooled expansion cohort is provided here.

Treatment-emergent adverse events (TEAEs) were observed in 1200 (92.3%) patients, with the most frequent (≥10%) being fatigue (27.4%), nausea (21.2%), infusion related reaction (16.2%), diarrhea (15.8%), constipation (15.7%), decreased appetite (14.9%), vomiting (14.5%), weight decreased (12.2%), abdominal pain (12.0%), anemia (11.9%), cough (11.7%), dyspnea (11.4%), pyrexia (11.4%), and chills (10.5%).

Treatment-related TEAEs were observed in 813 (62.5%) patients, and the most frequent (≥ 5%) were fatigue (16.3%), infusion-related reaction (16.1%), nausea (8.3%), chills (7.8%), diarrhea (6.1%), and pyrexia (5.5%).

A total of 124 patients (9.5%) experienced Grade ≥ 3 treatment-related TEAEs, with gamma-glutamyltransferase (GGT) increased and infusion-related reaction (IRR, 0.7% each), fatigue and lipase increased (0.6% each), anemia (0.5%), dyspnea (0.5%), aspartate aminotransferase (AST) increased (0.4%), autoimmune hepatitis and pneumonitis (0.3% each) being the most frequent.

A total of 509 of 1300 patients (39.2%) had at least 1 serious TEAE. Treatment-related serious TEAEs were reported in 71 (5.5%) patients, with the most frequent being infusion-related reaction (0.8%), pneumonitis (0.6%), pyrexia and dyspnea (0.4% each), and autoimmune hepatitis, asthenia, blood creatinine phosphokinase (CPK) increased, abdominal pain, colitis, diarrhea, vomiting, hyponatremia, adrenal insufficiency, and non-cardiac chest pain (0.2% each).

There were 466 deaths (35.8%) reported in the pooled expansion cohort. The majority of deaths were due to progressive disease (360 patients, 27.7%). There were 33 (2.5%) deaths attributed to TEAEs not related to trial treatment, and 5 deaths (0.4%) in which a related TEAE was considered the primary reason of the death by the investigator: pneumonitis radiation induced and dyspnea (1 case), acute liver failure associated with autoimmune hepatitis (1 case), respiratory distress and sepsis (1 case), autoimmune hepatitis with hepatic failure and fatigue (1 case), and pneumonitis (1 case). The cause of death was marked as "other" or "unknown" in 13 (1.0%) and 55 (4.2%) of cases, respectively.

A total of 175 patients (13.5%) discontinued avelumab treatment due to TEAEs, including 79 patients (6.1%) discontinuing because of treatment related TEAEs. The most frequent related TEAEs leading to treatment discontinuation were infusion related reaction (IRR, 1.9%), GGT increased (0.4%), blood CPK increased, AST increased, lipase increased, alanine aminotransferase (ALT) increased, colitis, myositis, arthralgia, fatigue, autoimmune hepatitis, and dyspnea (0.2% each).

Potential Immune-related Adverse Events (irAEs): a total of 149 patients (11.5%) experienced potential irAEs (based on a list of predefined Preferred Terms without further clinical evaluation of individual cases) which were considered treatment-related in 99 patients (7.6%) based on investigator's causality assessment. The most frequent treatment-related potential irAEs were hypothyroidism (3.5%), pneumonitis (1.0%), hyperthyroidism (0.5%), adrenal insufficiency and dry eye (0.4% each), autoimmune hepatitis and colitis (0.3% each), and myositis (0.2%). The majority of potential irAEs were Grade 1 or Grade 2 in severity, with 20 (1.5%) being related irAEs of Grade ≥3 severity. A total of 15 patients (1.2%) had treatment-related potential irAEs leading to treatment discontinuation. There were no delayed related irAEs identified with onset after the on-treatment period.

Infusion-Related Reactions: a total of 215 patients (16.5%) experienced at least 1 episode of IRR. Most of the events were of Grade 1 or Grade 2 severity. IRRs of Grade 3 severity occurred in 6 patients (0.5%), while 3 patients (0.2%) experienced Grade 4 IRRs. No there was no Grade 5 events of IRR reported. Most of the IRRs occurred after the first (11.5%) or second (3.7%) infusion. In 23 patients (1.8%), treatment was discontinued because of an IRR.

Immunogenicity of Avelumab in Humans: Based on the Phase 1/1b Trial EMR 100070-001, the incidence of ADAs was relatively low, with 1 out of 39 patients (2.6%) in the dose escalation cohorts and 10 out of 338 patients (2.9%) in a NSCLC expansion cohort. In 8 of these 10 patients, a positive signal was observed at a single time point and a decrease in avelumab serum exposure was observed in the 2 patients with multiple positive samples. From these 11 positive patients, 2 patients had symptoms on the day of the infusion compatible with an immune reaction (chills and fever, nausea and vomiting) and, therefore, these AEs could be ADA related. For the other 9 ADA-positive patients, no such AEs were recorded.

Complete information for avelumab may be found in the SRSD, which for this study is the avelumab IB.[41]

1.2.5. Rationale for Evaluating PF-06747775 as Single Agent or in Combination with Palbociclib or Avelumab in Patients with EGFRm NSCLC

Activating mutations in EGFR confer constitutive activity providing the oncogenic drive in EGFRm NSCLC. First and 2nd generation EGFR TKIs are effective drugs in this setting, but are constrained by DLTs attributed to inhibition of WT EGFR and by drug resistance caused, in the majority of cases, via a T790M secondary mutation in EGFR. Third generation EGFR TKIs, such as osimertinib (AZD9291), with activity against EGFR with activating and T790M mutations, but sparing WT EGFR, have been developed and are showing promising efficacy and safety profiles in preliminary clinical results. In late 2015, osimertinib was conditionally approved by the Food and Drug Administration in the US and by the European Medicine Agency in the European Union (EU) in February 2016 for use in advanced NSCLC in patients with EGFR containing the T790M mutation. However, the duration of response (DOR) to 3rd generation agents is also expected to be limited by tumor heterogeneity and intrinsic and acquired resistance, as recently published evidence has begun to corroborate in describing patients who become resistant to the 3rd generation agents osimertinib.[42,43] A next step in the evolution of EGFRm NSCLC treatment strategies is the combination of EGFR TKIs with additional agents that can potentially provide better response rates, increased magnitude of response, and longer DOR via potentiated inhibition of growth and viability for EGFR TKI-sensitive cells, and/or activity against EGFR TKI-insensitive cells that are selected or arise to become resistant disease. Such a strategy may be favored by employing an EGFR TKI that provides the maximal inhibitory pressure on the EGFR mutants. Additionally, the availability of several different 3rd generation agents provides options as drug-drug interactions and overlapping toxicities may rule out specific combination partners.

It is hypothesized that combination treatment with palbociclib and PF-06747775 in patients with EGFR-mutant NSCLC could further impede tumor growth with increased efficacy over treatment with PF-06747775 alone. This potential increased efficacy may reflect better inhibition of cell cycle progression with the combination. In addition, palbociclib may arrest the growth of EGFR TKI-resistant cells present or acquired and attempting to get a foot hold for growth in the heterogeneous tumor when the predominant EGFR-sensitive cell population is challenged with an EGFR TKI.

Separately, recent evidence has shown that tumors require suppression of the host immune system for continued growth and spread.

The development of agents targeting the interaction of PD-1 and its ligands has shown promise in the treatment of various cancers including NSCLC.[44] Substantial clinical activity was observed with anti-PD1 antibodies nivolumab and pembrolizumab, with an objective response rate of 15% and 20%, respectively, and long duration of response in unselected heavily pretreated NSCLC patients.[45,46] Similarly impressive activity was observed in the first-line setting, demonstrating objective response rates of 30% and 26% for nivolumab and pembrolizumab, respectively.[47,48] Anti-PD-L1 antibodies have also been studied in pre-treated unselected NSCLC, demonstrating response rates of 16% to 23% for MEDI-4736 and MPDL3280a, respectively.[49,50] Of note, some of these studies reported objective responses in EGFR-mutant patients, but estimation of response rate was difficult due to small size of this subgroup.[49] Activity was observed in both PD-L1-positive and PD-L1-negative patients with a trend towards higher response rates in PD-L1-positive patients.[44]

Although immune checkpoint inhibitors, including avelumab, are demonstrating promising activity in a variety of tumor types, there continues to be a need for new therapies. Tumor-directed therapies such as chemotherapy and targeted agents improve tumor antigenicity by inducing cell death, providing the basis for potential synergy with immune checkpoint inhibitors.[51,52]

Recent studies in genetically-engineered mouse models demonstrate that EGFR mutations promote tumorigenesis not only by stimulating tumor cell proliferation, but also by suppressing antitumor immunity, in part by upregulating PD-1 on tumor-infiltrating T cells through a non-cell-autonomous mechanism.[63,64] Consistent with these observations, in a retrospective cohort of human NSCLC tumor samples, the frequency of PD-L1 overexpression was significantly elevated in EGFRm compared to EGFR WT tumors. Erlotinib and gefitinib demonstrated higher response rates, time to progression and overall survival in PD-L1 positive tumors compared to PD-L1 negative tumors.[68] Taken together, these findings suggest that the immunosuppressive tumor microenvironment mediated by the PD-1/PD-L1 axis plays a potentially important role in the pathogenesis of EGFR mutant tumors, providing a rationale to combine PF-06747775 with avelumab in this setting.

Single-agent activity of immune checkpoint inhibitors has been observed in EGFR-mutant NSCLC patients.[45] A study of the combination of nivolumab and erlotinib in 21 patients (20 previously treated with EGFR TKI; 1 TKI-naïve) demonstrated an ORR of 19% and 24 week PFS rate of 47%. Among the patients with acquired erlotinib resistance, 3/20 patients achieved a partial response (PR, 15%) with 9/20 patients (45%) with stable disease (SD). The patient who was TKI-naïve also achieved a durable PR. Safety profile of the combination was reported as manageable. Nineteen percent (19%) of patients discontinued treatment due to adverse events. Grade 3/4 treatment-related AEs occurred in 5/21 patients (24%) and included diarrhea, increased ALT and increased AST.[61]

These initial promising preclinical and clinical findings provided the rationale for testing the combination of an EGFR TKI plus an anti-PD-1/-L1 agent in patients with advanced EGFRm NSCLC. In addition to erlotinib plus nivolumab as mentioned above, several additional clinical trials have been planned or initiated including gefitinib plus durvalumab (ClinicalTrials.gov identifier NCT02088112), erlotinib plus atezolizumab (NCT02013219), afatinib plus pembrolizumab (NCT02364609), and EGF816 plus nivolumab (NCT02323126).

In contrast to the initial positive supporting data as summarized above, other results addressing the potential for EGFR TKI combinations with anti-PD-1/-L1 agents have been less supportive. Regarding single agent activity of anti-PD-1/-L1 agents in patients with advanced NSCLC, some studies have found lower ORR and shorter PFS in patients with EGFRm tumors compared to EGFR WT tumors.[53,54] Evidence across different tumor types suggests a higher overall mutational burden leading to increased potential for neo-antigenicity shows a correlation with higher response rates to anti-PD-1/-L1 agents,[55] and that smoker status correlates with higher mutational burden.[56] As EGFRm NSCLC is known to correlate with non-smoker status, and the overall mutation burden is less in EGFRm versus EGFR WT tumors, this has been proposed as a rationale to explain the lower response rates.

Current evidence suggests even stronger correlates with anti-PD-1/-L1 response are tumor expression of PD-L1 and the presence of CD8-positive tumor infiltrating lymphocytes (TILs), which together are considered necessary for a response to anti-PD-1/-L1 agents. These key biomarkers, while clearly linked to the mechanism of action of PD-1 pathway immune checkpoint inhibitors, still lack robust standardized assays to facilitate their use for selecting patients and predicting response. With this limitation noted, results on the presence of these biomarkers in EGFRm NSCLC biopsies are also mixed. As mentioned above, some studies showed increased frequency of PD-L1 overexpression in EGFRm versus EGFR WT NSCLC tumors. The opposite has been observed in other studies, for example, no enrichment was found for PD-L1 expression in EGFRm NSCLC biopsies.[56] In a recent and thorough study that examined various parameters of anti-PD-1/L1 in EGFRm NSCLC,[53] only a subset of EGFRm NSCLC biopsies were found to express PD-L1 or show presence of CD8-positive TILs, and only rarely did these tumors contain both. This was found to be the case in biopsies taken prior to EGFR TKI exposure, as well as in biopsies taken at the time of acquired resistance. The authors suggest the lack of these mechanistic biomarkers could explain the low response rate to PD-1/-L1 agents they observed in their accompanying meta-analysis of clinical trials. However more work is needed to resolve current sources of variability in detection of these key biomarkers including the use of different anti-PD-L1 antibodies and assay methodologies, different scoring cut-offs, attention to type of specimen used, and intra-tumoral heterogeneity. Meanwhile it is important to acknowledge that not all studies provide strong supporting evidence for anti-PD-1/L1 agents in EGFRm NSCLC, as discussed in a recent mini-review.[57]

Tagrisso® (osimertinib) is a third generation EGFR TKI with a similar activity profile to PF-06747775, along with numerous differences between the compounds. Tagrisso combined with the anti-PD-L1 durvalumab was tested in patients with advanced EGFRm NSCLC in the Phase 1b TATTON study and the Phase 3 CAURAL study. While promising tumor responses were seen with the combination, it was too early to tell if the combination response was any different from single agent Tagrisso, and both studies revealed an increased incidence of interstitial lung disease (ILD).[58,59] The TATTON study preliminary results indicated a 38% rate of ILD including 5 cases of Grade 3/4 in severity.[59] Enrollment was suspended and both trials were put on hold in order to further assess the risk associated with the combination. It is not known currently what causes increased risk of ILD but causality due to the interaction of Tagrisso and durvalumab cannot be ruled out.

Tagrisso has been approved for single agent use and carries a warning and precaution on the label for ILD/pneumonitis, occurring in 3.3% of patients.[60] In clinical testing of PF-06747775, to date no ILD/pneumonitis AEs have been observed.

Compared with anti-PD-1 antibodies that target T cells, avelumab is an anti-PD-L1 antibody that targets tumor cells. Avelumab is expected to have fewer side effects, including a lower risk of autoimmune related safety issues, as blockade of PD-L1 leaves the PD-L2/PD-1 pathway intact to promote peripheral self tolerance. The anti-PD-1 antibodies pembrolizumab and nivolumab do carry a low risk of immune-related (ir) pneumonitis, with overall incidence of <3%. Hence the combination of PF-06747775 plus avelumab in patients with EGFRm NSCLC has the potential to differentiate from other EGFR TKI / anti-PD-1/-L1 combinations via a safer profile.

The clinical efficacy of avelumab in NSCLC is based on data from the unselected NSCLC expansion cohort in the ongoing Phase 1 trial EMR 100070-001 using a data cutoff date of 15 January 2015, 13 weeks after the start of avelumab treatment of the last patient in this expansion cohort (a total of 184 treated patients). This group of NSCLC patients presented with a median age of 65 years with Stage IIIB or IV NSCLC that had progressed after at least 1 line of platinum-containing doublet chemotherapy for locally advanced or metastatic disease. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 30% of patients and 1 in 70% of the patients. The histologies treated were adenocarcinoma (62%), squamous cell carcinoma (29%), or other (9%). These patients received avelumab 10 mg/kg Q2W. Promising activity has been seen among patients with NSCLC that has progressed after platinum-based chemotherapy when using avelumab. The median duration of treatment was 12.2 weeks (range 2.0-64.0). As of the date of data cutoff, 41 of the 184 patients remained on treatment. The ORR for the NSCLC expansion cohort was 13.6% (95% CI: 9.0 -19.4) including confirmed and unconfirmed responses. One patient (0.5%) had a complete response (CR) while 24 patients had confirmed and unconfirmed PR (13.0%). The disease control rate (DCR), patients with confirmed and unconfirmed CR, PR, and SD, was 50.5%. The median PFS in the NSCLC expansion cohort was 11.6 weeks (95% CI: 8.4 – 13.7) with the proportion of patients alive and progression-free at 24 weeks and 48 weeks equal to 26.2% (95% CI: 19.9 – 33.0) and 18.1% (95% CI: 12.0 – 25.2), respectively. The median overall survival (OS) in the NSCLC expansion cohort was 8.4 months (95% CI: 7.3 – 10.7) with 37.0% of patients alive at 12 months (95% CI: 27.1-46.9) in this heavily pretreated group of patients. The toxicity profile of avelumab was noted to be in line with other immune checkpoint inhibitors of PD-1 and PD-L1

In summary, based on promising activity of immune checkpoint inhibitors including avelumab in NSCLC, and the preclinical rationale for the combination with PF-06747775 in EGFR-mutant NSCLC, the proposed Phase 1/2 study will assess the safety and efficacy of the PF-06747775-avelumab combination in first-line treatment of EGFRm NSCLC.

1.2.6. Rationale for Selection of the Starting Doses

1.2.6.1. PF-06747775

1.2.6.1.1. Single Agent

Definitive 1-month toxicity studies in rats and dogs identified epithelial atrophy as the primary toxicity in multiple organs in both species (Section 1.2.2.2 Nonclinical Safety Data). Dog was identified as the more sensitive species based on an increased severity of these findings at similar unbound concentrations. Although a HNSTD was not identified in this definitive toxicity study in dogs, based on the lack of adverse body weight change at 15 mg/kg/day, the monitorable and reversible nature of the findings, as well as the thorough clinical characterization of the toxicity profile (ie, inhibition of wild type EGFR), the low dose (15 mg/kg/day) was used in lieu of the HNSTD to calculate a human starting dose. Using the International Conference on Harmonization (ICH) S9 Guideline (ie, 1/6 the HNSTD in non-rodents) and interspecies scaling via direct body surface area, a dose of 81 mg was calculated to be an appropriate human starting dose. However, single dose studies performed in dogs comparing fasted and fed states at 90 mg/kg and 15 mg/kg indicated that food increased exposure (AUC_{inf} and C_{max}) up to 2.4-fold relative to fasted

conditions. In light of these data, a lower (approximately 3-fold) human starting dose of 25 mg PF-06747775 was selected. This dose (25 mg) was modeled in the fed state with hepatic clearance mechanisms identified as 62% CYP3A4 and 38% GSTM1 and is predicted to yield an unbound average concentration (C_{av}) of 118 nM (49 ng/mL), unbound C_{max} of 171 nM (71 ng/mL) and unbound AUC_{24} of 2832 nM•h (1177 ng•h/mL). This dose is predicted to provide reasonably safe but pharmacologically active human exposure with expected safety margins of 2.2x and 10x based on mean unbound C_{av} and C_{max}, respectively. The geometric mean plasma fraction unbound (f_u) for rat is 0.224, 0.753 for dog, and 0.266 for human.

Based on PK/PD modeling and assuming biomarker (pEGFR) inhibition IC_{50} and mutant EGFR enzyme turnover rates acquired from nonclinical in vitro and in vivo studies, tumor stasis is associated with average inhibition of pEGFR within the dosing interval of approximately 70 -80%. The unbound efficacious concentration range (C_{eff}) for single agent PF-06747775, defined as the steady state concentration required to achieve static tumor load, was determined by PK/PD modeling. Both estimated human and observed mouse exposures of PF-06747775 were used, thus providing a range of C_{eff} estimates. The C_{eff} range is projected to range from 56 (human exposure) to 139 (mouse exposure) nM. The resulting predicted PF-06747775 human dose range for tumor stasis is 9-22 mg per day. This range is below the proposed starting dose of PF-06747775.

1.2.6.1.2. PF-06747775 Single Agent Recommended Phase 2 Dose

In the Phase 1 dose escalation portion of this study, there were no DLTs up to the maximum dose tested (600 mg daily), but the longer term tolerability of the higher doses were limited by persistent EGFR-WT driven toxicities (Grades 1 and 2 skin toxicities and diarrhea). Therefore, a recommended Phase 2 Dose (RP2D) of 200 mg once daily was selected which provided good tolerability and clinical activity (a high rate of objective responses).

A new tablet formulation with a change to one of the excipients to improve the stability will be introduced at RP2D in Phase 1b/2 cohorts (Cohorts 1, 2, and 3). Subsequently, patients from the Phase 1 cohorts who continue on treatment will convert to taking the new tablet after the initial tablet supply is exhausted.

In the event that PK of the new tablet were to differ to an extent that would cause clinical safety or efficacy concerns, the dose may be adjusted accordingly to account for the difference in systemic exposure in subsequent patients or cohorts.

1.2.6.1.3. Combination with Other Anti-Cancer Agents

The starting dose, which is the RP2D for PF-06747775 is 200 mg PO continuous dosing in 21-day cycles (Cohort 1 and Cohort 2) and 28-day cycles (Cohort 3).

1.2.6.2. Palbociclib

Palbociclib has been studied as a single agent in a Phase 1 dose-finding study (Study A5481001) in patients with solid tumors or lymphomas with doses ranging from 25 to 150 mg QD administered for 3 weeks followed by 1 week off treatment (Schedule 3/1) and 100 to 225 mg QD administered for 2 weeks followed by 1 week off treatment

(Schedule 2/1). The Schedule 3/1 was used in the subsequent breast cancer studies, and this is the FDA-approved dosing schedule in breast cancer, but current studies are ongoing evaluating a continuous dosing schedule to potentially better inhibit retinoblastoma (RB) phosphorylation. The current study will evaluate the safety and efficacy of palbociclib given on a continual dosing regimen in combination with PF-06747775 in patients with EGFRm NSCLC.

Cumulative clinical data suggest that a significant number of patients treated with palbociclib on the FDA approved dosing regimen experience dose interruptions and delays due to neutropenia without any apparent increase in febrile neutropenia compared to placebo. In addition, preclinical studies suggest that palbociclib exerts an antiproliferative effect on cancer cells that is released when the drug is discontinued.[67] These data suggest that a better therapeutic index may be obtained by maintaining continuous exposure using a lower but still biologically relevant dose of palbociclib. Simulated trough and absolute neutrophil profiles based on actual and modelled data indicate that a 100 mg continuous daily dose will be associated with an absolute neutrophil count (ANC) >1000 and greater systemic exposure to drug compared with the FDA-approved dosing schedule of 125 mg for 3 out of 4 weeks. A dose of 100 mg continuous daily dosing is currently being evaluated in clinical trials and emerging data appears to support its tolerability.

