CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc

Investigational Product: PF-06747775

Clinical Study Report Synopsis: Protocol B7971001

Protocol Title: 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

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: 14 May 2015

Study Completion Date: 28 May 2020 (This study was terminated prematurely.)

Report Date: 19 October 2020

Previous Report Date(s): Not Applicable

Phase of Development: Phase 1/2

Primary and Secondary Study Objectives and Endpoints:

The objectives and endpoints are presented in Table S1, Table S2 and Table S3.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints - Phase 1

Type	Objective	Endpoint
Primary		
Safety	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 recommended Phase 2 dose (RP2D) in patients with advanced epidermal growth factor receptor mutant (EGFRm) non-small cell lung cancer (NSCLC) (exon deletion 19 or exon 21 L858R substitution, with or without T790M) following ≥1 prior line of therapy, which must have included an approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)	• Cycle 1 dose limiting toxicities (DLTs)
Secondary		
Safety	To evaluate the overall safety profile of PF-06747775	• Overall safety profile of PF-06747775 characterized by type, incidence, severity, seriousness, and relationship to study therapy of adverse events (AEs) • Laboratory test abnormalities
	To characterize the effects of single-agent PF-06747775 on corrected QT (QTc)	• QTc for heart rate using Fridericia's formula (QTcF) and QTc for heart rate using Bazett's formula (QTcB)
Pharmacokinetics (PK)	To characterize single dose and steady state PK profiles of single-agent PF-06747775	• Plasma area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}), maximum observed plasma concentration (C_{max}), terminal plasma half-life ($t_{½}$), apparent oral clearance (CL/F), and apparent volume of distribution (V_z/F) of PF-06747775 after single dose • Pre-dose concentration (C_{trough}), area under the curve at steady state (AUC_{tau}), CL/F, observed accumulation ratio for AUC_{tau} (R_{ac}), and steady state accumulation ratio (R_{ss}) of PF-06747775 after multiple doses

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints - Phase 1

Type	Objective	Endpoint
	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	• Plasma AUC_{inf}, C_{max}, and CL/F of sildenafil alone and in combination with steady state plasma concentrations of PF-06747775
	To characterize the effect of food on the exposure of PF-06747775 at the RP2D	• Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D under fed and fasted conditions
	To characterize the effect of esomeprazole, a proton pump inhibitor (PPI), on the exposure of PF-06747775 at the RP2D	• Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and in combination with esomeprazole treatment
	To characterize the effect of itraconazole, a strong CYP3A4 inhibitor, on the exposure of PF-06747775 at the RP2D	• Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and in combination with itraconazole treatment
	To characterize the effect of rifampin, a strong CYP3A4 inducer, on the exposure of PF-06747775 at the RP2D	• Plasma AUC_{tau} and C_{max} of PF-06747775 at the RP2D alone and in combination with rifampin treatment
Pharmacodynamics (PD)	To assess in tumor and plasma the presence/absence of EGFR mutations	• EGFR mutations in tumor and plasma
Efficacy	To evaluate the anti-tumor activity of PF-06747775 in both T790M-positive and T790M-negative NSCLC tumors	• Confirmed objective response (OR), per Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 for those patients with measurable disease
Exploratory		
PD	To assess tumor and blood-based biomarkers of sensitivity and/or resistance to PF-06747775	• Tumor and plasma biomarkers of sensitivity and resistance

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Objectives and Endpoints - Phase 1b/2