Lower concentrations of palbociclib simulating clinical dose reduction were tested in combination with PF-06747775 in combination efficacy experiments in vitro.[27] The increased efficacy observed from the combination was the same using a fixed concentration of PF-06747775 at 600 nM (approximates clinical exposure of 200 mg QD) plus palbociclib at either 100 nM, 75 nM, or 50 nM, indicating combination efficacy is maintained at lower concentrations of palbociclib, down to approximately one-half of the approved dose. In vivo combination efficacy experiments gave similar results. A clear and substantial increase in tumor growth inhibition in vivo was observed for the combination as compared to PF-06747775 alone. The combination efficacy was equally impressive using a palbociclib dose equivalent to the approved dose, and using a palbociclib dose equivalent to one-third of the approved dose.[27]

Neutropenia is the most frequently reported adverse event across all clinical studies of palbociclib. In general, neutropenia is reversible, non-cumulative, and managed by dose interruptions, cycle delays, and dose reductions. Population PK/PD analysis has demonstrated that higher exposure of palbociclib is associated with lower neutrophil counts. Through model-based simulation, the average neutrophil count time profiles at different dose levels of palbociclib revealed a dose-response relationship and the shape of neutrophil profile was significantly driven by dosing schedule. The total exposure per cycle with 100 mg QD on continual dosing regimen (Dose Level 1 in Cohort 2A) is expected to be lower than that with 125 mg QD on Schedule 3/1. In addition, the predicted average nadir of neutrophil count with 100 mg QD on CDD regimen was shown to be higher than that with 125 mg QD on Schedule 3/1, suggesting lower risk of developing Grade 3 or 4 neutropenia.

1.2.6.3. Avelumab

In this study, a dose of 10 mg/kg avelumab administered as a 1-hour IV infusion every Q2W will be administered in combination with PF-06747775. Avelumab 10 mg/kg IV Q2W is the recommended dosing regimen and has been administered to a total of 1300 patients in the ongoing dose-expansion phase of Study EMR 100070-001. See Section 1.2.4.3 for a summary of avelumab clinical experience to date.

1.2.7. Rationale for Drug-Drug and Food-Drug Interaction Sub-Studies

In vitro, PF-06747775 appears to be predominately cleared through oxidative metabolism and cysteine conjugation, with primary and secondary gluthathione (GSH) conjugation occurring in nonclinical species. Investigations of human cytochrome P450 metabolism using rCYP enzymes (rCYP1A2, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C19, rCYP2D6, rCYP3A4, and rCYP3A5) and human hepatocytes with a CYP3A4 specific chemical inhibitor were conducted with PF-06747775. PF-06747775 was stable in all rCYP incubations except those containing rCYP3A4, with minimal metabolism (~1%) observed in rCYP3A5. Due to the low observed clearance in standard human hepatocyte and human liver microsome incubations, the CYP3A4 contribution was determined using a human hepatocyte relay assay with and without CYP3cide, a CYP3A4 specific inhibitor. These data suggest that CYP3A4 accounts for ~60% of the hepatic metabolism of PF-06747775. PF-06747775 had very little reactivity in buffer fortified with GSH and was stable in all rGST incubations except those containing GST M1-1 (human hepatic GST).

Initial evaluation of the in vivo metabolism of PF-06747775 was conducted by profiling pooled plasma, bile, and urine samples from bile duct cannulated rats after single oral administration of PF-06747775. The plasma circulating metabolites observed were consistent with cysteine conjugation of PF-06747775, hydroxylation on the imidazole of PF-06747775, and secondary glucuronidation or cysteine conjugation of hydroxylated PF-06747775. Metabolites detected in rat bile or urine were consistent with the plasma circulating metabolites as well as demethylation of PF-06747775 and the increased formation of secondary conjugative metabolites (ie, detection of N-acetyl cysteine versions of hydroxylated metabolites). Hydroxylation on the pyrazole of PF-06747775 was not detected in any of the in vivo matrices even though it was determined to be a major metabolite in rat hepatocytes (as well as in monkey and human hepatocytes). However, it is possible that the hydroxylated pyrazole metabolite was formed in vivo and subsequently rapidly metabolized into some of the secondary conjugative metabolites observed.

Based on the cumulative in vitro DDI data (direct inhibition, metabolism-dependent inhibition, and induction), PF-06747775 has the potential to cause PK drug interactions with compounds for which CYP1A2, CYP2B6, CYP2C8, and/or CYP3A4/5-mediated metabolism constitutes the primary mechanism of clearance. However, in vitro time dependent inhibition and induction kinetic parameters indicate a low probability of impact to the exposure of CYP1A2, CYP2B6, and CYP2C8 substrates in humans based on the project total C_{max} exposure at, or well above (X5) the projected efficacious dose. In vitro data also indicates a low probability of PF-06747775 to cause CYP3A4 time dependent inhibition in humans, but based on the induction of CYP3A4 mRNA, PF-06747775 has the potential to impact CYP3A4 substrates.

To further investigate the DDI potential of PF-06747775 human PK prediction, SimCYP® (version 13.1) simulations of DDI were conducted with PF-06747775 as either a perpetrator or as a victim. SimCYP® simulations were performed to assess the net effect of steady state PK of PF-06747775 on the human PK of a single dose of midazolam (5 mg). At a projected human efficacious dose of 20 mg QD of PF-06747775, the AUC and C_{max} of midazolam decreased by 27% and 23%, respectively. Due to the potential solubility limited absorption of PF-06747775 in the crystalline form and the limitation of SimCYP® (version 13.1) to model fed state for the inhibitor, increasing the dose of PF-06747775 to 80 mg decreased the AUC and C_{max} of midazolam by 39% and 33%, respectively. The change in AUC and C_{max} of midazolam indicate a net effect of induction.

An early evaluation of the potential drug-drug interactions described above will identify the effect of concomitant medications in PF-06747775 exposure and the impact of PF-06747775 on other drugs, which will help to provide the appropriate directions for concomitant medication restrictions with the ultimate goal of an optimal PF-06747775 exposure.

Administration of a drug product with food may change the bioavailability (BA) by various means, including: delay in gastric emptying, stimulation of bile flow, changes in gastrointestinal pH, increase of splanchnic blood flow, changes in luminal metabolism of the studied drug, physical or chemical food interactions with the drug product, etc.[17] The solubility and permeability of PF-06747775 suggests that at high doses it is a class II drug according to the biopharmaceutics classification system (BCS), and for this type of compound, food effects are most likely to occur as a result of a combination of factors that influence the *in vivo* drug dissolution and absorption. Similarly, antacid medication may considerably alter PF-06747775 exposure. An early evaluation of food and antacid effect on PF-06747775 exposure will allow an effective and optimal dose administration to patients.

1.3. Safety Considerations in the Clinical Trial

1.3.1. Benefit-Risk Assessment for PF-06747775 Single Agent

As detailed below and in Section 1.2.2.2, the toxicities observed in the nonclinical safety studies are all known EGFR WT mediated effects (with evidence of secondary effects from mucosal surface compromise). Since these are class effects, Investigators are very familiar with them and their clinical management. PF-06747775 is anticipated to have a wider margin of safety against EGFR WT activation than prior generation compounds of the EGFR TKI class, so it is predicted that it will have less EGFR WT mediated toxicity for patients than agents to which they have already been exposed. Nevertheless, specific management guidelines will also be incorporated in the clinical trial and emphasized with Investigators.

PF-06747775-related gastrointestinal findings were observed in rats and dogs. Body weight loss was significant in the 14-day exploratory toxicity study in rats and the 1-month definitive toxicity study in dogs at doses ≥100 mg/kg/day and ≥60 mg/kg/day, respectively, resulting in unscheduled euthanasia. Body weight losses were accompanied by transient and generalized observations including hunched posture, rough haircoat, anogenital staining, decreased skin turgor, and soft feces in rats, and abnormal feces (soft, mucoid, watery, and/or

red-tinged), decreased food consumption, decreased activity, and sporadic emesis in dogs. At ≥100 mg/kg/day in rats there was epithelial (esophagus) and/or mucosal (glandular and/or nonglandular stomach, duodenum, ileum, cecum and/or colon) atrophy. Stomach erosions/ulcers were seen at the highest dose in both the 14-day and 1-month toxicity studies in rats; this finding was partially recovered after 1 month. At 90 mg/kg/day in dogs there were tongue and esophageal findings (erosions/ulcers) that might have interfered with eating, and at ≥60 mg/kg/day there was multi-segment, intestinal crypt dilatation coupled with mild mucosal atrophy and/or erosions. In the 14-day study in dogs, minimal atrophy of the intestinal mucosa was only seen at the 120 mg/kg/day dose. Following a 1-month recovery phase, all findings fully reversed except non-adverse epithelial atrophy of the cecum at 30 mg/kg/day in rats which was only partially recovered. Based on the observations above, patients with existing significant gastrointestinal disease will be excluded from this study. Proscriptive guidelines on early intervention for mucositis and diarrhea management are part of the investigational plan and will be emphasized with Investigators as noted above.

Skin-related clinical observations and microscopic findings were present in rats and dogs, although the presentation and location of findings were slightly different between species. In the 14-day exploratory study in rats, there was microscopic epidermal atrophy at ≥100 mg/kg/day. In the 1-month study in rats, skin hair granulomas, which corresponded to the in-life observations of swollen lip or muzzle and skin lesions at 60 mg/kg/day, and granulomatous inflammation in the Harderian gland at ≥30 mg/kg/day were due to foreign body reactions from epithelial atrophy (ie, atrophic hair follicle epithelium and Harderian gland acinar epithelium). In male dogs at ≥15 mg/kg/day and female dogs at 90 mg/kg/day, PF-06747775-related macroscopic skin findings consisted of abnormal color and thickened skin, and wound/scar/crust of the fore- and hindpaws, eyelid, ear, and/or scrotum leading to unscheduled euthanasia. Microscopically the principal features were minimal to moderate erosions/ulcers with crust formation and/or bacterial colonization, often associated with minimal to mild chronic active inflammation in the subjacent dermis and subcutis. Following a 1-month recovery phase, all findings reversed except for mononuclear cell infiltrates in the Harderian gland and adnexa atrophy of the skin at 60 mg/kg/day in rats. Proscriptive guidelines on early intervention for skin toxicity management are part of the investigational plan and will be emphasized with investigators as noted above.

Multiple clinical ocular observations involving the eye were seen in rats and dogs and generally correlated with minimal to marked atrophy of the corneal epithelium in rats at ≥30 mg/kg/day and in dogs at ≥15 mg/kg/day in studies up to 1-month in duration. These clinical observations included multifocal corneal opacities, rough corneal surface, and partially closed eyelids in rats and dogs, as well as conjunctival hyperemia, corneal edema with mucus/discharge, excessive lacrimation, constricted pupil/miosis, sclera congestion, and eye lid swelling in dogs, all of which contributed to unscheduled euthanasia at doses ≥60 mg/kg/day. At the end of the recovery phase, the previous finding of corneal opacities in rats and dogs had resolved; however, corneal neovascularization (a further progression of the corneal findings) had developed in one rat at 60 mg/kg/day. The applicability of these nonclinical findings to human clinical trials is limited. Although EGFR TKIs are known to cause ocular findings clinically, the most common adverse ocular effect for patients on

EGFR inhibitors is dysfunctional tear syndrome; clinical cases of epithelial defects and/or corneal abrasions are rare.[18] Nevertheless, Investigators will be reminded to attend to any ocular symptoms and management guidelines for ocular events are included in the trial.

In the kidney at ≥100 mg/kg/day in rats, there was PF-06747775-related tubular basophilia. At 500 mg/kg/day there was papillary necrosis and dilatation of tubules. Tubular basophilia and tubular dilatation were both bilateral and were associated with macroscopic observations of abnormal kidney color (mottled) in 1/5 rats at 500 mg/kg/day. The kidney findings were associated with increases in BUN and/or creatinine. There were no kidney findings in dogs in studies up to 1-month in duration. BUN and creatinine will be routinely monitored in the study at every cycle.

Cardiovascular effects of PF-06747775 were rat-specific minimal increases in blood pressure (20 mg/kg). There were no observed direct effects in ECG parameters in dogs after single or repeat-dosing up to 90 mg/kg/day. ECGs will be closely monitored on the study and QTc evaluation performed.

There were no effects on the liver after repeated dosing of PF-06747775 in nonclinical toxicity studies in rats and dogs up to 1-month in duration. Liver function tests (LFTs) will be monitored closely with testing at each cycle start.

The SRSD for PF-06747775 is the PF-06747775 IB.

Complete information for esomeprazole, sildenafil, rifampin and itraconazole may be found in their corresponding package inserts.

1.3.2. Benefit-Risk Assessment Combinations with Palbociclib (Cohort 2) and Avelumab (Cohort 3)

PF-06747775 has proven efficacy in the Phase 1 portion of this trial with sustained (longest is 12 months and ongoing) objective responses in patients with EGFRm NSCLC who had progressed on prior EGFR TKI therapy. The toxicity profile for single-agent PF-06747775 at the RP2D appears tolerable for a prolonged duration of therapy, and no DLTs were observed at doses 3x higher. Preclinical studies combining PF-06747775 with palbociclib suggest significant improvement in tumor regrowth kinetics relative to PF-06747775 alone that may translate to improved PFS in clinical evaluation. Such an improvement in PFS with a manageable toxicity profile would represent an improved benefit-risk balance of PF-06747775 and palbociclib for patients with resistant EGFRm NSCLC, over treatment with PF-06747775 alone or any other currently available therapy.

Similarly, the combination of PF-06747775 with an immune checkpoint inhibitor such as avelumab has the potential to provide significantly improved clinical efficacy than either agent alone with manageable toxicities, and thus represents a reasonable benefit-risk for clinical evaluation.

2. STUDY OBJECTIVES AND ENDPOINTS

This study has separate primary and secondary objectives and endpoints for the Phase 1 and each of the subsequent sections of the study.

2.1. Objectives

2.1.1. Phase 1

2.1.1.1. 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 recommended phase 2 dose 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.

2.1.1.2. 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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2.1.2. Phase 1b/2

2.1.2.1. Primary Objectives

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

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

2.1.2.1.2. 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).

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

- To assess the 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).

2.1.2.1.4. 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 EGFRm NSCLC with a secondary T790M mutation (del 19 and T790M or L858 R and T790M).

2.1.2.2. Secondary Objectives

- To assess duration of response (DOR), and OS probability at 24 months (all Cohorts);
- To assess PFS (Cohort 1, Cohort 2A, and Cohort 3);
- To further characterize the 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 tumor and plasma the presence/absence of EGFR mutations (All Cohorts);
- To assess the immunogenicity of avelumab when given in combination with PF-06747775 (Cohort 3).

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2.1.3. Japanese Patient-Only Lead In Cohort

- To evaluate the safety and tolerability of PF 06747775 in Japanese patients (RP2D tolerability cohort).
- To characterize single dose and steady state PK profiles of single agent PF-06747775 in Japanese patients (RP2D tolerability cohort and PK cohort).

2.2. Endpoints

2.2.1. Phase 1

2.2.1.1. Primary Endpoint(s)

- Cycle 1 DLT.

2.2.1.2. Secondary Endpoints

- Overall safety profile of PF-06747775 characterized by type, incidence, severity, seriousness, and relationship to study therapy of AE (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03);
- Laboratory abnormalities;
- QT and RR for QTc effects of PF-06747775 when given as a single agent;
- Plasma AUC_{inf}, C_{max}, $t_{1/2}$, CL/F, and Vz/F of PF-06747775 as a single agent after single dose;
- C_{trough}, AUC_{tau}, CL/F, observed accumulation ratio (R_{ac}), and steady state accumulation ration (R_{ss}) of PF-06747775 as a single agent after multiple doses;
- Plasma AUC_{inf}, C_{max}, and CL/F of sildenafil alone and in combination with steady state plasma concentrations of PF-06747775;
- Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D under fed and overnight fasted conditions;
- Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and after esomeprazole treatment;
- Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and after itraconazole treatment;
- Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and after rifampin treatment;
- EGFR mutations in tumor and plasma;
- Objective tumor response (OR), confirmed and unconfirmed, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for those patients with measurable disease.

2.2.2. Phase 1b/2

2.2.2.1. Primary Endpoints

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

- Confirmed OR, per RECISTv 1.1.

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

- Cycle 2 DLT.

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

- PFS.

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

- Cycle 1 DLT.

2.2.2.2. Secondary Endpoints

- PFS (Cohorts 1, 2A, 3);
- ORR (Cohorts 2A, 2B, 3);
- DOR (All Cohorts);
- OS probability at 24 months (All Cohorts);
- Overall safety profile characterized by type, incidence, severity, seriousness, and relationship to study therapy of AE (NCI CTCAE v4.03); laboratory abnormalities (All Cohorts);
- PK parameters of PF-06747775 following single and multiple doses as data permit when given as a single agent (Cohort 1 and Cohort 2B single-agent patients);
- PK parameters of PF-06747775 following multiple doses as data permit when given in combination with palbociclib and avelumab (Cohorts 2 and 3);
- PK parameters of palbociclib and avelumab when given in combination with PF-06747775, as data permit (Cohorts 2 and 3);
- QT and RR for QTc effects of PF-06747775 when given as a single agent (Cohort 1) and in combination with palbociclib (Cohort 2A and 2B) and avelumab (Cohort 3);
- EGFR mutations in tumor and plasma (All Cohorts);

- Avelumab serum ADA (neutralizing antibodies) (Cohort 3).

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2.2.3. Endpoint for Japanese Patient-Only Lead In Cohort

- Cycle 1 DLT (RP2D tolerability cohort);
- Overall safety profile of PF-06747775 characterized by type, incidence, severity, seriousness, and relationship to study therapy of AE (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03);
- Laboratory abnormalities;
- PK parameters of PF-06747775 following single and multiple doses as data permit when given as a single agent (RP2D tolerability cohort and PK cohort).

3. STUDY DESIGN

3.1. Study Overview

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 NSCLC. The overall clinical study consists of a Phase 1 single agent dose-escalation and expansion part to determine the 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;

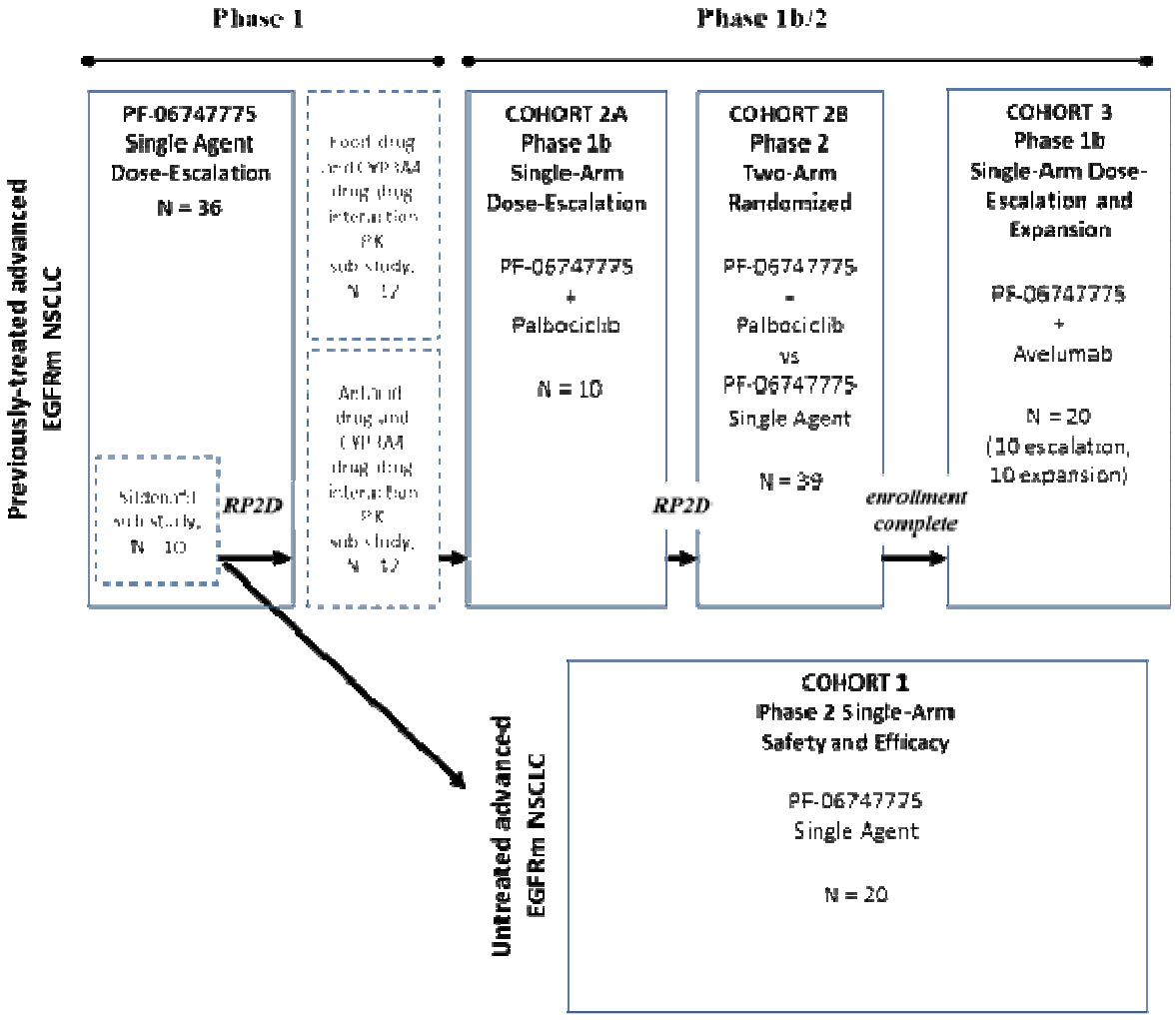
- Cohort 2: Phase 1b single arm evaluation of PF-06747775 in combination with palbociclib (Cohort 2A) followed by Phase 2 randomized evaluation of PF-06747775 in combination with palbociclib vs PF-06747775 single agent (Cohort 2B) in previously-treated patients with EGFRm NSCLC with a secondary T790M 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 (Cohort 2A) and Table 17 (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 3.1.3.1 (Cohort 2A) and Section 3.1.4 (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.

Figure 2. Study B7971001 Study Schema*



* Approximate enrollment totals indicated.
EGFRm = epidermal growth factor receptor mutant; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; RP2D = Recommended Phase 2 Dose

This study will include a Japanese patient lead in cohort (LIC) to evaluate the safety, tolerability and PK of PF-06747775 in Japanese patients with advanced EGFRm NSCLC. (See Section 3.1.5, Appendix 8) not pictured above.

The status of the EGFR mutations will be determined in all patients using tumor or plasma samples obtained at study entry. Patients providing tumor samples will be enrolled based on a local EGFR mutation test that includes the QIAGEN Therascreen EGFR RGQ PCR Kit, Roche cobas® EGFR mutation kit, or a Sponsor-approved laboratory developed test that is validated in a Clinical Laboratory Improvement Amendments (CLIA) laboratory. Patients providing plasma samples will be enrolled based on a local EGFR mutation test that includes the QIAGEN Therascreen EGFR Plasma RGQ kit, Roche cobas® EGFR mutation test v2

(US-IVD), Sysmex Inostic's OncoBEAM™ EGFR test, or a Sponsor-approved laboratory developed test that is validated in a CLIA laboratory, which will then be retrospectively confirmed by a validated cell free DNA (cfDNA) test as determined by the Sponsor. All patients — ie, in both Phase 1 and Phase 2 parts of the study — will have their tumor EGFR mutation status confirmed by the central lab test using FDA approved QIAGEN Therascreen EGFR RGQ PCR kit (tumor-based) or a validated cfDNA test as determined by the Sponsor (plasma-based). The tissue samples may also be tested retrospectively using the Thermo Fisher Scientific Oncomine Next Generation Sequencing (NGS) cancer panel, which detects exon 19 deletions, exon 20 insertions, T790M mutations, and exon 21 (L858R) substitution mutations.

Study design details specific to Phase 1 are provided in Section 3.1.1. Study design details specific to Cohorts 1, 2, and 3 are provided in Section 3.1.2, Section 3.1.3, and Section 3.1.4, respectively.

All patients (regardless of Phase or Cohort) will be allowed to continue therapy until disease progression or intolerable toxicity, withdrawal of consent, termination of the study by the Sponsor, or death. Treatment continuation beyond objective disease progression is acceptable if the Investigator deems the patient to have ongoing clinical benefit. Treatment with PF-06747775 alone is also permitted if the combination is intolerable, but no patients may continue on trial on palbociclib or avelumab as single agents. Antitumor activity will be determined based on Investigator assessment. Individual patients' imaging will be prospectively collected for potential follow-up assessment by Blinded Independent Central Review (BICR).

For all patients who have a RECIST response, confirmation of the response is required at least 4 weeks after initial assessment of response.

3.1.1. Phase 1

The Phase 1 part of this study is an open label, multi-center, multiple dose, non-randomized, safety, PK, PD, 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)[19] will be used to guide the dose assignment and estimate the MTD based on cumulative data on DLTs in the first cycle.

The target probability of DLT 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 (see Section 3.5).

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.

3.1.1.1. Starting Dose

The Phase 1 study will evaluate single-agent PF-06747775 PO (tablets) with continuous daily dosing in 21 day cycles. The starting dose for PF-06747775 will be 25 mg PO daily.

3.1.1.2. Dose Escalation Criteria

In Phase 1, dose escalation and de-escalation of PF-06747775 will follow the CRM approach.

The goal of the Phase 1 portion of the study is to determine the dose of PF-06747775 that is the closest to, but not higher than, a 30% probability of a DLT (ie, a target DLT rate of 0.30). Each dose level cohort will initially include at least 3 patients evaluable for toxicity within the first cycle. The first three patients (ie, the first cohort) will be treated at 25 mg, and the following dose level explored will be 50 mg.

To assign the dose level for each subsequent patient, the probability of DLT is estimated to a target rate of 30%. This estimate is achieved for each level taking into account all the collected toxicity data from all treated patients up to that time and the prior expectations of

toxicity. Based on the observed toxicity profile, CRM permits dose-level skipping during dose escalation. However, in order to prevent overly aggressive dose escalation, for every escalation the maximum allowed dose level skipped will be limited to one dose level. No restriction is applied for dose de-escalation.

The probabilities of DLT are estimated based on a Bayesian statistical model with prior distribution to learn about the overall dose-toxicity relationship. Patients' DLT data will be reported to the study statistician who will update the dose-toxicity model before the next dose cohort level is enrolled. Details on the CRM approach are provided in Section 9 and the Statistical Analysis Plan.

Patients who discontinue treatment before completing Cycle 1 (ie, the DLT evaluation time window) or receive less than 15 of the planned 21 PF-06747775 doses for reasons other than treatment-related toxicity (eg, missed appointments, misplaced investigational product supplies, development of coexisting medical condition rendering the patient unable to swallow medication, development of rapidly progressing disease) will be replaced for DLT evaluation but will remain in the overall safety and efficacy analyses.

Dose escalation stops if:

- 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.

To avoid overly rapid escalation and to retain the efficiency of dose administration when enrollment is fast, the following restrictions will be applied:

- For each dose level, patients will be enrolled in cohorts of minimum 3 patients (unless 2 DLTs are observed in the first 2 patients tested at that dose level). The first two patients may enroll together, but the next patient(s) will enroll at least 1 week later. The timing of patient enrollment may be further evaluated as safety and PK data become available.
- Enrollment for the next cohort of patients will open when patients on the current dose cohort have completed the pre-specified DLT observation period or experienced a DLT.
- Enrollment in dose level cohorts lower than the highest tested dose level cohort may occur before the completion of the pre-specified DLT observation period.

Dose level skipping in escalation to untested doses will be limited to only one level ($k \rightarrow k+2$). In particular, at least three patients should have been treated for at least one cycle at dose level k before escalation to dose level k+2.

Dose escalation recommendation by the CRM algorithm may be overruled (but frequency should be minimized) by the sponsor if the nature of the existing data causes safety concern.

Further exploration of doses lower than those recommended by the CRM model may be evaluated based on the totality of the safety data.

In case the DLT rate at the initial dose level of 25 mg QD exceeds 30%, the dose level of 20 mg QD will be tested.

3.1.1.3. Dose Levels to be Tested

The possible dose levels for evaluation of PF-06747775 during Phase 1 are shown in Table 13.

Dose escalation will continue as outlined in Table 13 until an MTD is defined, or the maximum dose to be tested is reached. If DL-2 is not tolerated based on the criteria defined in Section 3.2, then the study will not continue.

See Section 5.4.3 for more details regarding administration of investigational products.

In addition to the dose levels listed in Table 13, intermediate dose levels may be tested dependent upon tolerability, AE profile and other emerging data over the course of the study after discussion between the Investigators and the sponsor.

Table 13. Dose Levels for PF-06747775

Dose Level	PF-06747775 (mg/day)
-2	10
-1	20
1 (Starting Dose)	25
2	50
3	100
4	150
5	200
6	275
7	350
8	450
9	600

The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data.

Intra-patient dose escalation may be permitted if the following conditions are satisfied:

- Cycle 1 was completed without any DLTs.
- The first 3 evaluable patients at the next higher dose level have completed Cycle 1 with PF-06747775 without experiencing a DLT.

- The decision to increase the dose has been approved by discussion with both the Investigator and the Sponsor. A patient whose dose has been escalated will not contribute to the assessment of the number of DLTs at the escalated dose level.

- Intermediate dose levels will be permitted if agreed to between the Investigators and the Sponsor (ie, dose levels that are below the doses tested in the cohorts used for DLT assessments, but at a dose that was not itself tested, eg, 275/d was tested, but an individual patient on intra-patient dose escalation only increases to 200 mg/d).

3.1.2. 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.

3.1.3. 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 PD 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).

3.1.3.1. 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.

Dose finding will follow the mTPI method with adjustments using DLT rate, using the dosing regimen of PF-06747775 and palbociclib as shown in Table 14.

Table 14. PF-06747775 and Palbociclib Dose Levels

Dose Level	PF-06747775 (mg/day)	Palbociclib (mg/day)
DL-2	200	50
DL-1	200	75
DL1 (Starting Dose Level)	200	100

These are some of the possible dose finding scenarios based on the tolerability of the starting dose, DL1. DL-1 will be explored only if the design recommends de-escalation from DL1. DL-2 will be explored only if the design recommends de-escalation at DL-1. The proposed doses, schedule(s) and PK time points for Cohort 2 may be altered during the study based on the emerging safety and PK data from this study or other emerging data.

There are several potential dose-finding sequences for PF-06747775 and palbociclib. The specific sequence to be followed depends upon the number of patients enrolled in the study and the number of DLTs observed at each specific DL combination. Some possible sequences are listed below in Table 15.

Table 15. Some Possible Dose Finding Sequences

Possible sequences starting at Dose Level 1 (DL1)
DL1
DL1 →DL-1
DL1→ DL-1→DL-2

Dosing will begin at DL1 and may possibly be de-escalated to DL-1 according to Table 16. The patients who are enrolled in DL1 will be monitored for 2 cycles for DLTs. If permitted by mTPI, this dose level will be expanded in cohorts of 3 patients to a total of 6 patients. If at any point mTPI requires a de-escalation, the next patients will be enrolled at a lower dose level according to Table 16. In this case, DL-1 may start. Dose re-escalation will be allowed as long as the current dose level has not been determined to have exceeded the target probability of toxicity.

The re-escalation/de-escalation rules will follow the mTPI method (Section 9.2.1.1). Briefly, the mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same DL to determine whether future cohorts should involve dose re-escalation, no change in dose, or dose de-escalation. The detailed dose-finding rules based on the mTPI are illustrated in Table 16.

Table 16. Dose Escalation/De-Escalation Decision Algorithm

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

As an example, if the total number of patients treated at DL1 is 3, then the following dosing rules are to be applied:

- 0 - 1 DLT → remain at the same DL (DL1);
- 2 DLTs → de-escalate to DL-1 and allow for possible re-escalation back to DL1;
- 3 DLTs → de-escalate to DL-1 as DL1 is intolerable.

Rules for dose finding using the mTPI method include the following:

- The target enrollment cohort size is 3-4 patients.
- The next cohort will be enrolled, if necessary, when all patients evaluable for DLT at the current dose cohort have been evaluated for the 2 cycles, or when more than 1 patient in a cohort experiences a DLT, whichever comes first. The next cohort will receive the DL as assigned if a dose modification is required.
- If a patient does not receive at least 70% of the first 2 cycles of PF-06747775 or palbociclib within the DLT observation period (42 days) for reasons other than investigational product-related toxicity, another patient will be enrolled to replace that patient at the current dose level.
- Phase 1b is completed when at least 6 DLT-evaluable patients (see Section 9.1) have been treated at a dose level confirmed to be safe.

3.1.3.2. 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).

3.1.4. 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, PK and PD 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.

Dose finding will follow the mTPI design (see Section 9.2.1.2), using the dosing regimen of PF-06747775 and avelumab as shown in Table 17.

Table 17. PF-06747775 and Avelumab Dose Levels

Dose Level	PF-06747775 (mg/day)	Avelumab (mg/kg) Q2W
DL-1	150	10
DL1 (Starting Dose Level)	200	10

Dosing will begin at DL1 and may possibly be de-escalated to DL-1 according to Table 16. DL-1 will be explored only if the design recommends de-escalation at DL1. The proposed doses, schedule(s) and PK time points for Cohort 3 may be reconsidered and altered during the study based on the emerging safety and pharmacokinetic data from this study and other emerging data.

Dose finding sequences and dose finding decision rules based on mTPI will be similar as stated in Section 3.1.3 with a few exceptions:

- The patients who are enrolled in DL1 will be monitored for 1 cycle (28 days) for DLTs;
- If a patient does not receive at least 70% of the first 4 weeks doses of PF-6747775 or does not receive at least 2 infusions of avelumab within the DLT observation period (1 cycle = 28 days) for reasons other than investigational product-related toxicity, another patient will be enrolled to replace that patient at the current dose level.

Once RP2D of PF-06747775 in combination with avelumab is determined, the Dose Expansion Phase will continue to enroll patients until approximately 20 patients in total have been treated to further assess the safety, PK, PD, and antitumor activity of the combination.

3.1.5. Japanese Patient-Only Lead In Cohort

This study will include a Japanese patient lead in cohort (LIC) to evaluate the safety, tolerability and PK of PF-06747775 in Japanese patients with advanced EGFRm NSCLC at RP2D (PF-06747775 200 mg) when given as a single agent. This Japanese LIC will consists of 2 cohorts; RP2D tolerability cohort and PK cohort. The RP2D tolerability cohort will be enrolled first. Up to 3 patients will be enrolled and treated at RP2D. If no DLT is observed, no additional patients will be enrolled in this cohort. If a DLT is observed in 1 of the initial 3 treated patients, then 3 additional patients will be enrolled and treated. Following 1 cycle (21 days) of treatment, a safety review will be performed by Japanese investigators and the Sponsor to determine whether the emerging data from this cohort would support inclusion of patients at Japanese sites in Phase 2 (Cohort 1) and Phase 1b/2 (Cohort 2A, 2B and 3). After tolerability in Japanese patients has been confirmed in the RP2D tolerability cohort, an additional PK cohort will be initiated. In the second PK cohort, 3 patients will be enrolled and they will receive 100 mg single dose followed by once daily continuous dosing at the RP2D. In both cohorts, blood samples will be collected for PK assessment (See Appendix 8).

3.2. DLT Definitions

Severity of adverse events will be graded according to CTCAE version 4.03. For the purpose of dose escalation, any of the following adverse events occurring in the first cycle of treatment (21 days) which are attributable to PF-06747775 will be classified as DLTs.

3.2.1. Phase 1 PF-06747775 Single Agent

- Hematologic:
- Grade 4 neutropenia lasting >7 days;
- Febrile neutropenia (defined as neutropenia Grade ≥3 [absolute neutrophil count, ANC, <1000 cells/mm^3] and a body temperature ≥38.5°C) requiring antibiotic or antifungal treatment;
- Grade ≥ 3 thrombocytopenia with bleeding;
- Grade 4 thrombocytopenia.
- Non-hematologic:
- Grade ≥3 toxicities, except the 3 cases specified below:
    1. those that have not been maximally treated (eg, nausea, vomiting);
    2. rash (including all subtypes), mucositis, diarrhea;
    3. Laboratory abnormalities not requiring dose modifications as indicated in Table 18.
- Grade 4 rash, mucositis, or diarrhea; all of which must be maximally treated (see AE Management guidelines, Appendix 3) and persist at Grade 4 to be a DLT.
- Failure to receive at least 15 of the planned 21 doses (70%) of PF-06747775 due to toxicities attributable to PF-06747775 that were all maximally treated.

In an asymptomatic patient, Grade 3 QTcF prolongation (QTc >500 msec) will first require repeat testing, re-evaluation by a qualified person, and correction of reversible causes such as electrolyte abnormalities or hypoxia for confirmation. If, after correction of any reversible causes, the Grade 3 QTcF prolongation persists, then the event should be considered a DLT.

3.2.2. Phase 1b Cohort 2

In addition to the definitions described for the evaluation of PF-06747775 single agent above (Section 3.2.1), the following AEs occurring during the 42-day DLT period (ie, Cycles 1 and 2) that are attributable to one, the other, or both compounds in the combination of PF-06747775 plus palbociclib will be classified as DLTs:

- Any treatment-related, maximally treated AE that causes a palbociclib treatment delay of greater than 10 consecutive days;

- Any treatment-related AE, except for neutropenia, that is maximally treated but still causes omission of at least 12 of the 42 doses within the 2 cycles used for DLT determination of the combination (ie, either drug to be held).

3.2.3. Phase 1b Cohort 3

In addition to the definitions described for the evaluation of PF-06747775 single agent above (Section 3.2.1), the following AEs occurring during the first 28 day cycle that are attributable to one, the other or both compounds in the combination of PF-06747775 plus avelumab will be classified as DLTs:

- Hematologic:
  - Grade 4 thrombocytopenia >7 days.
  - Grade 4 anemia.
- Non-hematologic:
  - Grade ≥3 toxicities, except the 5 cases specified below:
    1. Transient (≤6 hours) Grade 3 flu like symptoms or fever, which is controlled with medical management;
    2. Transient (≤24 hours) Grade 3 fatigue, local reactions, or headache that resolves to Grade ≤1;
    3. Any Grade ≥3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis;
    4. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor;
    5. Single laboratory values out of normal range that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management.

3.3. Phase 1 MTD Definition

The MTD is defined as the highest dose with a DLT rate ≤ 30% from the CRM model estimate (see Section 9.2).

A patient is evaluable for the MTD determination according to the definition in the Protocol (MTD Evaluable) Analysis Set defined in Section 9.3.

3.4. Recommended Phase 2 Dose (RP2D) Definition

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

3.5. Phase 1 Drug Interaction Sub-Studies

Several drug interactions sub-studies will be conducted at the PF-06747775 RP2D once it is identified. A food effect sub-study (drug-food interaction), and several drug-drug interaction sub-studies will be performed in approximately 24 patients. The potential effect on the PK of PF-06747775 by a high-fat, high-calorie meal, a proton pump inhibitor, a CYP3A4 inhibitor, and a CYP3A4 inducer will be investigated. In these sub-studies, PF-06747775 will be considered the CYP3A4 substrate and the proton pump inhibitor, CYP3A4 inhibitor, and CYP3A4 inducer will be the interacting drugs.

In addition to these sub-studies at the PF-06747775 RP2D, an additional drug-drug interaction sub-study will be performed in the MTD expansion cohort where PF-06747775 will be the CYP3A4 inhibitor and sildenafil, a CYP3A4 probe, will be the CYP3A4 substrate.

3.5.1. Sildenafil Sub-Study

A drug-drug interaction sub-study with sildenafil, a CYP3A4 probe, as a CYP3A4 substrate and PF-06747775 as a CYP3A4 inhibitor will be conducted in the MTD expansion cohort of Phase 1 part of the study. The main purpose of this sub-study is to appropriately estimate the potential CYP3A4 inhibitory ability of PF-06747775.

A single 25 mg dose of sildenafil will be given in the morning at approximately the same time on Day -8 of the lead-in period and on Day 11 of Cycle 1, following an overnight fast of at least 10 hours. On Day 11 of Cycle 1, PF-06747775 will be given together with sildenafil following an overnight fast of at least 10 hours. Food and liquids other than water are allowed 2 hours after dose. PF-06747775 dose will be given in the morning at approximately the same time once daily in 21 day cycles, with a breakfast of 200-300 calories. Only on Day 11 of Cycle 1 will PF-06747775 be administered following an overnight fast of at least 10 hours (overnight fasting is not required on other study days). Pharmacokinetic sampling times are described in the Schedule of Activities (Table 3).

3.5.2. Food Effect and Rifampin DDI Sub-Study

This PK sub-study will be a randomized, multiple dose, 2 sequence, three period crossover study. Approximately twelve (12) patients will each receive a daily dose of PF-06747775 at the RP2D and serial PK collections will be performed under 3 different conditions or treatments (A-fasted, B-fed and C-with rifampin), with treatments in Period 1 and Period 2 assigned in random order and Period 3 as a fixed sequence. A minimum of 12 patients (PK evaluable) are required for this study. Patients who withdraw may be replaced at the discretion of the sponsor.

For patients who participate in this sub-study, the effect of a high-fat, high-calorie breakfast and co-administration with a strong CYP3A4 inducer (rifampin) on PF-06747775 pharmacokinetics will be studied. Each patient will serve as his/her own control in which the PF-06747775 at the RP2D will be given in the morning at approximately the same time once a day in 21 day cycles.

Sequence Group	PF-06747775 (C1 D1-7)	Period 1 (C1 D8)	Period 2 (C1 D9)	Rifampin+PF-06747775 (C1 D10-20)	Period 3 (C1 D21)
Sequence 1 (N=6)		A	B		C
Sequence 2 (N=6)		B	A		C

Serial blood sampling to determine plasma concentrations of PF-06747775 will be performed pre-dose and up to 24 hours post dose in each period (see Table 4 of the SOA).

Sequence 1: 6 patients will be tested under fasted (Day 8 of Cycle 1) followed by fed (Day 9 of Cycle 1) conditions. A fixed sequence with rifampin treatment will happen after the fasted/fed portion has been completed.

Sequence 2: 6 patients will be tested under fed (Day 8 of Cycle 1) followed by fasted (Day 9 of Cycle 1) conditions. A fixed sequence with rifampin treatment will happen after the fed/fasted portion has been completed.

- **Fasted Treatment**: Following an overnight fast of at least 10 hours, patients should be administered PF-06747775 at the RP2D with 240 mL (8 ounces) of water. No food or liquids other than water are allowed for at least 4 hours post dose. Water is allowed as desired except for one hour before and after drug administration.

- **Fed Treatment**: Following an overnight fast of at least 10 hours, patients should start the recommended high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800-1000 calories with 150, 250, and 500-600 calories from protein, carbohydrate and fat, respectively) breakfast 30 minutes prior to administration of PF-06747775. Breakfast will be consumed over a 25 minute period with PF-06747775 at the RP2D administered 5 minutes after completion of the meal. PF-06747775 should be administered with 240 mL (8 ounces) of water. No food or liquids other than water are allowed for at least 4 hours post dose. Water is allowed as desired except for one hour before and after drug administration.

    - An example test meal would be two eggs fried in butter, two strips of bacon (may be replaced with ham and cheese of similar caloric content), two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole-fat milk. Substitutions to this test meal can be made after discussion with the sponsor, as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity (if substitutions are made, the contents of the meal will be documented by a dietitian or designate to confirm it matches the Food and Drug Administration (FDA) requirements for protein, carbohydrate and fat

described above). However, it is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the test meal breakfast and the time it takes to be consumed.

- **Rifampin + PF-06747775 Treatment**: On Days 10 to 20 of Cycle 1, besides the daily dose of PF-06747775 at the RP2D, 600 mg of rifampin will be given to patients at approximately the same time once daily in the morning 2 hours prior to breakfast. The pharmaceutical forms should be swallowed whole. The pharmaceutical forms should not be chewed, crushed, or split. On the morning of Day 21 of Cycle 1, following an overnight fast of at least 10 hours, patients should be dosed with 600 mg dose of rifampin + PF-06747775 at the RP2D. PF-06747775 should be taken by the patient with 240 mL (8 ounces) of water. No food or liquids other than water are allowed for at least 4 hours post dose. Water is allowed as desired except for 1 hour before and after drug administration.

The Days for treatment A, B and C may be modified based on the PK profile observed during the lead-in period in the earlier portions of the study.

This PK sub-study may be completed after 1 or both of the combination studies (Cohorts 2 and 3) are completed.

3.5.3. Antacid Effect and Itraconazole DDI Sub-Study

This PK sub-study will be a randomized, multiple dose, 1 sequence, 3 period study. Approximately twelve (12) patients will each receive a daily dose of PF-06747775 and serial PK collections will be performed under 3 different conditions or treatments (A - fasted, B - with esomeprazole, and C - with itraconazole), with treatments assigned in a fixed sequence. A washout period of 3 days prior to dosing itraconazole is required to restore the pH of the stomach (C1 D14 - 16). During this washout period, PF-06747775 will be given daily in the morning, with a breakfast of 200-300 calories. Food and liquids other than water are allowed 2 hours after dose. A minimum of 12 patients (PK evaluable) are required for this study. Patients who withdraw may be replaced at the discretion of the sponsor.

For patients who participate in this sub-study, the effect of co-administration of an antacid (the proton pump inhibitor esomeprazole) or a strong CYP3A4 inhibitor (itraconazole) on PF-06747775 pharmacokinetics will be studied. Each patient will serve as his/her own control in which the PF-06747775 at the RP2D will be given in the morning at approximately the same time once a day in 21 day cycles.