Type	Objective	Endpoint
Primary		
Efficacy	To assess the anti-tumor activity (objective response rate [ORR]) of single-agent PF-06747775 in patients with EGFRm NSCLC (exon deletion 19 or exon 21 L858R substitution, with or without T790M) (Cohort 1)	• Confirmed OR, per RECIST version 1.1
	To assess the progression-free survival (PFS) of PF-06747775 plus palbociclib versus single-agent PF-06747775 in patients with EGFRm NSCLC with a secondary T790M mutation (exon deletion 19 and T790M or exon 21 L858R substitution and T790M) (Cohort 2B)	• PFS
Safety	To evaluate safety and tolerability and determine the RP2D of PF-06747775 plus palbociclib in patients with EGFRm NSCLC with a secondary T790M mutation (exon deletion 19 and T790M or exon 21 L858R substitution and T790M) (Cohort 2A).	• Cycles 1 and 2 DLTs
	To evaluate safety and tolerability and establish the RP2D of PF-06747775 plus avelumab in patients with EGFRm NSCLC with a secondary T790M mutation (exon deletion 19 and T790M or exon 21 L858R substitution and T790M) (Cohort 3)	• Cycle 1 DLTs
Secondary		
Efficacy	To assess duration of objective response (DOR) and overall survival (OS) probability at 24 months (all cohorts)	• DOR (all cohorts) • OS probability at 24 months (all cohorts)
	To assess ORR (Cohorts 2A, 2B, 3)	• ORR (Cohorts 2A, 2B, 3)
	To assess PFS (Cohorts 1, 2A, and 3)	• PFS (Cohorts 1, 2A, 3)
Safety	To further characterize the AE profile of PF-06747775 when given as a single agent (Cohorts 1 and 2B) and in combination with palbociclib (Cohorts 2A and 2B) and avelumab (Cohort 3)	• Overall safety profile characterized by type, incidence, severity, seriousness, and relationship to study therapy of AEs (all cohorts) • Laboratory test abnormalities (all cohorts)

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Objectives and Endpoints - Phase 1b/2

Type	Objective	Endpoint
	To further explore the effects of PF-06747775 on QTc when given as a single agent (Cohorts 1 and 2B) and in combination with palbociclib (Cohorts 2A and 2B) and avelumab (Cohort 3)	• QTcF and QTcB
PK	To further characterize PF-06747775 PK when given as a single agent (Cohorts 1 and 2B) and in combination with palbociclib (Cohorts 2A and 2B) and avelumab (Cohort 3)	• PK parameters of PF-06747775 as data permitted
	To characterize the PK of palbociclib in combination with PF-06747775 (Cohorts 2A and 2B)	• PK parameters of palbociclib, as data permitted
	To characterize the PK of avelumab in combination with PF-06747775 (Cohort 3)	• PK parameters of avelumab, as data permitted
PD	To assess in tumor and plasma the presence/absence of EGFR mutations (all cohorts)	• EGFR mutations in tumor and plasma (all cohorts)
Immunogenicity	To assess the immunogenicity of avelumab when given in combination with PF-06747775 (Cohort 3)	• Avelumab serum anti-drug antibody (ADA) (neutralizing antibody [Nab]) (Cohort 3)
Exploratory		
Efficacy	To explore the antitumor effect of avelumab in combination with PF-06747775 (Cohort 3) by immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)	• immune-related best overall response (irBOR) • immune-related progressive disease (irPD)
PK	To assess the presence and relative concentration of PF-06747775 in cerebral spinal fluid (CSF), as data permitted (all cohorts)	• PF-06747775 concentrations in CSF

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Objectives and Endpoints - Phase 1b/2

Type	Objective	Endpoint
PD	To explore the predictive and PD characteristics of tumor tissue, peripheral blood, and urine biomarkers that may be relevant to mechanism of action or resistance to PF-06747775 (all cohorts) To assess tumor and blood-based biomarkers of sensitivity and/or resistance to PF-06747775 (all cohorts)	• Tumor tissue, peripheral blood, and urine biomarkers of action mechanism or resistance to PF-06747775 (all cohorts) • Tumor tissue, peripheral blood and urine biomarkers including circulating lymphocytes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins that may be related to response or disease progression on treatment with PF-06747775 and palbociclib (Cohorts 2A and 2B)
	To evaluate the PD effect of PF-06747775 and avelumab on immune parameters in peripheral blood including lymphocyte subpopulations, serum biomarkers and gene expression (Cohort 3) To evaluate candidate immune-related predictive biomarkers of sensitivity or insensitivity to treatment with avelumab in combination with PF-06747775 in pre-treatment tumor samples (eg, programmed death ligand-1 [PD-L1] expression) (Cohort 3)	• Tumor tissue and peripheral blood biomarkers such as PD-L1 expression and tumor- infiltrating cluster of differentiation (CD)8+ T-lymphocytes; T, B, and natural killer (NK) cells; effector and memory T cells; cytokines; T cell receptor sequences; and expression of genes related to immune response and inflammation

Table S3. Study Objectives and Endpoints-Japanese Patients

Type	Objective	Endpoint
Safety	To evaluate the safety and tolerability of PF-06747775 in Japanese patients (RP2D tolerability cohort)	• Cycle 1 DLTs • Overall safety profile of PF-06747775 characterized by type, incidence, severity, seriousness, and relationship to study therapy of AEs • Laboratory test abnormalities
PK	To characterize single dose and steady state PK profiles of single-agent PF-06747775 in Japanese patients (RP2D tolerability cohort and PK cohort)	• PK parameters of PF-06747775 following single and multiple doses as data permitted

CLINICAL STUDY REPORT SYNOPSIS

METHODS

Study Design: This was a Phase 1/2 study of PF-06747775 as a single agent and in combination with palbociclib and avelumab in patients with advanced epidermal growth factor receptor mutant (EGFRm) non-small cell lung cancer (NSCLC). The overall clinical study consisted of a Phase 1 single-agent, dose-escalation and Phase 1b/2 dose-expansion part to determine the single-agent recommended Phase 2 dose (RP2D) of PF-06747775 in patients with previously-treated EGFRm NSCLC followed by sequential evaluations of PF-06747775 at the RP2D in 3 different clinical scenarios. Phase 1 was also planned to include a series of pharmacokinetic (PK) sub-studies. In addition, this study also included a Japanese patient lead-in cohort (LIC) to evaluate the safety, tolerability and PK of PF-06747775 as a single agent in Japanese patients with advanced EGFRm NSCLC. This Japanese LIC was planned to consist of 2 cohorts: RP2D tolerability cohort and PK cohort. Due to early study termination, enrollment into the food effect and rifampin drug-drug interaction (DDI) PK sub-study, Cohort 2B and Cohort 3 were not initiated. Most PD/biomarker analyses were also not completed.

Diagnosis and Main Criteria for Inclusion: Patients with evidence of histologically or cytologically confirmed diagnosis of locally advanced or metastatic EGFRm (exon deletion 19 or exon 21 L858R substitution) NSCLC were enrolled in this study. In Japanese patients-only LIC, locally advanced or metastatic EGFRm NSCLC patients who progressed on or were intolerant to standard therapy, for which no standard therapy was available or who declined standard therapy were included in this study.

RESULTS

Subject Disposition and Demography:

A total of 65 patients were assigned and treated in this study:

- 26 patients were treated in the dose escalation part (PF-06747775 doses: 25 mg to 600 mg once daily [QD]);
- 29 patients were treated with PF-06747775 200 mg QD, a combined group of PF-06747775 200 mg QD plus sildenafil 25 mg, PF-06747775 200 mg QD plus esomeprazole/itraconazole, Japan LIC and Cohort 1;
- 5 patients were treated with PF-06747775 300 mg QD plus sildenafil 25 mg;
- 5 patents were treated with PF-06747775 200 mg QD plus palbociclib 100 mg QD (Cohort 2A).

All 65 patients permanently discontinued from the study treatment. Thirty-five (53.8%) patients completed the study and 30 (46.2%) patients permanently discontinued from the study.

CLINICAL STUDY REPORT SYNOPSIS

Twenty-five male and 40 female patients were assigned and treated in this study, with the mean (standard deviation) age of 60.8 (11.1) years. A total of 47 (72.3%) patients were Asian.

Efficacy Results:

Objective Response: No patients achieved a complete response (CR). Twenty-seven (41.5%) patients achieved a partial response (PR). The objective response rate (ORR) (CR+PR) for the overall population without regard to T790M mutation status was 41.5% (90% confidence interval [CI]: 31.2%, 52.5%).

Duration of Objective Response (DOR): The median DOR for the overall population was 11.09 (range: 2.70-34.57) months.