Sequence Group	PF-06747775 (C1 D1-7)	Period 1 (C1 D8)	PF-06747775 + Esomeprazole (C1 D9-12)	Period 2 (C1 D13)	C1 D14-16	PF-06747775 + itraconazole (C1 D17-20)	Period 3 (C1 D21)
Sequence 1 (N=12)		A		B	Washout for esomeprazole effect. PF-06747775 will be given once a day with breakfast.		C

Serial blood sampling to determine plasma concentrations of PF-06747775 will be performed pre-dose and up to 24 hours post dose in each period (see Table 5 of the SOA).

- **PF-06747775 Alone**: Patients should receive PF-06747775 at the RP2D with 240 mL (8 ounces) of water and a breakfast of 200-300 calories. No food or liquids other than water are allowed for at least 2 hours post dose.

- **PF-06747775 + Esomeprazole**: On Days 9 to 12 of Cycle 1, besides the daily dose of PF-06747775 at the RP2D, 40 mg of esomeprazole once a day will be given to patients 2 hours prior to breakfast and PF-06747775 dose. Pharmaceutical forms should be swallowed whole. The pharmaceutical forms should not be chewed, crushed, or split. In the morning of Day 13 of Cycle 1, patients should take a 40 mg dose of esomeprazole and 2 hours post esomeprazole dose, patients should be dosed with PF-06747775 and 240 mL (8 ounces) of water and a breakfast of 200-300 calories. No food or liquids other than water are allowed for at least 2 hours post dose of PF-06747775.

- **PF-06747775 + Itraconazole Treatment**: On Days 17 to 20 of Cycle 1, PF-06747775 at the RP2D should be dosed together with 200 mg of itraconazole at approximately the same time once daily with a breakfast of 200-300 calories. Pharmaceutical forms should be swallowed whole. The pharmaceutical forms should not be chewed, crushed, or split. In the morning of Day 21 of Cycle 1, patients should be administered itraconazole. Three hours after itraconazole administration, patients should receive PF-06747775 at the RP2D with 240 mL (8 ounces) of water and a breakfast of 200-300 calories. No food or liquids other than water are allowed for at least 2 hours post dose of PF-06747775.

The days for treatment A, B, and C may be modified based on the PK profile observed during the lead-in period in the earlier portions of the study. The dose of PF-06747775 used in the itraconazole portion of this sub-study may also be modified in order to avoid increased PF-06747775 exposure in patients at RP2D due to potent CYP3A4 inhibition by itraconazole and/or if the results of the 4-β-hydroxycholesterol and cholesterol analysis suggest significant CYP3A4 inhibition by PF-06747775. After the sub-study is complete, all patients will continue on PF-06747775 treatment at the RP2D.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

2. Evidence of histologically or cytologically confirmed diagnosis of locally advanced or metastatic EGFRm (del 19 or L858R) NSCLC:

   a. As detected by local EGFR mutation test that includes QIAGEN therascreen EGFR RGQ PCR kit, Roche cobas® EGFR Mutation Test or a sponsor-approved laboratory developed test that is validated in a CLIA laboratory (with tissue submitted for central laboratory confirmation via FDA approved QIAGEN therascreen RGQ PCR kit).

   b. T790M disease as follows:

      Phase 1

      If a repeat biopsy was performed on the tumor following prior EGFR TKI therapy, then T790M positive disease must be present. Patients of unknown T790M status following EGFR TKI progression (ie, no post-EGFR TKI progression biopsy was performed) are eligible.

      In the PK sub-studies involving food/antacid and CYP3A4 effects, patients with EGFRm (del 19 or L858R) with any T790M status are eligible to enroll.

      Studies at RP2D

      Cohort 1: Patients may have de novo T790M mutation, but it is not required.

      Cohort 2 and Cohort 3: Patients must have EGRFm (del 19 AND T790M or L858R AND T790M) NSCLC tumors as detected by local EGFR mutation test that includes QIAGEN Therascreen EGFR RGQ PCR kit, Roche cobas® EGFR Mutation Test or a sponsor-approved laboratory developed test that is validated in a CLIA laboratory, which will then be retrospectively confirmed by the central

validated Thermo Fisher Scientific Oncomine Next Generation Sequencing (NGS) cancer panel test. Patients will also be enrolled if they solely test positive for EGFR mutations (del 19 AND T790M or L858R AND T790M) in plasma alone (no tissue diagnosis of T790M is required) detected by local EGFR mutation test that includes QIAGEN Therascreen EGFR Plasma RGQ kit, Roche cobas® EGFR mutation test v2 (US-IVD) or Sysmex Inostic's OncoBEAM™ EGFR test or a sponsor-approved laboratory developed test that is validated in a CLIA laboratory, which will then be retrospectively confirmed by a validated cfDNA test as determined by the Sponsor.

c. Prior treatment for EGFRm NSCLC as follows:

Phase 1

Has progressed after at least 1 prior line of therapy including and EGFR TKI. Patients may have also received other lines of therapy before or after the EGFR TKI.

Studies at RP2D

Cohort 1: no prior treatment for locally advanced or metastatic EGFRm NSCLC.

Cohorts 2 and 3: must have had disease progression on treatment with an approved 1st or 2nd generation EGFR TKI. Patients who have been treated with a 3rd generation EGFR TKI are ineligible for this study. Patients may have had multiple lines of therapy; however, the last therapy prior to study treatment must have been an approved EGFR TKI and received within 6 weeks prior to study registration.

3. Patients must have at least one measurable lesion as defined by RECIST version 1.1 that has not been previously irradiated.

4. Tumor tissue available. Requesting formalin fixed paraffin embedded (FFPE) block or 15 unstained sections (5 micron). If a lesser amount of tissue is available, contact the sponsor. If archival tissue is not available and de novo biopsy is taken, submit the newer tissue sample.

5. Patients must be willing to participate in additional PK studies as required (cohort dependent); patient will be informed of which PK studies are required prior to consenting for study participation.

6. Age ≥18 years (or other age above 18 years of age if required by local regulation).

7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) must be 0 or 1.

8. Adequate Bone Marrow Function, including:

    - Absolute neutrophil count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
    - Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
    - Hemoglobin ≥9 g/dL.

9. Adequate Renal Function, including:

    - Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥50 mL/min as calculated using the method standard for the institution.

10. Adequate Liver Function, including:

    - Total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome;
    - Aspartate and alanine transaminase (AST & ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement secondary to tumor;
    - Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).

11. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for adverse events (AEs) not constituting a safety risk by investigator judgement.

12. Serum or urine pregnancy test (for females of childbearing potential) negative at screening and within 72 hours prior to the patient receiving the investigational product.

13. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 90 days (at least 180 days if required by local regulation) after the last dose of assigned treatment. Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or
    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

14. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

For All Phases/Cohorts

1. Previously diagnosed brain metastases, unless the patient has completed the treatment that is clinically indicated, if any, and has recovered from the acute effects of any treatment that was delivered prior to study registration, have discontinued corticosteroid treatment for these metastases prior to registration, and are neurologically stable.

2. Major surgery within 2 weeks prior to registration.

3. Radiation therapy, excluding stereotactic radiosurgery (SRS), within 1 week prior to registration.

4. Systemic anti-cancer therapy within 2 weeks or 5 half-lives (whichever is longer) of registration excluding EGFR TKIs. Patients on EGFR TKIs must discontinue the agent for a minimum of:

    - 2 days prior to registration for erlotinib or afatinib, or 3 days for gefitinib if they will be part of the lead-in single dose PF-06747775 PK study (Phase 1 Dose Escalation Single and Multiple dose PK and ECG Assessments; Phase 1 Sildenafil at MTD; and Phase 1b/2 First-Line Single Agent). Please contact the Sponsor for direction for any other EGFR TKI.

    - 5 half-lives or 5 days (whichever is longer) prior to registration if they will be starting on continuous PF-06747775 dosing directly (Phase 1 PK sub-studies at RP2D; Phase 1b/2 Combination with Palbociclib; Phase 1b Combination with Avelumab).

5. Prior irradiation to >25% of the bone marrow (Appendix 1).

6. Persisting NCI CTCAE v4.03 Grade >1 toxicity related to prior therapy; however alopecia grade 2 is acceptable.

7. QTc >480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP) (Appendix 5).

8. Uncontrolled electrolyte disorders that can confound the effects of a QTc prolonging drug (eg, hypocalcemia, hypokalemia, hypomagnesemia).

9. Prior treatment with a T790M targeted compound (3rd generation EGFR TKI).

10. Active and clinically significant bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

11. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, stroke, transient ischemic attack or symptomatic pulmonary embolism, hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy), second degree or third degree atrioventricular (AV) block (unless paced), or any AV block with PR >220 msec.

12. History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis and pulmonary fibrosis. Patients with a history of prior radiation pneumonitis are not excluded.

13. Participation in other clinical studies within 2 weeks before registration and/or during study participation.

14. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

15. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

16. Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease or previous gastric resection or lap-band.

17. Diagnosis of any other malignancy within 5 years prior to randomization, except for superficial esophageal cancer (TIS or T1a) fully resected by endoscopy, prostate cancer (Gleason score ≤6) either curatively treated or deemed to not require treatment, ductal in situ carcinoma of the breast that has completed curative treatment, adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix or bladder.

18. Patients with gastroesophageal reflux disease under treatment are allowed, but those treated with a proton pump inhibitor (PPI) will need to be switched to a H_2 receptor antagonist with staggered dosing (twice daily [BID], 2 hours after PF-06747775 and 10 hours before the following PF-06747775 dose).

19. For the PK sub-studies, patients who have had a gastrectomy or have dietary or other restrictions that preclude at least a 10 hour overnight fast (water permitted) or consumption of the high-fat, high-calorie meal, will not be eligible to participate.

20. Current use or anticipated need for food, herbal supplements or drugs that are known strong CYP3A4 inhibitors, including their administration within 10-days prior to the first PF-06747775 dose (ie, strong CYP3A4 inhibitors include but are not limited to: grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos], ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan.[20]

21. Current use or anticipated need for drugs or herbal supplements that are known strong CYP3A4 inducers, including their administration within 10-days prior to the first PF-06747775 dose (strong CYP3A4 inducers include but are not limited to: phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St. John's Wort).[20]

22. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, such as but not limited to: astemizole, terfenadine, cisapride, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, (alfentanil and fentanyl, excluding transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine)[20] is not permitted.

23. Concurrent use of drugs that are strong P-glycoprotein (P-gp) inhibitors (such as but not limited to: dronedarone, erythromycin, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lapatinib, lopinavir/ritonavir, quinidine, rifampin, ritonavir, valspodar, verapamil, vorapaxar). Patients must avoid the use of drugs that are known strong P-gp inhibitors for the duration of the study.

24. Breastfeeding female patients (including patients who intend to interrupt breastfeeding)

Additional Exclusion Criteria For Cohort 2 (PF-06747775 Plus Palbociclib)

1. Prior treatment with a CDK 4/6 inhibitor.

2. In addition to the restricted concomitant strong CYP3A4 inhibitors listed above for PF-06747775, current use (within 10 days of initial dosing of palbociclib) or anticipated need for moderate to strong CYP3A4 inhibitors (ie, atazanavir, boceprevir, delavirdine, diltiazem, erythromycin, suboxone, telaprevir, and verapamil).

3. In addition to the restricted concomitant strong CYP3A4 inducers listed above for PF-06747775, current use (within 10 days of initial dosing of palbociclib) or anticipated need for moderate to strong CYP3A4 inducers (ie, felbamate, nevirapine, and primidone).

4. Any known or suspected contraindications to or hypersensitivity to palbociclib.

Additional Exclusion Criteria For Cohort 3 (PF-06747775 Plus Avelumab)

1. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA 4) antibody (including ipilimumab, tremelimumab or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).

2. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

3. Use of immunosuppressive medication at time of randomization, except the following:

    a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);

    b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;

    c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).

4. Prior organ transplantation including allogenic stem-cell transplantation.

5. Diagnosis of prior immunodeficiency or known HIV or AIDS-related illness.

6. HBV or HCV infection at screening (positive HBV surface antigen or HCV RNA [ribonucleic acid] if anti-HCV antibody screening test positive).

7. Vaccination within 4 weeks prior to randomization except for administration of inactivated vaccines.

4.3. Lifestyle Guidelines

4.3.1. Dietary Restrictions

PF-06747775 and palbociclib are to be taken with a breakfast of 200-300 calories with 240 mL (8 ounces) of water at approximately the same time each morning. Food and liquids other than water are allowed 2 hours after dose. Patients must be instructed to avoid ingesting grapefruit, grapefruit juice, or grapefruit-containing products and grapefruit related citrus fruits (eg, Seville oranges, pomelos) while taking PF-06747775 and palbociclib. For PK sub-studies, administration instructions may vary (see Section 3.5.1, Section 3.5.2, Section 3.5.3, and Section 5.4.4.1).

There are no specific dietary restrictions for avelumab administration.

4.3.2. Contraception

In this study, patients of childbearing potential will receive PF-06747775 as single agent or in combination with either palbociclib or avelumab, compounds for which the teratogenic risks is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 90 days after the last dose. The investigator or his/her designee, in consultation with the patient, will confirm the patient has selected two appropriate methods of contraception for the individual patient and his female partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet at least 2 of the selected methods of contraception. The Investigator or his/her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the Schedule of Activities (SOA) and document such conversation in the patient's chart. In addition, the Investigator or his/her designee will instruct the patient to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

- Established use of oral, inserted, injected* or implanted* hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
- Correctly placed copper-containing intrauterine device (IUD).
- Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
- Male sterilization with absence of sperm in the post vasectomy ejaculate.
- Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

- *Not commercially available in Japan.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.

4.3.3. Sun Exposure

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions should be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity ultraviolet B light (UVB) sources such as tanning beds, tanning booths and sunlamps. Patients should be encouraged to apply liberal amounts of sunscreen/sunblock daily and avoid sunbathing/suntanning or other excessive sun exposure. Patients should also be encouraged to wear protective clothing to limit sun exposure.

4.3.4. Smoking

Patients will be reminded that smoking should cease throughout the study period.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site/study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Screen Failures

Patients who completed the informed consent process but do NOT meet all eligibility criteria and therefore are NOT randomized to either treatment arm will be considered as screen failures. Please see Section 4.1 and 4.2 for detailed inclusion and exclusion criteria.

Clinical sites must provide the following information using the appropriate CRFs for all screening failures: screening number, demographic data as well as the final patient summary including the reason for screening failure.

5.2. Allocation to Treatment

In Phase 1, dose level allocation will be performed by the Sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will fax or email a complete Registration Form to the designated Sponsor study team member. Registration will be within 2 days prior to the Day -8 single dose lead-in as appropriate. The Sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other study-related documentation or correspondence referencing that patient and fax or email to the site.

No patient shall receive investigational product until the Investigator or designee has received the following information in writing from the Sponsor:

- confirmation of the patient's enrolment;
- specification of the dose level for that patient and
- permission to proceed with dosing the patient;

The Sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

Following dose escalation, study patients for Cohorts 1, 2, and 3 will be enrolled by the Sponsor after patients have provided written informed consent and have completed the necessary baseline assessments. Starting doses for those in Cohort 2A will be assigned as well.

For Cohort 2B , patients will be enrolled in a 2:1 ratio to either PF-06747775 in combination with palbociclib or PF-06747775 single agent. Enrollment and randomization will be according to a computer generated pseudo-random code. Randomization numbers will be assigned by a central web-based randomized system operated by Pfizer, Inc.

Allocation of patients to treatment groups will proceed through the use of an Interactive Response Technology (IRT) system The site personnel (study coordinator or specified designee) will be required to enter or select information including, but not limited to, the user's identification (ID) and password, protocol number, the patient number and date of birth of the patient. The site personnel will then be provided with a randomization number and date of dispensable unit (DU) or container number when drug is being supplied via the IRT. The IRT system will provide a confirmation report containing the patient number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24 hour a day, 365 days a year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use do the IRT.

Note: the IRT is the source of the patient number. The IRT system will provide the patient number at the end of the first IRT patient transaction.

5.3. Patient Compliance

Patients will be required to return all unused study medication as well as the patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. The number of units returned by the patient at the end of the cycle will be counted, documented and recorded. A patient dosing diary will be supplied and instructions on completing it will be given to patients at the beginning of each dosing cycle.

5.4. Drug Supplies

The investigational products used in the course of this trial are PF-06747775, palbociclib, and avelumab.

5.4.1. Dosage Form(s) and Packaging

5.4.1.1. PF-06747775

PF-06747775 will be supplied by the Sponsor for oral administration in, 25 mg, 50 mg and/or 100 mg tablets. Available tablet strengths will be described in the Investigational Product (IP) manual. All tablets will be supplied in HDPE (High Density Polyethylene) bottles and labeled according to local regulatory requirements. Tablets will have different sizes and shapes according to different strengths. Tablet count will be appropriate for the dosing regimen and treatment period.

5.4.1.2. Palbociclib

Palbociclib will be supplied by the Sponsor as capsules 25 mg, 75 mg, and 100 mg equivalents of palbociclib free base. The Sponsor will supply the oral drug formulation to sites in HDPE bottles and labeled according to local regulatory requirements. The capsules can be differentiated by their size and color. Labeling will occur according to local regulatory requirements. Capsule count will be appropriate for the dosing regimen and treatment period.

5.4.1.3. Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented at a concentration of 20 mg/mL with a nominal volume of 10 mL in glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal. Each vial is intended for single-use only.

5.4.1.4. Concomitant Agents Used in Phase 1 PK Sub-Studies

Sildenafil (25 mg PO once daily), esomeprazole (40 mg PO once daily), itraconazole (200 mg PO once daily), and rifampin (600 mg PO once daily) will each be supplied to the appropriate PK cohort patients by the site personnel for oral administration. Commercial form strength and count will be appropriate for the dosing regimen and treatment period.

5.4.2. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling and safe disposal of all investigational agents and drugs used in this study, including but not limited to: PF-06747775, sildenafil, palbocicilib, and avelumab.

5.4.2.1. PF-06747775 and Palbociclib

The patient number should be recorded on the bottle label for PF-06747775 and palbociclib in the spaces provided by the site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions of self medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Returned, unused medication MUST NOT be re-dispensed to the patient.

Both PF- 06747775 and palbociclib are agents that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not to transfer it to any other containers.

For palbociclib, due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

5.4.2.2. Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20 mg/mL solution and will be supplied by the sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practices (GMP) guidelines. Avelumab will be packed in boxes each containing one vial. The information on the trial drug will be in accordance with approved submission documents.

Avelumab will be shipped in transport cool containers (2°C to 8°C) with temperature monitoring devices.

5.4.3. Administration

5.4.3.1. PF-06747775

PF-06747775 will be provided in bottles containing, 25 mg, 50 mg and/or 100 mg tablets appropriate to the dose level the patient will receive. Each bottle will contain enough medication for 21 days (Phase 1 and Cohort 2) or 28 days (Cohort 3) of dosing, plus an additional amount to cover potential delays in visiting the site. Site personnel must ensure that patients clearly understand the directions for self-medication. Site personnel should call each patient to confirm compliance within a few days of each cycle where a new dose is

given (eg, Cycle 1 and any cycle where a patient has changed doses). Site personnel should also contact each patient prior to visits in which the patient has pre-dose assessments such as PK blood samples that require the patient avoids taking PF-06747775 at home prior to the clinic visit. Patients should be given sufficient supply to last until their next study visit.

PF-06747775 will be dispensed at the beginning of each treatment cycle (or as otherwise indicated). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

Patients are to take PF-06747775 by mouth (PO). Patients will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing.

PF-06747775 is to be self-administered on an outpatient basis, except on visit days that include PK sampling (ie, pre-dose or serial PK collection) or visits in which the patient is administered avelumab on site (Cohort 3). On these visit days, study treatments should be taken in clinic after any pre-dose assessments are completed.

PF-06747775 will be administered once daily (QD) on a continuous basis at approximately the same time each day, with the exception of the single dose lead-in period for those patients participating in the Phase 1 dose escalation cohort or first line single-agent cohort (Cohort 1).

PF-06747775 is to be taken with a breakfast of 200-300 calories with 240 mL (8 ounces) of water. Food and liquids other than water are allowed 2 hours after dose. For PK sub-studies, administration instructions may vary (see Section 3.5.1, 3.5.2, 3.5.3 and Section 5.4.4.1). Following completion of PK sub-study (if applicable), patients will continue on once daily dosing of PF-06747775 as described above.

Alternate administration may be explored based upon emerging PK or AE data. For the purposes of this study and DLT assessments, a cycle is defined as 21 days for Phase 1 and Cohort 1 and Cohort 2 and as 28 days for Cohort 3, regardless of missed doses or dose delays. Once the RP2D has been determined, in the event that observed PF-06747775 plasma exposure with the new tablet formulation differs in relation to the exposure observed at RP2D with the initial tablet formulation to the extent that would cause clinical safety or efficacy concerns, the RP2D may be adjusted accordingly to account for the difference in systemic exposure for any subsequent patients or cohorts. Patients should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time.

If a patient misses a day of treatment, they must be instructed NOT to “make it up,” but to resume subsequent doses the next day as prescribed.

If a patient vomits any time after taking a dose, they must be instructed NOT to “make it up,” but to resume subsequent doses the next day as prescribed.

If a patient inadvertently takes 1 extra dose during a day, the patient should NOT take the next dose of PF-06747775.

5.4.3.2. Palbociclib

Palbociclib is to be self-administered with food on an outpatient basis, except on visit days that include PK sampling (ie, pre-dose or serial PK collection). Palbociclib will be taken concomitantly with PF-06747775 with a breakfast of 200-300 calories with 240 mL (8 ounces) of water. Food and liquids other than water are allowed 2 hours after dose.

Patients should be instructed to swallow one palbociclib capsule daily, whole, and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.

Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.

Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose of palbociclib.

Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

5.4.3.3. Avelumab

Avelumab will be administered over 1 hour by IV infusion. The IP Manual for this protocol contains specific instructions for avelumab dose calculation, reconstitution, preparation of the infusion fluid, and administration. In order to mitigate avelumab infusion related reactions, a premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (as per local practice) is mandatory approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate. On days in which patients receive avelumab, pre-dose PK should be drawn, followed by the premedication regimen described above, followed then by PF-06747775 dosing in clinic along with a breakfast of 200-300 calories, and then immediately followed by the start of avelumab infusion.

Patients will be observed in the clinic for at least 2 hours after each infusion of avelumab. If, following the 4th dose of avelumab, no infusion-related reactions are observed, no further premedication will be required for subsequent administrations and patients will require only 1 hour of observation following the infusion.

5.4.3.4. Concomitant Agents Used in Phase 1 PK Sub-Studies

Sildenafil, esomeprazole, itraconazole, and rifampin will be dispensed using commercially available strengths and commercial sources to the appropriate PK cohort patients. Site personnel must ensure that patients clearly understand the directions for self-medication for those PK cohorts that require self dosing at home. Patients should be given sufficient supply as required to complete the PK studies.

The study medication should be dispensed at each visit per the schedule of treatment. Dispensing will be performed by a qualified staff member in bottles (or blister cards, as appropriate) provided, in quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle (or blister cards, as appropriate) provided throughout the course of dosing and return the bottle (or blister cards, as appropriate) to the site at the next study visit.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of the investigational products.

- Sildenafil will be taken in the morning with water following at least a 10 hour overnight fast as indicated in Table 3.
- Esomeprazole will be taken in the morning 2 hours prior to breakfast, with water, as indicated in Table 5.
- Itraconazole will be taken with food, except on the day of serial PK assessments where it should be taken while fasting, as indicated in Table 5.
- Rifampin will be taken in the morning 2 hours prior to breakfast, with water, as indicated in Table 4.

5.4.4. Food Requirements

5.4.4.1. Food Requirements for PF-06747775 (Except for the Food Effect Cohort)

PF-06747775 will be administered every day (QD) with 240 mL (8 ounces) of water and a breakfast of 200-300 calories. No food or liquids other than water will be consumed for 2 hours following each dose. The requirement to take with a limited amount of food may be removed (via a letter to the investigators) if the data from the food effect study indicate that there is no significant food effect on the bioavailability of PF-06747775. Patients should not take PF-06747775 with grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos). For PK sub-studies, administration and food and water restrictions may vary (see Section 3.5.1, 3.5.2, 3.5.3, and Section 5.4.4.1).

5.4.4.2. Requirements for PF-06747775 for the Phase 1 Food Effect Cohort

Please refer to Section 3.5.2.

5.4.4.3. Requirements for PF-06747775 Plus Palbociclib (Cohort 2)

PF-06747775 will be administered every day just as described above with water and a small breakfast. Palbociclib will be taken at the same time as the investigational product, along with water and breakfast, as palbociclib must be taken with food. Patients should not take PF-06747775 and palbociclib with grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos).

5.4.5. Recommended Dose Modifications

5.4.5.1. PF-06747775

Every effort should be made to administer PF-06747775 on the planned dose and schedule.

In the event of significant toxicity related to PF-06747775, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

PF-06747775 dose modifications may occur in 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

5.4.5.1.1. Dosing Interruptions

Patients experiencing Grade 3 or 4 potentially PF-06747775-related toxicity or intolerable Grade 2 toxicity despite maximal supportive care should have PF-06747775 treatment interrupted. For Grade 3 toxicities (see Appendix 3 for management guidelines) that are well characterized EGFR TKI toxicities, (diarrhea, mucositis, rash) the decision to hold PF-06747775 is at the discretion of the Investigator and is not mandated. Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described Section 5.4.5.1.2.

PF-06747775 doses may be held as needed until toxicity resolution to a tolerated level (eg, baseline or a tolerable Grade 2 or 3, depending on the specific event. See Table 18 for details). Depending on when the AE resolved, a PF-06747775 interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the AE that led to the PF-06747775 treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a PF-06747775 dose reduction at the time of treatment resumption should be based on the criteria defined in Section 5.4.5.1.3, unless expressly agreed otherwise following discussion between the Investigator and the Sponsor. If a dose reduction is applied in the same cycle, the patient may need to return to the clinic to receive new drug supply.

In the event of a PF-06747775 treatment interruption lasting >2 weeks, treatment resumption will be decided in consultation with the Sponsor and prior agreement from the Sponsor must be documented.

5.4.5.1.2. Dose Delays

Re-treatment following PF-06747775 treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC ≥1,000/mm^3.
- Platelets count ≥50,000/mm^3.
- Non-hematologic toxicities have returned to baseline or Grade ≤ 2 severity, whichever is greater.

If a PF-06747775 treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 2 weeks of treatment interruption or cycle delay, PF-06747775 may be resumed. Refer to Dose Reductions Section for AEs requiring PF-06747775 dose reduction at the time of PF-06747775 treatment resumption.

If these conditions are not met, PF-06747775 treatment resumption may be delayed up to a maximum of *3* weeks. If these parameters have not been met after *3* weeks of dosing interruption, then permanent discontinuation of treatment with PF-06747775 should be considered. PF-06747775 treatment resumption for patients recovering from PF-06747775 -related toxicity after 3 weeks of treatment interruption or cycle delay may be considered only if the patient is deemed to be deriving obvious clinical benefit per the Investigator's best medical judgment and needs to be agreed between the Investigator and the Sponsor.

5.4.5.1.3. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-06747775 dose may need to be reduced when treatment is resumed.

Dose reduction of PF-06747775 by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions of PF-06747775 will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the Investigator and the Sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and CRF.

Once the PF-06747775 dose has been reduced for a given patient, the patient should remain on the new dose for at least 2 cycles before considering re-escalation. Dose re-escalation may be undertaken thereafter at the Investigator's discretion by no more than 1 dose level per 2 cycles back to the previously obtained highest dose level.

Patients experiencing a DLT during Phase 1 or Cohorts 2A or 3 may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved. No dose reductions are planned for patients experiencing toxicities other than those listed as DLTs. However, Investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances and patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower PF-06747775 or palbociclib dose level once recovery to Grade ≤1 or baseline is achieved.

Recommended PF-06747775 dose reductions are described in Table 18.

Table 18. PF-06747775 Dose Modifications for Drug-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤2 or has returned to baseline, whichever is higher, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.[a] If the event is a lab value change only, evaluation of the underlying AE and patient will guide dose modifications and DLT considerations. If the Grade 3 event is a typical EGFR TKI toxicity and tolerable (eg, rash) dosing may continue at the discretion of the investigator.[b]	Withhold dose until toxicity is grade ≤2, or has returned to baseline, whichever is higher, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.[a]
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at the same dose level.[b]	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment.[b]

a. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification.
b. Cycle will not be extended to cover for the missing doses.

5.4.5.2. Palbociclib

Recommendations for palbociclib dose modifications are listed in Table 19. Modifications from these guidelines should only occur after discussion between the Investigator and the Sponsor. Appropriate follow up assessments should be performed until the Investigator has determined the patient has adequately recovered.

Table 19. Recommended Dose Modifications for Adverse Events Associated with Palbociclib

Toxicity (NCI CTCAE version 4.03)	Proposed Action for Palbociclib
Hematologic	
Neutropenia and/or thrombocytopenia	See Table 20
Grade 3 Neutropenia + Fever ≥38.5ºC and/or infection	Withhold until fever resolves and ANC ≥1000; resume at next lower dose level
Cardiovascular	
QTc prolongation	See Table 21
Gastrointestinal	
Mucositis, Grade 3	Withhold until symptoms resolve to Grade ≤ 1; resume at the same or next lower dose level at the discretion of the investigator.
Mucositis, Grade 4	Permanently discontinue if symptoms uncontrollable by supportive care
Nausea, Vomiting, or Diarrhea Grade 3	Withhold dose until toxicity is Grade ≤2 or has returned to baseline, whichever is higher, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator. Must persist at Grade 3 despite maximal medical therapy to require dose modification
Nausea, Vomiting, or Diarrhea Grade 4	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, whichever is higher, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator. Must persist at Grade 4 despite maximal medical therapy to require dose modification
Hepatic	
AST and/or ALT >10 - ≤20 x ULN	Withhold until recovery to ≤ Grade 1or baseline, then resume at next lower dose level or discontinue
ALT, Grade 2 with bilirubin > 2x ULN	Withhold until recovery to ≤ Grade 1or baseline. Resume at next lower dose level or discontinue
Infection	
Sepsis (with or without neutropenia)	Withhold until resolution and ANC ≥1000; resume at next lower dose level
Lung	
Uncomplicated Pulmonary Embolism (Grade 3)	Withhold until recovery; then resume at same or next lower dose level or discontinue as per investigator judgment
Pulmonary Embolism(a) (Grade 4)	Withhold until recovery; then resume at same or next lower dose level or discontinue as per investigator judgment
Immune System	
Hypersensitivity reactions Grade 3 or 4(b)	Withhold until symptoms resolve, then resume at the same dose level
Other	
Any other Grade ≥3 non-hematologic toxicity	Withhold until Grade 1 or Grade 2 (if not considered a safety risk); resume at the next lower dose

Abbreviations: ANC=Absolute Neutrophil Count

a. If a patient develops pulmonary embolism, only low molecular weight heparin may be used for treatment. Oral anticoagulants and oral anti-thrombins are excluded from use.
b. Severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of investigational product administration and aggressive symptomatic therapy.

5.4.5.2.1. Dose Modifications for Hematologic Toxicities

The below table presents guidelines for palbociclib dose modifications for patients who experience hematologic toxicities.

Table 20. Recommended Dose Modifications for Neutropenia and/or Thrombocytopenia

Cycle Day	Absolute Neutrophil Count (ANC) (cells/mm^3)		Platelet count (cells/mm^3)	Proposed Action for Palbociclib
Day 1 (cycle start)	<1000	OR	<100,000	Delay dose until recovery (ANC≥1000 AND platelet count ≥100,000

5.4.5.2.2. Dose Modifications for QTc Prolongation

Patients experiencing QTc prolongation (QTc ≥501 msec on at least two separate ECGs) should have their palbociclib treatment interrupted/delayed.

In the event of QTc prolongation, possible alternative reversible causes such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval should be evaluated.

If such reversible causes are identified, then they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval).

Recommended dose modifications in the event of QTc prolongation are provided in the following table.

Table 21. Palbociclib Dose Modifications in the Event of QTc Prolongation

	Toxicity (NCI CTCAE Grade, Version 4.03)		
	Grade 2 QTc prolongation	**Grade 3 QTc prolongation**	**Grade 4 QTc prolongation**
Reversible cause identified	Treat reversible cause Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the same dose level	Treat reversible cause Withhold treatment until QTc<501 msec Resume treatment at the same dose level. Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec.	Permanently discontinue
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the same dose level	Withhold treatment until QTc<501 msec Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec. Resume treatment at the next lower dose level	Permanently discontinue

1. If the QTc remains above 480 msec more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, then dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the Sponsor, taking into account the emerging safety data from palbociclib trials and the investigator's best medical judgment.

2. If the Grade 3 QTc prolongation occurs again after one DL reduction, further dose adjustment and/or discontinuation should be discussed with the Sponsor in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.

5.4.5.3. Avelumab

5.4.5.3.1. Special Precautions for Avelumab Administration

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

In order to mitigate avelumab infusion-related reactions, a premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (as per local practice) is mandatory approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate.

Patients will be observed in the clinic for at least 2 hours after each infusion of avelumab. If, following the 4th dose of avelumab, no infusion-related reactions are observed, no further premedication will be required for subsequent administrations and patients will require only 1 hour of observation following the infusion.

Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. If an infusion/allergic reaction occurs, the patient must be treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Treatment recommendations for the management of infusion related reactions, severe hypersensitivity reactions, and tumor lysis syndrome are outlined in Section 5.4.5.3.3, Section 5.4.5.3.4, and Section 5.4.5.3.5, respectively.

Investigators should also monitor patients closely for potential irAEs, which may become manifest at the earliest weeks of treatment. Immune-related AEs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, rash, nephritis and other immune-mediated reactions including eye disorders (uveitis, iritis), myositis, and myocarditis. Treatment recommendations for the management of irAEs are outlined in Section 5.4.5.3.5.

5.4.5.3.2. Management of Avelumab Infusion Related Reactions

Since avelumab is administered IV, infusion related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion related reaction and modifications of avelumab infusion are mainly dependent upon severity, as indicated in Table 22.

Table 22. Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening. The total infusion time for avelumab should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Stop avelumab infusion. Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the avelumab infusion immediately and disconnect bag infusion tubing from the patient. Avelumab treatment must be permanently discontinued.

IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% due to an infusion related reaction, it must remain so for all subsequent infusions. The total infusion time for avelumab should not exceed 120 minutes (2 hours).

Additional Modifications for Patients with Grade 2 Infusion Related Reactions

In the event of a Grade 2 infusion related reaction that does not improve or worsens after implementation of the modifications indicated in Table 7 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the Investigator may consider the addition of H_2 blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

5.4.5.3.3. Management of Avelumab Related Severe Hypersensitivity Reactions and Flu like Symptoms

As with all monoclonal antibody therapies, avelumab can induce flu like symptoms and hypersensitivity reactions, including impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale/clammy skin, and cyanosis.

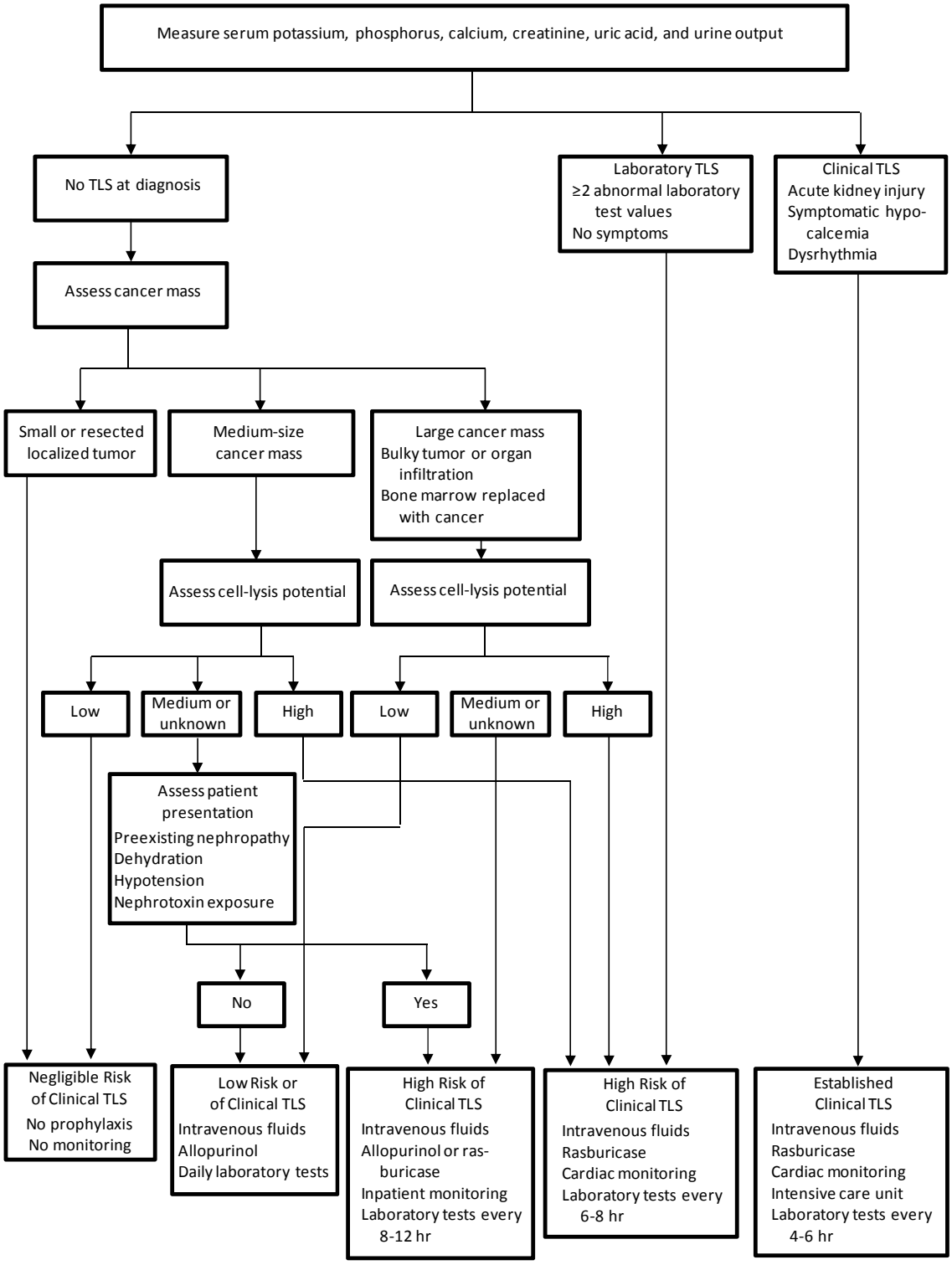
Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment, if required. Patient should be placed on monitor immediately and epinephrine injection and dexamethasone infusion should be available for immediate access.

For prophylaxis of flu like symptoms, 25 mg indomethacin or comparable non-steroidal anti-inflammatory drug (NSAID) dose (eg, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered at Investigator discretion 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (eg, paracetamol or ibuprofen) and rigors (eg, meperidine) may be given to patients at the discretion of the Investigator.

5.4.5.3.4. Management of Tumor Lysis Syndrome

Avelumab can induce antibody directed cellular cytotoxicity (ADCC) in preclinical models, so there is a potential risk of tumor lysis syndrome (TLS). Should this occur, patients should be treated as per local guidelines and the management algorithm (Figure 3) published by Howard et al.[65]

Figure 3. Assessment and Initial Management of Tumor Lysis Syndrome



5.4.5.3.5. Management of Avelumab Immune Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v4.03):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring;
- Grade 1 to 2 (persistent): manage similar to Grade 3 to 4 AE;
- Grade 3 to 4: treat with high dose corticosteroids.

Treatment of irAEs should follow guidelines set forth in the following table.

Table 23. Management of Avelumab Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	• Continue avelumab therapy • Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with activities of daily living (ADL) Colitis: abdominal pain; blood in stool	• Delay avelumab therapy • Symptomatic treatment	If improves to Grade 1: • Resume avelumab therapy If persists >5-7 days or recur: • 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol. If worsens or persists >3 to 5 days with oral steroids: • Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	• Discontinue avelumab therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until Grade 1, then taper over at least 1 month If persists >3 to 5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication); Note: infliximab should not be used in cases of perforation or sepsis

Table 23. Management of Avelumab Immune-Related Adverse Events

Dermatological irAEs		
Severity of Rash (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	• Symptomatic therapy (eg, antihistamines, topical steroids) • Continue avelumab therapy	If persists >1 to 2 weeks or recurs: • Consider skin biopsy • Delay avelumab therapy • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy If worsens: • Treat as Grade 3 to 4
Grade 3 Covering >30% body surface area	• Delay avelumab therapy • Consider skin biopsy • Dermatology consult • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume avelumab therapy If Grade ≥3 toxicity recurs: • Discontinue avelumab
Grade 4 Life-threatening consequences	• Discontinue avelumab therapy. • Consider skin biopsy, • Dermatology consult. • 1.0 to 2.0 mg/kg day methylprednisolone IV or equivalent	If improves to Grade 1: • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.
Pulmonary AEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	• Consider delay of avelumab therapy • Monitor for symptoms every 2 to 3 days • Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	• Delay avelumab therapy • Pulmonary and Infectious Disease consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3 to 4

Table 23. Management of Avelumab Immune-Related Adverse Events

Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	• Discontinue avelumab therapy • Hospitalize • Pulmonary and Infectious Disease consults • 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Liver Function Tests (LFT) Increase (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	• Continue avelumab therapy	Continue liver function monitoring If worsens: • Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	• Delay avelumab therapy • Increase frequency of monitoring to every 3 days. • Permanently discontinue investigational product therapy if AST/ALT >3X ULN with concurrent elevation if total bilirubin >2X ULN without another obvious cause.	If returns to baseline: • Resume routine monitoring, resume v therapy If elevations persist >5 to 7 days or worsen : • 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
Grade 3 to 4 AST or ALT >5 x ULN and /or total bilirubin >3 x ULN	• Discontinue avelumab therapy • Increase frequency of monitoring to every 1 to 2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist • Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: • Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily • If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

Table 23. Management of Avelumab Immune-Related Adverse Events

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic thyroid stimulating hormone (TSH) abnormality	• Continue avelumab therapy • If TSH <0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	• Evaluate endocrine function • Consider pituitary scan • Symptomatic with abnormal lab / pituitary scan: • Delay avelumab therapy ▪ 1.0 to 2.0 mg/kg/day methylprednisolone IV or by mouth equivalent • Initiate appropriate hormone therapy • No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume avelumab therapy • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay avelumab therapy • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist • If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy • Patients with adrenal insufficiency may need to continue steroids with a mineralcorticoid component. • Avelumab therapy may be discontinued based on clinical judgment.	

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, irAE=immune-related adverse event, IV=intravenous, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs, T4=thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

5.5. Investigational Drug Storage

The investigator, or an approved representative, eg, pharmacist will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product must be stored in its original container and in accordance with the drug label.

Storage conditions stated in the single reference safety document (SRSD), the investigator brochure, will be superseded by the storage conditions stated on the label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, must be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions must be reported upon discovery. The site must actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the storage requirements for take home medications.

The Investigational Product Manual must be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range and will have details for each of the investigational products.

5.6. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. The Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

5.7. Concomitant Treatment(s)

Medications or vaccinations specifically prohibited in the Exclusion Criteria are also not allowed during the active treatment period.

Concomitant treatment considered necessary for the patient's wellbeing may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as non-drug interventions (eg, paracentesis) received by patients from screening until the end of study visit will be recorded on the CRF.

5.7.1. Considerations Specific to PF-06747775

Pre-clinical data suggests that PF-06747775 could be a CYP3A4 time-dependent inhibitor, and a CYP3A4, CYP1A2 and glutathione S-transferase isoform M1 (GST-M1) substrate. All concomitant treatments must be reviewed during Cycle 1 prior to serial PK collections.

Based on the preclinical data of PF-06747775, the use of CYP3A4 substrates with Narrow Therapeutic Index (NTI) and strong CYP3A4 inducers or inhibitors are prohibited (see Section 4.2). However, the following concomitant medications should be discussed with the sponsor:

Because inhibition of CYP3A4 isoenzymes may increase PF-06747775 exposure leading to a potential increases in toxicities, caution should be warranted with co-administration of moderate CYP3A4 inhibitors (Moderate CYP3A4 inhibitors are but not limited to: erythromycin, verapamil, atazanavir, fluconazole, darunavir, diltiazem, delavirdine, aprepitant, imatinib, tofisopam, ciprofloxacin, cimetidine).[20] Concomitant use of PF-06747775 and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Therefore, caution should be warranted with co-administration of PF-06747775 with drugs that are not NTI but are mainly metabolized via CYP3A4.

Concomitant use of PF-06747775 and proton pump inhibitors (PPIs) may significantly decrease the exposure of PF-06747775. Therefore, PPIs are prohibited. Patients with gastroesophageal reflux disease under treatment are allowed, but treatment with a PPI will need to be switched to a H_2 receptor antagonist with staggered dose (BID, 2 hours after PF-06747775 and 10 hours before the following PF-06747775 dose). The restriction on PPIs may be removed (via a letter to the investigators) based on the emerging data from the Phase 1 PK sub-study with esomeprazole.

5.7.1.1. PF-06747775 in Combination with Palbociclib (Cohort 2A and 2B)

All concomitant treatment restrictions listed in the Exclusion Criteria for palbociclib (Section 4.2) also pertain to the combination with palbociclib. Clinical data suggest palbociclib is a weak time-dependent inhibitor of CYP3A4/5, and clinical exposure of palbociclib was impacted by strong CYP3A4 inhibitors and inducers. Therefore the use of CYP3A4 substrates with Narrow Therapeutic Index (NTI) and strong CYP3A4 inducers or inhibitors are still prohibited in patients receiving this combination. The solubility of palbociclib free base is pH-dependent and therefore concomitant administration of agents which increase gastric pH can alter the solubility and absorption of palbociclib free base formulations. As described above, patients on PPIs will need to be switched to a H_2 receptor antagonist with staggered dose (BID, 2 hours after PF-06747775 + palbociclib and 10 hours before the following PF-06747775 + palbociclib dose).

Dexamethasone use is not recommended with palbociclib. Alternative steroid choices are suggested. A patient requiring systemic dexamethasone treatment should be discussed with the Sponsor. Topical use of dexamethasone is permitted.

Further clinical experience with palbociclib and concomitant treatments is explained in detail in the palbociclib IB.[67]

5.7.1.2. PF-06747775 in Combination with Avelumab (Cohort 3)

All concomitant treatment restrictions listed in the Exclusion Criteria for avelumab (Section 4.2) above for single-agent PF-06747775 also pertain to the combination with avelumab. In addition, patients are prohibited from receiving the following therapies during treatment with avelumab:

- Immunotherapy, immunosuppressive drugs [unless otherwise indicated for the treatment of irAEs (Section 5.4.5.3.5)], or other experimental pharmaceutical products (ie, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs) (Section 5.7.6 contains further details regarding use of corticosteroids);

- Any vaccine therapies for the prevention of infectious disease except for inactive vaccines;

- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin);

- Acetaminophen use should be restricted to no more than 2 g/day.

Further clinical experience with avelumab and concomitant treatments is explained in detail in the avelumab IB.[67]

5.7.2. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional systemic anti-tumor treatment will be permitted while patients are receiving study therapy.

Palliative radiotherapy on study is permitted for the treatment of painful lesions providing that the lesions were known at the time of study entry, have not increased in size more than 20% and are not target lesions, and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. If a patient has progressed, and it has been documented as such for study purposes, but the patient remains on investigational product for clinical benefit, they may also receive palliative radiotherapy for a painful lesion or single site progression. In view of the current lack of data about the interaction of PF-06747775 with radiotherapy, PF-06747775 treatment should be interrupted during palliative radiotherapy, stopping 2 days before and resuming treatment after recovery to baseline.

In view of the current lack of data about the interaction of palbociclib with radiotherapy, palbociclib treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after.

5.7.3. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

Patients who are receiving bisphosphonates may continue while on therapy but initiation of bisphosphonate therapy after registration will be considered progression of disease unless otherwise agreed by the investigator in consultation with the sponsor.

For prevention of dry skin, patients should begin a regimen of moisturizers prior (ideal) or with start of dosing, and use appropriate measures to prevent excessive sun exposure.

Treatment of acneiform rash may include topical steroids, topical antibiotics, and oral antibiotics.

Mucositis can be treated with antibiotic-free oral rinse; chlorhexidine should be avoided.

Primary prophylactic use of granulocyte-colony stimulating factors (G-CSFs) is not permitted, but they may be used to treat treatment-emergent neutropenia as indicated by ASCO guidelines or local regulations. If neutropenic complications are observed in a cycle in which primary prophylaxis with colony stimulating factors (CSFs) was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose delay is not considered a reasonable alternative. For the safety evaluation cohort, G-CSFs should not be used in Cycles 1 and 2, as this may interfere with the evaluation of the cohort.

5.7.4. Anti-Diarrheal and Anti-Emetic Therapy

See Appendix 3 for AE management guidelines.

For diarrhea, patients should begin therapy with loperamide at first evidence of increased frequency of bowel movement with adjustment in dose or prescription of alternative medication when necessary. The potential need for increased oral hydration (including electrolyte-containing fluids) should also be evaluated early.

Other measures may be utilized per the investigator judgment or emerging data-driven guidelines where these are available.

5.7.5. Anti-inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not prohibited in the Concomitant Treatment(s) section.

5.7.6. Corticosteroids

Chronic, systemic corticosteroid use for palliative or supportive purpose is not permitted. Symptomatic treatment on an individual basis may be considered upon discussion and prior agreement with sponsor. Acute emergency administration, topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed.

5.7.6.1. Cohort 2A and 2B (PF-06747775 Plus Palbociclib):

In addition to recommendations in Section 5.7.6 above, use of dexamethasone is not recommended with palbociclib. Alternative steroid choices are suggested. A patient requiring systemic dexamethasone treatment should be discussed with the Sponsor. Topical use of dexamethasone is permitted.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Short course of oral steroids or inhaled/topical steroids are allowed.

5.7.6.2. Cohort 3 (PF-06747775 Plus Avelumab):

With all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit. However, studies with anti-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes. Therefore, in addition to recommendations in Section 5.7.6 above, the use of steroids in this cohort (Cohort 3) is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of irAEs is permitted according to the modalities indicated in Table 23;
- Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable;
- Prophylactic use, eg, for the prevention of acute infusion-related reactions is prohibited.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.7.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06747775 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06747775 is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate PF-06747775 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

Caution is advised on theoretical grounds for any non-cancer related surgical procedures during the study. The appropriate interval of time between surgery and administration of any of the investigational products required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping palbociclib is recommended at least 7 days prior to elective surgery. Stopping PF-06747775 is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate investigational treatment(s) should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

All patients must sign an informed consent document prior to undergoing any study-specific procedures (unless considered standard of care).

6.1. Screening

See SOA and Assessments section.

To establish eligibility patients must have the following (see SOA):

- General Medical History with focus on active and pertinent clinical history (signs and symptoms experienced within 14 days of registration). Full cardiac and respiratory history must be obtained.

- Tumor History - oncology history (including smoking status), prior systemic therapy regimen and dates of administration as well as reason for discontinuation), symptoms from prior EGFR TKI therapy if applicable, history of concomitant medications, and information on prior anticancer treatments.

- Physical Examination – at a minimum must include pulmonary, cardiac, abdominal and skin exams. A basic neurologic exam is also a minimum requirement for patients with known disease involvement of the neurologic system.

- Tumor Tissue sample – patients will provide a sample of their tumor prior to beginning any study therapy.

    - In Phase 1, the sample can be from archival sampling, but if no stored sample is available, then a new biopsy is required for enrollment. For enrollment in the Phase 1 portion, patients must have confirmed del 19 or L858R disease by a biopsy after progression of prior EGFR TKI therapy and T790M status is known, it must be T790M positive in the dose finding and MTD expansion parts of the Phase 1 study. Enrollment will be based on local EGFR mutation testing that includes QIAGEN Therascreen EGFR RGQ PCR kit, Roche cobas® EGFR Mutation Test or a Sponsor-approved laboratory developed test that is validated in a CLIA laboratory.

    - In the Phase 1b/2 portions of the study, patients enrolled in Cohort 1 must have either del 19 or L858R mutations and may have de novo T790M mutations, but T790M is not required. Patients enrolled in Cohorts 2a, 2b and 3, must be confirmed T790M+, with either del 19 or L858R (del 19 and T790M or L858R and T790M). Acceptable local testing methods include QIAGEN Therascreen EGFR RGQ PCR kit, Roche cobas® EGFR Mutation Test or a Sponsor-approved laboratory developed test that is validated in a CLIA laboratory. Patients will also be enrolled if they solely test positive for EGFR mutations (del 19 AND T790M or L858R AND T790M) in plasma alone (no tissue diagnosis of T790M is required) detected by local EGFR

mutation test that includes QIAGEN Therascreen EGFR Plasma RGQ kit, Roche cobas® EGFR mutation test v2 (US-IVD) or Sysmex Inostic's OncoBEAMTM EGFR test or a sponsor-approved laboratory developed test that is validated in a CLIA laboratory. EGFR mutation status will be confirmed by retrospective central lab testing on the submitted specimen. Central confirmation will use the FDA approved QIAGEN Therascreen EGFR RGQ PCR kit (tumor) or a validated cfDNA test as determined by the Sponsor (plasma). The tissue samples may also be tested retrospectively using Thermo Fisher Scientific Oncomine Next Generation Sequencing (NGS) cancer test panel.

- A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be provided that is of sufficient size to allow, if possible, for sectioning of fifteen (15) 5-micron tissue sections. If an FFPE tumor tissue block cannot be provided, sites should try to provide fifteen (15) unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. If archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample must be obtained in accord with local institutional practice for tumor biopsies. Archived or de novo tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Acquisition of the mandatory tumor tissue and submission to the Sponsor-designated Central Laboratory (see Study Manual) can be completed outside the 28-day screening window, but is required for enrollment.

In the case of discrepant results, the central lab test will be considered definitive and the patient, while eligible to continue on study, may need to be replaced in the statistical analyses.

6.2. Study Period

For treatment period procedures, including follow up, see SOA and Assessments section.

6.3. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site. Treatment continuation beyond objective disease progression may be considered on a case-by-case basis if the investigator deems the patient to have ongoing clinical benefit.

Reasons for withdrawal of study treatment may include:

- Disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;

- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refusal of further treatment;
- Study terminated by Sponsor;
- Death.
- Reasons for withdrawal from study follow-up may include:
- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Refusal of further follow-up for survival.

If a patient is to continue on investigational treatment despite objective progression, the following must be confirmed and documented appropriately:

- Patients must still meet initial selection criteria of ECOG performance status 0 - 1 and adequate hematologic, renal, hepatic and coagulation function.
- Patients must not show rapid tumor progression or symptomatic progression that requires urgent medical intervention (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression).

Also, at the time of disease progression, patients eligible to continue on investigational treatment must sign an additional informed consent form that clearly specifies that treatment with the investigational drug beyond initial evidence of tumor progression is not the standard of care, outline the potential risks of continuing such treatment, and list alternative treatment options, including FDA-approved or locally-approved therapy for the population.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All such efforts and outcomes should be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return for a final visit and return any unused investigational product, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival (Phase 1b/2; for 24 months following last subject first visit [LSFV]) unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator which may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

Patients participating in any of the Phase 1 PK sub-studies, including the sildenafil sub-study (MTD expansion cohort), the food effect/rifampin DDI sub-study, or the antacid effect/itraconazole DDI sub-study, will continue to complete study assessments as outlined in Table 1 (Phase 1 Schedule of Activities), upon completion of the Cycle 1 sub-study portion with the exceptions noted on the relevant SOA footnotes.

7.1. Safety Assessment

Safety assessments will include collection of adverse events (AEs), serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

A full physical examination, including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at Screening only), weight, blood pressure, and pulse rate, which may be performed by a physician, registered nurse, or other qualified health care provider, will be required at Screening. Symptom-directed physical examinations, blood pressure, and pulse rate assessments will be performed at all other timepoints.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, who do not fit the definition of “female patients who are not of childbearing potential” in inclusion criterion 13, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy-once at the start of screening and once at the baseline visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit within 5 days of the first day of the menstrual period before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during

the active treatment period, at the end of study therapy, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from the study medication and will be withdrawn from the study. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

Qualitative urine pregnancy tests must be sensitive to at least 25 mIU/mL. Qualitative urine point-of-service pregnancy tests are to be conducted with the test kit in accord with instructions provided in its package insert and will be performed on 2 occasions prior to starting study therapy-once at the start of screening and once at the baseline visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Patients who have missed a menstrual period or who show an indeterminate or positive result on the qualitative point-of-service urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory). In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication and from the study. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

7.1.2. Contraception Check

Male patients who are able to father children, and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly-effective contraception methods consistently and correctly, and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruction the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

7.1.3. Adverse Events

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

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the adverse events CRF page.

7.1.4. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories.

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test
Hemoglobin	ALT	PT or INR	Urine dipstick for urine protein: If positive and if clinically indicated collect 24-hr and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine (to be specified in the protocol)
Platelets	AST	PTT		
WBC	Alk Phos			
Absolute Neutrophils	Sodium			
Absolute Lymphocytes	Potassium			
Absolute Monocytes	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	
Absolute Eosinophils	Chloride			
Absolute Basophils	Total Calcium			
	Total Bilirubin***			
	BUN or Urea			
	Creatinine			
	Uric Acid			
	Glucose			
	Albumin			
	Phosphorous or Phosphate			

*** For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.

In addition, for patients participating in Cohort 3 of the study, thyroid function tests consisting of Free T4, thyroid stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH) will be performed at the time points outlined in the respective SOA (Table 11).

7.1.5. Vital Signs and Physical Examination

Patients will have a physical exam to include weight, vital signs, assessment of ECOG PS and height. Height will be measured at the first patient study assessment only. Vital signs will be collected as per SOA.

7.1.6. 12-Lead ECG

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. The ECG data that will be summarized in the clinical study report will be centrally read by an independent laboratory. However, for patient safety, the ECG reading at the clinical site will drive any clinically required intervention. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities and relevant PK and ECG assessment tables), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged >500 msec, ie, CTC AE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the

potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to <500 msec. Patients will then re-start the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to <500 msec after 2-weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of QTcF prolongation is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by a specialist.

If the patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

When matched with PK sampling (see Table 2, Table 10, and Table 12), the ECG must be carried out **before** each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast.

7.2. Pharmacokinetics Assessments

7.2.1. Blood for PK analysis of PF-06747775 and Sildenafil

Blood samples (4 mL whole blood in K_2EDTA tubes) will be collected for PK analysis of PF-06747775 and sildenafil as outlined in the SOA (Table 2 to Table 12). PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs and the date and time documented in the CRF.

Where noted in the SOA, blood samples for PF-06747775 concentrations will be collected at approximately the same time as other assessments such as pharmacodynamic samples, ECGs and bone marrow aspirate collections etc., wherever possible.

Blood samples for sildenafil will be collected only in the MTD expansion cohort on Day -8 of lead-in period and on Day 11 of Cycle 1 (see Table 3).

Blood samples for PK analysis of PF-06747775 will be collected in the Phase 1 (following both single and multiple doses of PF-06747775) and in Phase 1b/2 (following single and/or multiple doses of PF-06747775) portions of the study (see Table 2 to Table 12) for detailed information). PK tools will be provided to the clinical sites summarizing the different PK assessments.

Patients participating in any of the Phase 1 PK sub-studies, including the sildenafil sub-study (MTD expansion cohort), the food effect/rifampin DDI sub-study, or the antacid effect/itraconazole DDI sub-study, will complete PK assessments as outlined in the SOA (See Table 3, Table 4, or Table 5). Upon completion of the sub-study portion, no additional scheduled PK or 4-β-hydroxycholesterol/cholesterol assessments are required, and patients will continue to complete all other study assessments as outlined in Table 1 (Phase 1 Schedule of Activities) with the exceptions noted on the relevant SOA footnotes.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. The exact time of the sample collection will always be noted on the CRF, as this information will be used in the pharmacokinetic analysis. However, samples obtained within 30% of the nominal time (eg within 18 minutes of a 60 minute sample) will be considered protocol compliant, with the actual time of the sample collection noted on the CRF. Pre-dose PK samples should be collected within 1 hour of dosing. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and sponsor. All samples, regardless of protocol compliance, which contain actual time of collection will be used by the sponsor in pharmacokinetic analyses.

PK samples will be assayed for all the analytes using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

As part of the understanding of the pharmacokinetics of the investigational product, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for PF-06747775 and their metabolites. The results of such analyses may be included in the clinical report.

7.2.2. Blood for 4-β-Hydroxycholesterol and Cholesterol Analysis

Three (3) mL of blood will be collected in lithium heparin tubes for the analysis of 4-β-hydroxycholesterol and cholesterol as outlined in the SOA for Phase 1 (Table 2, Table 3, Table 4, or Table 5).

Patients participating in any of the Phase 1 PK sub-studies, will complete 4-β-hydroxycholesterol/ cholesterol assessments as outlined in the SOA (See Table 3, Table 4, or Table 5). Upon completion of the sub-study portion, no additional scheduled PK or 4-β-hydroxycholesterol/cholesterol assessments are required, and patients will continue to complete all other study assessments as outlined in the SOA (Table 1).

Samples will be assayed for all the analytes using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

As part of the understanding of the pharmacokinetics of the investigational product, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for 4-β-hydroxycholesterol and cholesterol and their metabolites. The results of such analyses may be included in the clinical report.

7.2.3. Blood for Metabolite Profiling of PF-06747775

Metabolite profiling will be conducted in the RP2D expansion cohort for all patients. The remaining plasma collected for PF-06747775 PK analysis will be used for metabolite profiling.

Once the metabolite profiling samples have been analyzed and the report completed, the samples will be disposed.

7.2.4. Blood for PK Analysis of Palbociclib

Blood samples (4 mL in K_2EDTA tubes) will be collected following multiple doses for PK analysis of palbociclib along with PF-06747775 as outlined in the SOAs (Table 9 and Table 10). PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs and the date and time documented in the CRF.

Where noted in the SOA, blood samples for palbociclib concentrations will be collected at approximately the same time as other assessments such as pharmacodynamic samples, ECGs and bone marrow aspirate collections etc., wherever possible. PK tools will be provided to the clinical sites summarizing the different PK assessments.

PK samples will be assayed for all the analytes using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

7.2.5. Blood for PK Analysis of Avelumab

Blood samples (3.5 mL in Serum Separator Tubes [SST]) will be collected following single and multiple doses for PK analysis of avelumab as outlined in the SOA (Table 12). PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs and the date and time documented in the CRF.

Where noted in the SOA, blood samples for avelumab concentrations will be collected at approximately the same time as other assessments such as pharmacodynamic samples, ECGs and bone marrow aspirate collections etc., wherever possible. PK tools will be provided to the clinical sites summarizing the different PK assessments. On days when both a PK sample and avelumab infusion are performed, the PK sample is to be drawn from the arm opposite (contralateral) from that arm which is receiving the avelumab infusion.

PK samples will be assayed for all the analytes using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

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7.2.6.1. Shipment of Genotyping Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

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7.5. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule of Activities, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 6 weeks).

Measurable Disease per RECIST v1.1 is required for patients in both the Phase 1 and Phase 1b/2 portions of the study. Assessment of response will be made using RECIST version 1.1. (Appendix 4). Responses must be confirmed per RECIST v1.1 guidelines. Patients in Cohort 3 will also have their responses assessed by irRECIST (Appendix 6).

All patients' files and radiologic images must be available for source verification and for potential peer review. In addition, radiologic images will be collected at the time of acquiring the images for potential central review at a later date.

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7.6.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions;

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Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Markers of Drug Response section will be used. Patients may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;

- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of the protocol stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE grade 5 (see section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT OR AST OR total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller);

Concurrent with:

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN or if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

3. A male patient has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE Report Form and a EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE Report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See also the Section Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of a SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis Sets

9.1.1. 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. The safety analysis set will be the primary population for evaluating treatment administration/compliance and safety.

9.1.2. 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. The full analysis set will be the primary population for evaluating all efficacy endpoints and patient characteristics.

9.1.3. 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. 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.

9.1.4. Pharmacokinetic Analysis Sets

The PK concentration population is defined as all treated patients who have at least one concentration in at least 1 treatment period.

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.

9.1.5. 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 enrolled in Cohort 1 must have either del 19 or L858R mutations and may have de novo T790M mutations, but T790M is not required. Patients enrolled in Cohorts 2a, 2b and 3, 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.

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9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose Escalation/De-Escalation

9.2.1.1. Continual Reassessment Method (Phase 1)

Many alternative designs have been proposed to the standard 3+3 design for Phase I dose escalation studies that improve its accuracy, efficiency and statistical validity.

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 $Pr(DLT|dose\ x) = f(x, \beta)$, 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).[19]

9.2.1.2. Modified Toxicity Probability Interval (mTPI) (Phase 1b)

The mTPI design[62] 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 (Appendix 7). 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.[62] 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.

9.3. Sample Size Determination

9.3.1. 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.

9.3.2. 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, PD, and antitumor activity 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.

9.4. Efficacy Analysis

9.4.1. 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.

9.4.2. Phase 1b/2

In the Phase 1b/2 portion of the study efficacy is the primary objective. Objective Response Rate (ORR) 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 or for Cohort relative to all randomized patients. Patients who die, progress, or drop out for any reason after enrollment/randomization prior to responding will be included in the analysis as nonresponders. An exact 2-sided 90% CI for objective response rate will be presented for each group and treatment arm. In addition for Cohort 2B, the 2-sided 90% confidence interval for the difference in objective response rates will be provided.

Duration of response will be calculated for patients with an objective response. Duration of PR or CR is the time from start date (date of first documentation of PR or CR) to date of first documentation of objective progression or death. The median duration of response from the Kaplan-Meier curve and corresponding 2-sided 90% confidence interval will be computed.

Progression Free Survival (PFS) is defined as the time from the date of cycle 1 day 1 (first dose) to the date that objective progressive disease is documented or death due to any cause, whichever occurs first. PFS will be characterized in terms of the median, and the probability of remaining progression-free at 6 months (based on Kaplan-Meier estimates). Approximate 90% confidence intervals corresponding to these estimates will also be computed.

Patients last known 1) to be alive 2) not to have started new (non-protocol) anti-cancer treatment and 3) to be progression-free, and who have a baseline and at least one on-study disease assessment, are censored at the date of the last objective disease assessment that verified lack of disease progression.

Patients with inadequate baseline disease assessment are censored at the date of first dose. Patients with no on-study disease assessments are censored at the date of first dose unless death occurred prior to the second planned assessment (in which case the death is an event).

Patients starting new anti-cancer treatment prior to progression are censored at the date of last objective disease assessment documenting no progression prior to the new treatment.

Patients who had an unacceptably long interval between tumor assessments (2 or more missed assessments) will be censored at the date of last objective disease assessment documenting no progression prior to the long interval, regardless of the objective response status at the tumor assessment following the long interval.

Survival is defined as the time from the date of first dose to the date of death. The probability of being alive at 24 months (based on Kaplan-Meier estimates) will be estimated. To calculate the confidence interval for 24 months survival probability, 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.

In Cohort 2B randomized part, PFS, duration of response, and OS at 24 months will be presented by using the Kaplan-Meier method and the start date will be the date of randomization for PFS and OS. For these endpoints, median event time and a 2-sided 90% confidence interval for the median for each treatment arm will be provided using the Brookmeyer-Crowley method. An exact 2-sided 90% CI for objective response rate will be presented for each group and treatment arm as well as the 2-sided 90% confidence interval for the difference in ORR.

Additional details will be provided in the Statistical Analysis Plan.

9.5. Analysis of Other Endpoints

9.5.1. Analysis of Pharmacokinetics

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

For Phase 1 and all groups in Phase 1b/2, plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC_{inf}, AUC_{tau}) for PF-06747775 will be estimated using non-compartmental analysis. Area under the plasma concentration versus time curve to the last quantifiable concentration (AUC_{last}), terminal elimination half-life ($t_{1/2}$), oral plasma clearance (CL/F), apparent volume of distribution (V_z/F), observed accumulation ratio (R_{ac}) and steady state accumulation ratio (R_{ss}) will be also estimated. The single dose and steady state PK parameters will be summarized descriptively by dose, cycle and day. The PK parameters for the food-drug and drug-drug interaction studies will be summarized descriptively by sub-study and treatment.

The single dose and steady state PF-06747775 concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day, and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle, and day (single dose and steady state) using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

For the food-drug and drug-drug interaction studies, PF-06747775 and sildenafil (when appropriate) 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. Individual patient and median profiles of the concentration-time data will be plotted by treatment using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

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

Trough concentrations from steady state assessments in Phase 1 and 1b/2 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.

9.5.1.2. Effect of Food on PF-06747775 Pharmacokinetics

PF-06747775 at the RP2D will be evaluated for the effect that a high-fat, high-calorie meal may have on PF-06747775 exposure.

Natural log transformed area under the curve (AUC_{tau}) and C_{max} values will be analyzed using a mixed effects model with sequence, period/visit and treatment (fed, fasted) as fixed effects and patient within sequence as a random effect to estimate the effect of food on PF-06747775 PK. Estimates of the adjusted mean differences (fed-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 (fed/fasted) and 90% confidence intervals for the ratios.

9.5.1.3. Sildenafil Sub-Study: MTD Expansion Cohort

The main purpose of this sub-study is to appropriately estimate the potential CYP3A4 inhibitory ability of PF-06747775.

Natural log transformed area under the curve (AUC_{inf}) and C_{max} values will be analyzed using a mixed effects model with treatment as fixed effects and patient as random effect to estimate the effect 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.

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9.5.1.5. PF-06747775-Esomeprazole Drug-Drug Interaction Study

PF-06747775 at the RP2D will be evaluated for the effect that an acid reducing agent, esomeprazole, a proton pump inhibitor, may have on PF-06747775 exposure.

Natural log transformed area under the curve (AUC_{tau}) and C_{max} values will be analyzed using a mixed effects model with treatment as a fixed effects and patient as a random effect to estimate the effect of esomeprazole on PF-06747775 PK. Estimates of the adjusted mean differences (with and without esomeprazole [PF-06747775 alone]) 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 esomeprazole) and 90% confidence intervals for the ratios.

9.5.1.6. PF-06747775-Itraconazole Drug-Drug Interaction Study

PF-06747775 at the RP2D will be evaluated for the effect that a strong CYP3A4 inhibitor, itraconazole, may have on PF-06747775 exposure.

Natural log transformed area under the curve (AUC_{tau}) and C_{max} values will be analyzed using a mixed effects model with treatment as fixed effects and patient as a random effect to estimate the effect itraconazole on PF-06747775 PK. Estimates of the adjusted mean differences (with and without itraconazole [PF-06747775 alone]) 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 itraconazole) and 90% confidence intervals for the ratios.

9.5.1.7. Palbociclib PK Analysis

Cohort 2A and 2B: For palbociclib, plasma pharmacokinetic parameters including the minimum plasma concentration (C_{trough}), maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC_{last}, AUC_{tau}) will be estimated as data permit using non-compartmental analysis. The steady state PK parameters will be summarized descriptively by dose, cycle, and day.

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, cycle, day, and nominal time.

The trough concentrations for palbociclib 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.

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9.6. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set.

All patients who receive any study treatment will be included in the final summaries and listings of safety data. Summaries of AEs and other safety parameters will be provided as appropriate.

Frequencies of patients experiencing at least 1 AE will be displayed by system organ class (SOC) and preferred term according to MedDRA terminology. Detailed information collected for each AE will include: a description of the event; duration; whether the AE was serious; intensity (severity) of event; relationship to investigational product; action taken; and clinical outcome. Intensity (severity) of the AEs will be graded according to the NCI CTCAE version 4.0. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Summary tables will present the number of patients observed with AEs and corresponding percentages. The denominator used to calculate incidence percentages consists of patients receiving at least 1 dose of study medication. Within each table, the AEs will be categorized by MedDRA SOC and preferred term. Additional subcategories will be based on event intensity and relationship to investigational product.

Individual patient listings will be prepared for all AE data. Summary tables for extent of exposure to study medication will also be provided.

9.6.1. Analysis of Phase 1 and Phase 1b Primary Endpoint

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation/ dose finding component of the following groups: Phase 1, Phase 1b Cohort 2A, and Phase 1b Cohort 3. The occurrence of DLTs observed in these dosing cohorts will be used to estimate the MTD and select the RP2D as described in the Study Design Section. Adverse Events constituting DLTs will be listed by dose level.

9.6.2. Analysis of Secondary Safety Endpoints

The Safety Analysis Set will be used for all secondary safety evaluations. Summaries of AEs and other safety parameters will be presented separately for each group. For Cohort 2B randomized part, summary will be presented by treatment arm.

9.6.2.1. Adverse Events

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).

9.6.2.2. Laboratory Test Abnormalities

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 study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal or not done.

9.6.2.3. ECG

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. Baseline will be defined as the ECG measurement performed prior to dosing (Cycle 1 Day 1).

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

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate), by dose. Individual QT` (all evaluated corrections) intervals will be listed by treatment, 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 treatment, dose 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 will be provided for baseline vs worst on treatment corrected QT (one or more correction method will be used) using Maximum CTCAE 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).

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.

9.7. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review committee with medical and statistical expertise to review individual and summary data collected in the safety and clinical databases. Procedures include:

- Surveillance for serious adverse events (SAEs) according to regulatory guidelines;
- Surveillance for nonserious AEs and lab abnormalities in an ongoing manner, and DLT evaluations at the end of Cycle 1;
- Discussions between the investigators and the sponsor of AEs and laboratory tests abnormalities observed at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and decide if further patient enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study linking their numerical code to the patient's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study specific activity, excluding standard of care, is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06747775 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 4 weeks. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

If the study is part of a multicentre study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

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17. APPENDICES

Appendix 1. Bone Marrow Reserve in Adults (to be Used in Support of Exclusion of >25% Prior Irradiation of the Bone Marrow)

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head :			136.6		
	Cranium	165.8	0.75	124.3	13.1	13.1
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle :			86.7		
	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs :			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	10.2
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	36.2
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		3.8

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
VERTEBRAE	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
	5	13.4		10.1	14.1	28.4
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar) :			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		1497.7		1045.7	100.0	100.0

Appendix 2. ECOG PS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 3. AE Management Guidelines

In all instances, it is recommended that patients be instructed at time of starting drug therapy to call the Investigator/Site if no improvement in symptoms has been observed after 24 hours of patient taking the recommended/optimal pharmacologic treatment.

Abbreviations:

BSA: Body Surface Area.

ADL: Activities of Daily Living.

Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden. (definitions per CTCAEv4).

GABA: gamma-Aminobutyric Acid.

DIARRHEA

- Patients should be encouraged to drink 8 to 10 large glasses of clear liquids per day while on study in order to maintain adequate hydration.
- General dietary measures to limit impact of diarrhea could include:
    - Stop all lactose-containing products in patients with evidence of lactose intolerance;
    - Eat frequent small meals if experiencing increased frequency of stools;
    - Consider low fat regimen enriched with bananas, rice, applesauce, and toast.

	Diarrhea Management Guideline
Grade of Event	
Grade 1: increase of <4 stools per day over baseline;	Loperamide 4 mg at the first onset of diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. (During the night the patient may take 4mg of loperamide every 4 hours). Fluid intake of at least 2 liter (L) should be maintained to avoid dehydration: patients are to drink 8-10 large glasses of clear liquids. Consideration for maintenance of electrolyte balance would include electrolyte-containing drinks, broth, clear juices.
Grade 2: increase of 4-6 stools per day over baseline;	Loperamide as above, or consider use of diphenoxylate hydrochloride and atropine sulfate formula (eg Lomotil®, Diarced®, Co-Phenotroope®) at standard doses. Fluid intake of at least 2 L should be maintained to avoid dehydration. Monitor patient closely and consider intravenous hydration.
Grade 3: increase of ≥7 stools per day over baseline; or incontinence; or limiting self care ADL: or hospitalization indicated	Oral therapy with diphenoxylate hydrochloride and atropine sulfate formula, or tincture of opium. Fluid intake of at least 2 L should be maintained, intravenously if necessary. Consider use of octreotide (Sandostatin®) 100-150 microgram (μg) subcutaneously twice daily with escalation to 500 μg three times daily.
Grade 4: life-threatening	Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of investigator for fever, leucocytosis, marked dehydration, etc.

DERMATOLOGIC TOXICITY

Acneiform/Papulopustular Rash:

	Acneiform/ Papulopustular Rash Management Guideline
Grade 1: <10% body surface area (BSA) papules and / or pustules (with or without symptoms of pruritis or tenderness)	**Topical steroids *** **And** **Topical antibiotic bid** (clindamycin 1 - 2%, erythromycin 1% - 2%, metronidazole 1%)
Grade 2: 10 to 30% BSA papules and / or pustules (with or without symptoms of pruritis or tenderness), or psychosocial impact, or limited instrumental ADL	**Oral antibiotic for at least 4 weeks** (doxycycline 100mg bd, minocycline 100mg bd or oxytetracycline 500mg bd); Stop topical antibiotic if being used **And** **Topical steroids ***
Grade 3: >30% BSA papules and / or pustules (with or without symptoms of pruritis or tenderness); *or* • limiting self-care ADL: or • associated with local superinfection with oral antibiotics indicated	**Oral antibiotic for 4 weeks** (doxycycline 100 mg bd, minocycline 100mg bd or oxytetracycline 500 mg bd) **If infection suspected** (yellow crusts, purulent discharge, painful skin / nares): switch oral antibiotic to broad spectrum/gram negative cover for at least 10 days consider skin swab for bacterial culture, **And** **Topical steroids (continue)*** Consider dermatology consultation
*** Moderate/Low strength steroids include:**	*Triamcinolone acetonide 0.025%* Desonide 0.05% Alclometasone 0.05% cream Fluticasone propionate 0.05% For patients intolerant or allergic to tetracycline antibiotics, use an antibiotic with Staphloccoccus coverage (eg, cephalexin, sulfamethoxazole/ trimethoprim)

Dry Skin/ Xerosis:

Prophylaxis against dry skin would include:

- Initiation of skin moisturizing cream or ointment regimen upon establishment of eligibility (ie prior to first dose). (avoid skin lotions, as they may contain alcohol);
- Avoidance of excessive exposure to hot water during showering/ bathing;

- Avoidance of household tasks involving immersion in hot water/ detergent/ solvents;
- Avoidance of excessive sun exposure/ tanning. Use sunscreen containing zinc oxide or titanium dioxide with SPF at least 30: apply every two hours when exposed to sun.

	Xerosis/ Dry Skin Management Guideline
Grade 1: <10% BSA and no associated erythema or pruritis	Over-the-counter Moisturizing cream or ointment to face bid **AND** Ammonium lactate 12% (or equivalent) cream to body bid
Grade 2: 10 to 30% BSA and associated with erythema or pruritis; or limited instrumental ADL	OTC Moisturizing cream or ointment to face bid; **AND** Ammonium lactate 12% cream OR salicylic acid 6% cream to body bid
Grade 3 >30% BSA and associated with pruritis; or limiting self care ADL	OTC Moisturizing cream or ointment to face bid; **AND** Ammonium lactate 12% cream OR salicylic acid 6% cream to body bid **AND** Topical steroid* to eczematous areas bid
*Moderate/Low strength steroid include:	*Triamcinolone acetonide 0.025% (Aristocort A cream)* Desonide 0.05% (DesOwen cream, lotion) Alclometasone 0.05% cream (Allocate cream) Fluticasone propionate 0.05%

Paronychia:

Minimization of periungual trauma and superinfection is advised:

- Wearing comfortable shoes,
- trimming nails but avoiding aggressive manicuring,
- wearing gloves while cleaning (eg, household, dishes).

	Paronychia Management Guideline
Grade 1 Nail fold edema or erythema; or disruption of the cuticle	Topical Antibiotics and vinegar soaks *
Grade 2 Localized intervention indicated; or oral intervention indicated (eg, antibiotic, antifungal, antiviral); or nail fold edema or erythema with pain; or associated with discharge or nail plate separation; or limiting instrumental ADL	Topical antibiotics and vinegar soaks* Apply silver nitrate weekly
Grade 3 Surgical intervention, or IV antibiotics indicated; or limiting self-care ADL	Topical antibiotics and vinegar soaks* Apply silver nitrate weekly Surgical consultation as needed
*Topical antibiotics/ vinegar soaks	*Topical antibiotics: Clindamycin 1%, erythromycin 1%* *Vinegar soaks consist of soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day* ± For a video on how to apply silver nitrate, visit: http://www.youtube.com/watch?v=HF5oopqheJY

Pruritus/ Itching guidelines:

Prophylaxis against dry skin would include:

- Initiation of skin moisturizing regimen prior to first dose. Non-scented emollient skin cream should be used;
- Avoidance of excessive exposure to hot water during showering/ bathing;
- Avoidance of household tasks involving immersion in hot water/ detergent/ solvents;
- Avoidance of excessive sun exposure/ tanning. Use sunscreen containing zinc oxide or titatinium dioxide with SPF at least 30: apply every two hours when sun exposure is anticipated.

	Pruritus Management Guideline
Grade 1: Mild or localized; or topical intervention indicated	Topical steroid moderate/ low strength (as listed above for acneiform rash) or Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily

Grade 2 Intense or widespread, intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); or oral intervention indicated; or limiting instrumental ADL	Topical steroid moderate strength or Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily **AND** Oral antihistamines
Grade 3: Intense or widespread, constant; or limiting self-care ADL or sleep; or oral corticosteroid or immunosuppressive therapy indicated	Oral antihistamines **AND** GABA agonists (gabapentin or pregabalin) or Doxepin
	Antihistamines: diphenhydramine 25-50 mg tid; hydroxizine 25 mg tid; fexofenadine 60 mg tid GABA agonists (adjust if renal impairment) : Gabapentin 300 mg every 8 hours or Pregabalin 50-75 mg every 8 hours Tricyclics: Doxepin 25-50 mg every 8 hours

MUCOSITIS

Patients who have not had dental checkup within 6 months prior to start of dosing are encouraged to do so, especially to identify any persistent issue related to recent chemotherapy. Once on treatment, patients are to consult the site health care team prior to undertaking any dental or oral surgery procedure to determine if it would be appropriate to proceed depending on presence of any ongoing mucosal inflammation/ stomatitis.

Between scheduled visits, patient self-report of oral mucosal discomfort or of visible changes in appearance to oral mucosa is encouraged. Periodic systemic examination of the oral cavity is required at scheduled visits and as otherwise indicated by patient self-report between visits.

Patients should practice good oral care including a soft-bristle toothbrush replaced frequently and use of bland rinses or moisturizers.

Regular use of warm water non-medicated saline rinse is recommended if stomatitis develops. Frequent sips of water during meals may assist swallowing and therefore maintain caloric intake and hydration in patients experiencing oral pain

Use of chlorhexidine is to be avoided.

Topical anesthetics or systemic analgesics may be used as indicated in judgment of the investigator and according to local clinical practices. Topical steroid rinses have been reported to be helpful in severe cases (eg, dexamethasone 0.5 mg/ 5 mL swish and expectorate four times daily).

Consultation with nutritionist is to be considered if toxicity may compromise maintenance of adequate caloric intake.

Keratoconjunctivitis

	Keratoconjunctivtis Guideline
Grade 1 Asymptomatic or mild symptoms; intervention not indicated	No intervention or dose modification is mandated
Grade 2 Symptomatic; topical intervention indicated; or limiting instrumental ADL	Patients should be examined within 72 hours. Exam should include slit-lamp, fundoscopic exam and visual acuity and other investigation required per investigator judgement.Preservative free artificial tears, ointments, and /or other therapies as clinically indicated. ***Study Treatment***: If symptom lasts ≥2 weeks, withhold treatment until≤ Grade 1 and then reduce one dose level.
Grade 3 Limiting self-care ADL	Patients should be examined within 72 hours. Exam should include slit-lamp, fundoscopic exam and visual acuity and other investigation required per investigator judgement. Preservative free artificial tears, ointments, and/or other therapies as clinically indicated. ***Study Treatment:*** Drug should be withheld until recovers to≤ Grade 1 and then reduce one dose level.

Appendix 4. RECIST Version 1.1

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

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 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

Subjects 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 discontinuation 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

Best Overall Response

The best overall response (BOR) is the best response recorded from the start of treatment until disease progression. This is derived from the sequence of objective statuses. Objective statuses are not considered after objective progression is documented or after start of the first anticancer treatment post discontinuation of protocol treatment. BOR for each patient will be derived as one of the following categories.

- **Complete response (CR)**: At least one objective status of CR documented before progression.
- **Partial response (PR)**: At least one objective status of PR documented before progression.
- **Stable disease (SD)**: At least one objective status of stable documented at least 6 weeks after start of treatment date and before progression but not qualifying as CR, PR.
- **Progressive Disease (PD):** Objective status of progression within 12 weeks of start of treatment date, not qualifying as CR, PR or SD.
- **Indeterminate (IND):** Progression not documented within 12 weeks after start of treatment date and no other response category applies.

Appendix 5. List of Drugs Known to Predispose to Torsade de Pointes

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S. ®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

*when administered intravenously at high dose (32 mg).

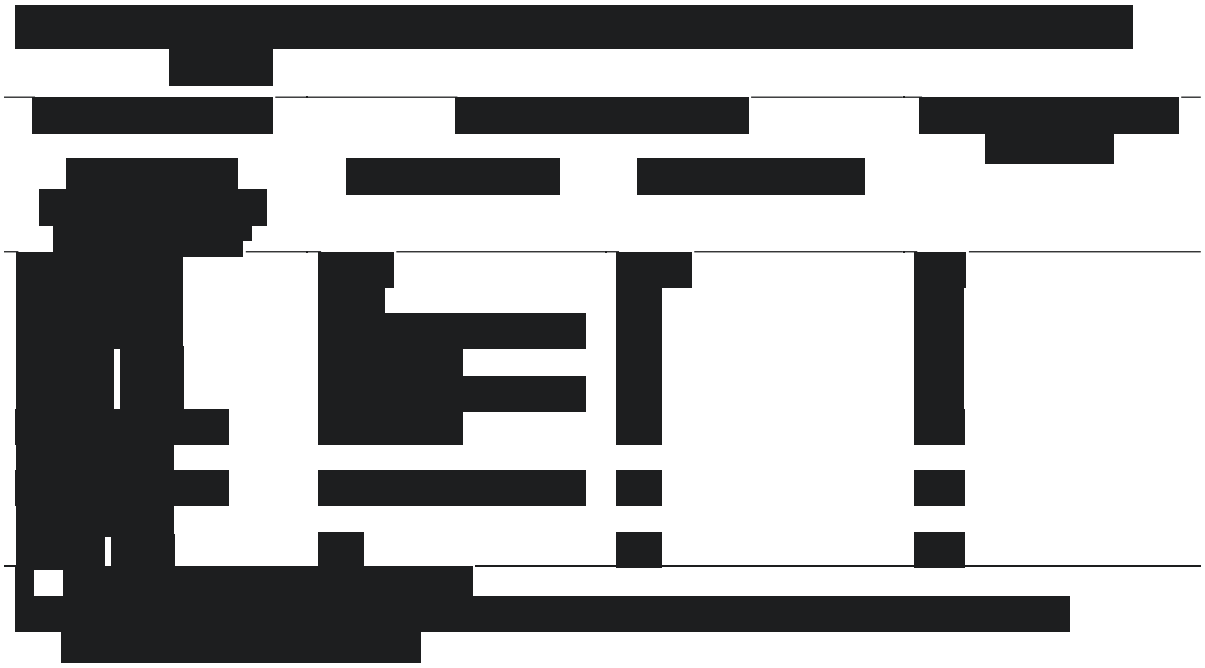
Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://www.crediblemeds.org/. This list is not meant to be considered all inclusive. See website for current list

CCI

[redacted]

CCI

[redacted]



Appendix 7. 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	E	E	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 8. Japanese Patient-Only Lead In Cohort

To date, there is no documented experience with PF-06747775 in Japanese patients. Therefore, this study will include a Japanese patient lead in cohort (LIC) to evaluate the safety, tolerability and PK of PF-06747775 in Japanese patients with advanced EGFRm NSCLC. This Japanese LIC will include 2 cohorts; RP2D tolerability cohort and PK cohort.

The PK cohort will not form part of the RP2D tolerability cohort and therefore does not need to have completed enrollment prior to Japanese enrollment in the other study cohorts (cohorts 1, 2A/2B, 3).

- **Objective**

RP2D tolerability cohort

To evaluate the safety and tolerability of PF 06747775 in Japanese patients.

PK cohort

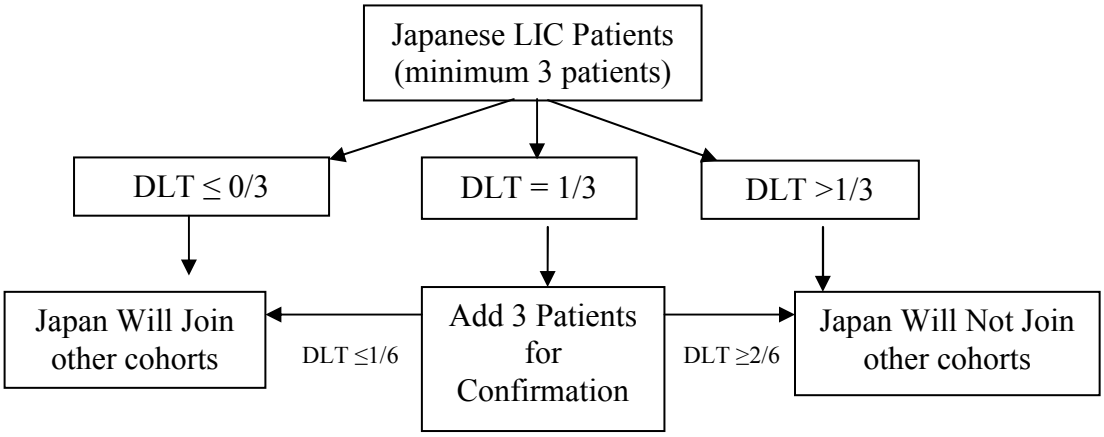
To characterize single dose and steady state PK profiles of single agent PF-06747775 in Japanese patients

- **Study design**

RP2D tolerability cohort

Initially up to 3 patients will be enrolled and treated. If a DLT [DLT definitions are same as Phase 1 PF-06747775 Single Agent (See Section 3.2)] is observed in 1 of the initial 3 treated patients, then 3 additional patients will be enrolled and treated. Patients who discontinue treatment before completing Cycle 1 (ie, the DLT observation period) or receive less than 15 of the planned 21 PF-06747775 doses for reasons other than treatment related toxicity (eg, missed appointments, misplaced study drug supplies, development of coexisting medical condition rendering the patient unable to swallow medication, development of rapidly progressing disease) will be replaced for DLT evaluation but will remain in the overall safety and efficacy analyses. If ≤33% patients experience DLT (0/3 or 1/6), then the tested dose would be considered tolerable in Japanese patients. If >33% patients experience DLT, then Japan sites will not join the other cohorts and a lower dose cohort may be explored if deemed necessary. Additional patients may be included for further safety and tolerability assessments in the LIC as appropriate.

RP2D tolerability cohort Schema



PK cohort

After tolerability has been confirmed in RP2D tolerability cohort, PK cohort will be initiated. In PK cohort, 3 patients will be enrolled and they will have 100 mg single dose followed by once daily multiple dose at RP2D. Both in RP2D tolerability cohort and PK cohort, blood samples will be collected for PK assessment. Single dose PK in 100 mg and RP2D and multiple dose PK at RP2D in Japanese patients will be assessed in this Japanese LIC.

Table A8-1. Japanese patient-Only LIC RP2D Tolerability Cohort Schedule of Assessments

		LEAD-IN PK	CYCLE 1[30] (21 days)			CYCLE 2 (21 days)	CYCLES ≥3 (21 days)	End of Treatment[28]	Follow- up[29]
Visit Identifier	**Screening[2]**	**Day -4**	**Day 1[1]**	**Day 8**	**Day 15**	**Day 1**	**Day 1**		
Visit Window	**≤28 days from registration**		**±1**	**±1**	**±1**	**±2**	**±2**	**±3**	+7
Informed consent[3]	X								
Tumor history	X								
Medical history	X								
Physical examination	X		(X)			X	X		
Baseline signs and symptoms[4]			X						
Height	X								
Weight	X		X			X	X		
Vital signs[5]	X		X	X	X	X	X	X	X
Performance status (ECOG)[6]	X		X	X	X	X	X	X	X
Contraception check[7]	X		(X)			X	X	X	
Laboratory									
Hematology[8]	X		(X)	X	X	X	X	X	
Blood Chemistry[9]	X		(X)	X	X	X	X	X	
Coagulation[10]	X		(X)	X	X			X	
Urinalysis[11]	X		(X)					X	
Pregnancy test[12]	X		X			X	X	X	
(12-lead) ECG[13]	X	See TableA8-2						X	
Pulse Oximetry[14]	X		X	X	X	X	X (up to Cycle 5)	X	
Chest X ray or Chest CT[15]	X								
Registration and Treatment									
Registration[16]		X							
PF-06747775[17]		X	Once daily PO continuous						
Tumor assessments									
CT or MRI imaging[18]	X						X and every other cycle (every 6 weeks) +/- 7 days	X	
Other clinical assessments									

		LEAD-IN PK	CYCLE 1[30] (21 days)			CYCLE 2 (21 days)	CYCLES ≥3 (21 days)	End of Treatment[28]	Follow- up[29]
Visit Identifier	**Screening[2]**	**Day -4**	**Day 1[1]**	**Day 8**	**Day 15**	**Day 1**	**Day 1**		
Visit Window	**≤28 days from registration**		**±1**	**±1**	**±1**	**±2**	**±2**	**±3**	+7
Adverse Events[19]			X	X	X	X	X	X	X
Concomitant treatments and non-drug supportive interventions[20]	X		X			X	X	X	X
Other samplings									
[redacted] CCI	[redacted]							[redacted]	
Pharmacokinetics[22]		See TableA8-2							
[redacted] CCI	[redacted]								
[redacted]	[redacted]						[redacted]	[redacted]	
[redacted]	[redacted]						[redacted]	[redacted]	
Survival[27]									X

CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

Footnotes:

1. Day relative to start of study treatment (Day 1).
2. **Screening:** to be obtained within 28 days prior to registration.
3. **Informed Consent:** must be obtained prior to undergoing any study specific procedures unless considered standard of care. After completion of Cycle 1, patients will be asked to sign an additional consent document for confirmation of the patient's willingness to continue participation in this study before starting Cycle 2.
4. **Baseline Signs & Symptoms:** patients will be asked about any signs and symptoms experienced within the past 14 days of registration. Baseline signs and symptoms (including NCI CTCAE grade, if applicable) will be recorded on the Medical History case report form (CRF) page.
5. **Vital signs:** vital signs include blood pressure (BP) and heart rate (HR). Vital signs will be taken and recorded during the site clinic visit.
6. **Performance status:** use Eastern Cooperative Oncology Cohort (ECOG) – see Appendix 2.
7. **Contraception Check:** Male patients who are able to father children, and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly, and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
8. **Hematology:** See Section 7.1.4 for specific required tests. No need to repeat on Cycle 1 Day 1 (C1D1) if baseline assessment performed within 7 days prior to that date.

9. **Blood Chemistry:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within *7* days prior to that date.
10. **Coagulation:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within *7* days prior to that date.
11. **Urinalysis:** See Section 7.1.4 for specific required tests. Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
12. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, ie, who do not fit the definition of "female patients who are not of childbearing potential" in inclusion criterion 13, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory>, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
13. **Triplicate 12-lead ECGs:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed according to the schedule outlined in Table A8-2.
14. **Pulse Oximetry:** Pulse oximetry will be performed within 14 days prior to the first dose of investigational product treatment, and during treatment as described in the table above. Pulse oximetry should be repeated if clinically indicated.
15. **Chest X ray or Chest CT:** Chest X ray or Chest CT will be performed within 14 days prior to the first dose of study drug. Chest X ray or CT should be repeated if clinically indicated and at the discretion of the investigator. Patients who have had a CT scan including chest for the purpose of tumor assessment for this study will not need to be repeated at baseline.
16. **Registration:** Patients will be enrolled according to a computer generated pseudo-random code. Randomization numbers will be assigned by a central web-based randomization system operated by Pfizer Inc.
17. **Study Treatment**: The recommended Phase 2 Dose (RP2D) of PF-06747775 will be given with a breakfast of 200-300 calories in the morning every day at approximately the same time once daily in 21 day cycles. A single lead-in dose will be given on Day -4, and continuous daily dosing with start on Cycle 1 Day 1. See Table A8-2 for more details.
18. **CT or MRI Tumor Assessments: Baseline assessments must be within 28 days of first study treatment.** Tumor assessments will include all known or suspected disease sites. Tumor response will be assessed per RECIST v1.1. Imaging may include chest, abdomen and pelvis CT or MRI scans. Minimally, chest, liver and adrenals must be imaged. Brain scans are required at baseline and every assessment if intra-cerebral disease is present; if no intra-cerebral disease is found at baseline, then brain imaging is only required on study if clinically indicated. Bone scans will be performed at baseline if clinically indicated and on-study as appropriate to follow disease. For all patients with RECIST measurable disease who have a RECIST response, confirmation of the response is required at least 4 weeks after initial assessment of response. Tumor assessment should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. <u>For patients that have discontinued the treatment period due to reasons other than disease progression:</u> Tumor assessments must continue until documented progression of disease by investigator. Patients who discontinue treatment without PD should continue to have tumor assessments performed every 6 weeks until PD is confirmed by investigator regardless of subsequent anti-cancer treatments.

19. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version *4.0*. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
20. **Concomitant Treatments:** all concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF.

CCI [redacted]

22. **PK Sampling:** serial blood samples will be collected after single and multiple doses (steady state) of PF-06747775 to characterize PK behavior. See Table A8-2 for more detailed information.

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CCI [redacted]

CCI [redacted]

CCI [redacted]

27. **Survival:** Will be performed every 2 months for up to 24 months after PD or new anti-cancer therapy has commenced (telephone contact is acceptable).
28. **End of Treatment visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
29. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. For patients that have discontinued the treatment period due to reasons other than disease progression: Tumor assessments will continue to be performed every 6 weeks during long term follow up until documented disease progression, start of a new anti-cancer treatment, death or lost to follow-up (whichever occurs first). All patients will be followed for at least 24 months after initial dose of last patient treated.
30. Patients will be hospitalized at least the first 14 days on Cycle 1.

Table A8-2.Japanese Patient-Only LIC RP2D Tolerability Cohort - PK and ECG Assessments

Visit Identifier	Lead-in									Cycle 1									Cycles 2 - 4
Day	-4						-3	-2	-1	1 (± 1)		2-10	11 (± 2)						12	1 (± 2)
Hours Post Dose	0[a]	1	2	4	6	8	24	48	72	96[f] (Pre-Dose[b])	0[a]	Pre-Dose[b]	Pre-Dose[b]	1	2	4	6	8	24 (Pre-Dose[b])	Pre-Dose[b]
PF-06747775 Dose[c]	X										X	Once daily PO continuous, with breakfast								
PK blood sampling[d]	X[b]	X	X	X	X	X	X	X	X	X[b]		X[b]	X[b]	X	X	X	X	X	X[b]	X[b]
12-Lead ECG[e]	X		X										X		X		X			X

a. **0 hrs. Dose time:** dose time of PF-06747775 triggers the defined post dose sample collection times.

b. **Pre-dose sample collection:** before study treatment dose.

c. **PF-06747775 dose:** PF-06747775 dose will be given in the morning with a breakfast of 200-300 calories, at approximately the same time once daily in 21 day cycles starting continuous dosing on Cycle 1 Day 1. On days in which pre-dose ECG or PK assessments are conducted, dosing should occur in clinic with breakfast after pre-dose ECGs are completed and pre-dose PK samples are drawn. Food is allowed 2 hrs. after dose.

d. **PK blood sampling for PF-06747775 analysis:** On Day -4, 4 mL of blood in K_2EDTA tubes will be collected as shown above for single dose PK analysis. On Day 1 of Cycle 1, (96 hr post lead-in dose) a PK sample will be taken before dose of PF-06747775 (the start of continuous daily dosing). On days 2-10, trough samples will be collected prior to PF-06747775 dose (pre-dose) to determine attainment of steady state. The samples will be collected every day from Day 2 to 5. After that, samples will be collected on every other day, ie., trough samples will be collected on Cycle 1 Days 2, 3, 4, 5, 7 and 9, until serial PK sampling occurs on Day 11 (± 1). On Day 11 of Cycle 1, 4 mL of blood in K_2EDTA tubes will be collected as shown above for multiple dose PK analysis. On Day 1 of Cycles 2 - 4, 4 mL of blood in K_2EDTA tubes will be collected prior to PF 06747775 dose (pre-dose) for steady state PK analysis. If, during the course of treatment, a patient needs to reduce the dose of PF-06747775, serial PK samples may be taken at least 1 week after starting the reduced dose using the same PK blood sampling schedule as outlined above for Cycle 1 Day 11 through pre-dose on Day 12.

e. **Triplicate 12-Lead ECG:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed at pre-dose and 2 hrs. post dose on Day -4, pre-dose and 2 hrs. and 6 hrs. post dose on Day 11 of Cycle 1, and pre-dose on Days 1 of Cycles 2 - 4. The 2 hrs. post dose ECG assessment is intended to target C_{max}, this time point may be re-assessed as data emerge.

f. If the -1 day window is utilized for the Cycle 1 Day 1 visit, then the 72 hrs. PK blood draw should occur prior to the dose of PF-06747775, which starts the once daily continuous dosing; in this case the 96 hrs. PK blood draw will not be completed.

Abbreviations: PK = pharmacokinetic; PO = by mouth; QTcF = QT interval corrected by Fridericia's formula

Table A8-3. Japanese Patient-Only LIC PK Cohort Schedule of Assessments

		LEAD-IN PK	CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES ≥3 (21 days)	End of Treatment[28]	Follow- up[29]
Visit Identifier	**Screening[2]**	**Day -7**	**Day 1[1]**	**Day 8**	**Day 15**	**Day 1**	**Day 1**		
Visit Window	**≤28 days from registration**		**±1**	**±1**	**±1**	**±2**	**±2**	**±3**	+7
Informed consent[3]	X								
Tumor history	X								
Medical history	X								
Physical examination	X		(X)			X	X		
Baseline signs and symptoms[4]			X						
Height	X								
Weight	X		X			X	X		
Vital signs[5]	X		X	X	X	X	X	X	X
Performance status (ECOG)[6]	X		X	X	X	X	X	X	X
Contraception check[7]	X		(X)			X	X	X	
Laboratory									
Hematology[8]	X		(X)	X	X	X	X	X	
Blood Chemistry[9]	X		(X)	X	X	X	X	X	
Coagulation[10]	X		(X)	X	X			X	
Urinalysis[11]	X		(X)					X	
Pregnancy test[12]	X		X			X	X	X	
(12-lead) ECG[13]	X	See TableA8-4						X	
Pulse Oximetry[14]	X		X	X	X	X	X (up to Cycle 5)	X	
Chest X ray or Chest CT[15]	X								
Registration and Treatment									
Registration[16]		X							
PF-06747775[18]		X	Once daily PO continuous						
Tumor assessments									
CT or MRI imaging[18]	X						X and every other cycle (every 6 weeks) +/- 7 days	X	
Other clinical assessments									

		LEAD-IN PK	CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES ≥3 (21 days)	End of Treatment[28]	Follow- up[29]
Visit Identifier	**Screening[2]**	**Day -7**	**Day 1[1]**	**Day 8**	**Day 15**	**Day 1**	**Day 1**		
Visit Window	**≤28 days from registration**		**±1**	**±1**	**±1**	**±2**	**±2**	**±3**	+7
Adverse Events[19]			X	X	X	X	X	X	X
Concomitant treatments and non-drug supportive interventions[20]	X		X			X	X	X	X
Other samplings									
[redacted] CCI	[redacted]							[redacted]	
Pharmacokinetics[22]		See TableA8-4							
[redacted] CCI	[redacted]								
	[redacted]								
	[redacted]						[redacted]	[redacted]	
	[redacted]						[redacted]	[redacted]	
Survival[27]									X

CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

Footnotes:

1. Day relative to start of study treatment (Day 1).
2. **Screening:** to be obtained within 28 days prior to registration.
3. **Informed Consent:** must be obtained prior to undergoing any study specific procedures unless considered standard of care.
4. **Baseline Signs & Symptoms:** patients will be asked about any signs and symptoms experienced within the past 14 days of registration. Baseline signs and symptoms (including NCI CTCAE grade, if applicable) will be recorded on the Medical History case report form (CRF) page.
5. **Vital signs:** vital signs include blood pressure (BP) and heart rate (HR). Vital signs will be taken and recorded during the site clinic visit.
6. **Performance status:** use Eastern Cooperative Oncology Cohort (ECOG) – see Appendix 2.
7. **Contraception Check:** Male patients who are able to father children, and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly, and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
8. **Hematology:** See Section 7.1.4 for specific required tests. No need to repeat on Cycle 1 Day 1 (C1D1) if baseline assessment performed within *7* days prior to that date.
9. **Blood Chemistry:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within *7* days prior to that date.

10. **Coagulation:** See Section 7.1.4 for specific required tests. No need to repeat on C1D1 if baseline assessment performed within *7* days prior to that date.
11. **Urinalysis:** See Section 7.1.4 for specific required tests. Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
12. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, ie, who do not fit the definition of "female patients who are not of childbearing potential" in inclusion criterion 13, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory>, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
13. **Triplicate 12-lead ECGs:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed according to the schedule outlined in Table A8-4.
14. **Pulse Oximetry:** Pulse oximetry will be performed within 14 days prior to the first dose of investigational product treatment, and during treatment as described in the table above. Pulse oximetry should be repeated if clinically indicated.
15. **Chest X ray or Chest CT:** Chest X ray or Chest CT will be performed within 14 days prior to the first dose of study drug. Chest X ray or CT should be repeated if clinically indicated and at the discretion of the investigator. Patients who have had a CT scan including chest for the purpose of tumor assessment for this study will not need to be repeated at baseline.
16. **Registration:** Patients will be enrolled according to a computer generated pseudo-random code. Randomization numbers will be assigned by a central web-based randomization system operated by Pfizer Inc.
17. **Study Treatment**: PF-06747775 will be given with a breakfast of 200-300 calories in the morning every day at approximately the same time once daily in 21 day cycles. A single lead-in dose will be given on Day -7, and continuous daily dosing with start on Cycle 1 Day 1. See Table A8-4 for more details.
18. **CT or MRI Tumor Assessments: Baseline assessments must be within 28 days of first study treatment.** Tumor assessments will include all known or suspected disease sites. Tumor response will be assessed per RECIST v1.1. Imaging may include chest, abdomen and pelvis CT or MRI scans. Minimally, chest, liver and adrenals must be imaged. Brain scans are required at baseline and every assessment if intra-cerebral disease is present; if no intra-cerebral disease is found at baseline, then brain imaging is only required on study if clinically indicated. Bone scans will be performed at baseline if clinically indicated and on-study as appropriate to follow disease. For all patients with RECIST measurable disease who have a RECIST response, confirmation of the response is required at least 4 weeks after initial assessment of response. Tumor assessment should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation. <u>For patients that have discontinued the treatment period due to reasons other than disease progression:</u> Tumor assessments must continue until documented progression of disease by investigator. Patients who discontinue treatment without PD should continue to have tumor assessments performed every 6 weeks until PD is confirmed by investigator regardless of subsequent anti-cancer treatments.

19. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version *4.0*. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.
20. **Concomitant Treatments:** all concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF.

CCI [redacted]

22. **PK Sampling:** serial blood samples will be collected after single and multiple doses (steady state) of PF-06747775 to characterize PK behavior. See Table A8-4 for more detailed information.

CCI [redacted]

CCI [redacted]

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CCI [redacted]

CCI [redacted]

27. **Survival:** Will be performed every 2 months for up to 24 months after PD or new anti-cancer therapy has commenced (telephone contact is acceptable).
28. **End of Treatment visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
29. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. For patients that have discontinued the treatment period due to reasons other than disease progression: Tumor assessments will continue to be performed every 6 weeks during long term follow up until documented disease progression, start of a new anti-cancer treatment, death or lost to follow-up (whichever occurs first). All patients will be followed for at least 24 months after initial dose of last patient treated.

Table A8-4. Japanese Patient-Only LIC PK Cohort - PK and ECG Assessments

Visit Identifier	**Lead-in**											**Cycle 1**															**Cycles 2 - 4**
Day	**-7**						**-6**	**-5**	**-4**	**-3**		**1 (± 1)**						**2**	**8 (± 1)**	**15 (± 2)**						**16**	**1 (± 2)**
Hours Post Dose	0[a]	1	2	4	6	8	24	48	72	96	**Wash out**	0[a] (Pre-Dose[b])	1	2	4	6	8	24 (Pre-Dose[b])	Pre-Dose[b]	Pre-Dose[b]	1	2	4	6	8	24 (Pre-Dose[b])	Pre-Dose[b]
PF-06747775 Dose[c]	X (100 mg)											X (RP2D)						Once daily PO continuous, with breakfast (RP2D)									
PK blood sampling[d]	X[b]	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X[b]	X[b]	X[b]	X	X	X	X	X	X[b]	X[b]
12-Lead ECG[e]	X		X									X		X						X		X		X			X

a. **0 hrs. Dose time:** dose time of PF-06747775 triggers the defined post dose sample collection times.

b. **Pre-dose sample collection:** before study treatment dose.

c. **PF-06747775 dose:** PF-06747775 dose will be given in the morning with a breakfast of 200-300 calories, at approximately the same time once daily in 21 day cycles starting continuous dosing on Cycle 1 Day 1. On Day -7, subject will take a 100 mg single dose. Starting on Day 1 in Cycle 1, a once daily dose of RP2D (200 mg) will be taken.

d. **PK blood sampling for PF-06747775 analysis:** For PK analysis, 4 mL of blood in K_2EDTA tubes will be collected as shown above. Serial PK samples will be collected on days -7 to -3 in lead-in, Days 1 to2 and Days 15 to 16 in Cycle 1. In addition, trough samples will be collected on Day 8 of Cycle 1. On Day 1 of Cycles 2 - 4, 4 mL of blood in K_2EDTA tubes will be collected prior to PF 06747775 dose (pre-dose) for steady state PK analysis. If during the course of treatment a patient needs to reduce the dose of PF-06747775, serial PK samples may be taken at least 1 week after starting the reduced dose using the same PK blood sampling schedule as outlined above for Cycle 1 Day 15 through pre-dose on Day 16.

e. **Triplicate 12-Lead ECG:** At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG assessments pre-dose should happen prior to breakfast. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional

triplicate ECGs may be performed as clinically indicated. ECG assessments will be performed at pre-dose and 2 hrs. post dose on Day -7 and Day 1 in cycle 1, pre-dose and 2 hrs. and 6 hrs. post dose on Day 11 of Cycle 1, and pre-dose on Days 1 of Cycles 2 - 4. The 2 hrs. post dose ECG assessment is intended to target C_{max}, this time point may be re-assessed as data emerge.

Abbreviations: PK = pharmacokinetic; PO = by mouth

- **Patient Selection for Japanese patient-Only LIC**

Inclusion and exclusion criteria are same as Phase 1 (See Section 4.1, 4.2) except for prior treatment with a 3rd generation EGFR TKI. Patients who are prior treatment with a 3rd generation EGFR TKI are not excluded in Japanese patient-Only LIC.

- **Safety Review Process for RP2D tolerability cohort**

Following 1 cycle (21 days) of treatment, a safety review will be performed as described in "Data Analysis/Statistical Methods for Japanese patient-Only LIC" by Japanese investigators and the Sponsor to determine whether the emerging data from this cohort will support inclusion of patients at Japan sites in Phase 2 (Cohort 1) and Phase 1b/2 (Cohort 2A, 2B and 3). The PK cohort data or enrollment does not need to be completed to allow this determination.

- **Data Analysis/Statistical Methods for Japanese patient-Only LIC**

Japanese patients enrolled into the LIC will be analyzed separately from patients enrolled in the main part of the study. DLT is the primary endpoint of the analysis for the LIC, and the occurrence of DLTs will be used to assess safety and tolerability at the RP2D in Japanese patients. AEs constituting DLTs will be listed. The definition of the per protocol analysis set for the LIC is described in the section of study design in Appendix 8. See Section 9 for additional details regarding the statistical analysis.

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