Overall Survival (OS): The OS analysis included 9 patients in Japan LIC and Cohort 1 from PF-06747775 200 mg QD group. The median OS was not estimable since the majority of patients were censored. The survival probability at 12 months was 87.5% (90% CI: 50.0%, 97.5%).

Progression-Free Survival (PFS): The PFS analysis included 29 patients in PF-06747775 200 mg QD group. Of these, 19 (65.5%) patients had objective progression. The medium PFS was 8.1 (90% CI: 5.4, 23.3) months. The probability of being event free at 24 months was 22.8% (90% CI: 9.6%, 39.5%).

Pharmacokinetic Results:

Dose Escalation: The PK of PF-06747775 was observed to be generally proportional to dose over the range of 25 mg to 600 mg following both single and multiple dose administration; there was no major accumulation or evidence of non-linearity.

Sildenafil Sub-Study: The results demonstrated a minor decrease in area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}) and maximum observed plasma concentration (C_{max}) of sildenafil by approximately 34% and 17%, respectively, when co-administered with PF-06747775, suggesting potential weak induction of cytochrome P450 (CYP)3A with multiple doses of PF-06747775.

Itraconazole Sub-Study: The results demonstrated a slight increase in dose-normalized area under the concentration-time profile from time 0 to time tau (AUC_{tau}[dn]) and dose-normalized C_{max} (C_{max}[dn]) of PF-06747775 by approximately 16% and 22%, respectively, when co-administered with itraconazole, suggesting CYP3A-based metabolism is a contributor to the elimination of PF-06747775 following multiple doses. This degree of increase in PF-06747775 exposure is not expected to be clinically meaningful.

Esomeprazole Sub-Study: The results demonstrated a slight decrease in PF-06747775 area under the concentration-time profile from time 0 to time tau (AUC_{tau}) and C_{max} by

CLINICAL STUDY REPORT SYNOPSIS

approximately 17% and 22%, respectively, when co-administered with esomeprazole, suggesting an increase in gut pH may slightly decrease the absorption of PF-06747775 following oral dosing. This degree of decrease in PF-06747775 exposure is not expected to be clinically meaningful.

PF-06747775 in Combination With Palbociclib: There was no evidence of changes in the PK of PF-06747775 when administered in combination with palbociclib 100 mg QD compared to administration alone. Due to the very limited palbociclib concentration data in few patients, no further interpretation is made at this time regarding palbociclib PK behavior when given under this dose regimen in combination with PF-06747775.

PF-06747775 in Japanese-Only Patients: The PK of PF-06747775 in Japanese patients was similar between the 2 cohorts (Japan RP2D and Japan PK) following single and multiple dose administration.

Safety Results:

Dose Limiting Toxicity (DLTs): No DLTs were observed in the dose escalation cohorts and the Japan LIC. Two patients in Cohort 2A had DLTs.

Adverse Events (AEs): All 65 treated patients had at least 1 all-causality treatment-emergent adverse event (TEAE) and 61 of them had at least 1 treatment-related TEAE. In the overall population, the most frequently reported all-causality AEs were diarrhea and paronychia. Both diarrhea and paronychia were experienced by 45 (69.2%) patients each and all of these events were considered as treatment-related AEs. Other frequent AEs included rash (39 [60.0%] patients), stomatitis (30 [46.2%] patients), dermatitis acneiform (28 [43.1%] patients) and dry skin (27 [41.5%] patients). Grade 5 AEs were reported for 3 patients, none of which were related to study treatment. The frequency of treatment-related serious adverse events (SAEs) reported for this study was low (6 [9.2%] patients).

Other safety evaluations: The most frequent shifts from Grade ≤2 at baseline to Grade 3 or 4 post-baseline for hematology laboratory results were lymphopenia (8 [12.3%] patients) and anemia (5 [7.7%] patients). The most frequent shift from Grade ≤2 at baseline to Grade 3 or 4 post-baseline for chemistry results was hyponatremia (8 [12.3%] patients). No patients were observed with a post-dose corrected QT for heart rate using Fridericia's formula (QTcF) ≥500 msec or a maximum increase from baseline of QTcF ≥60 msec.

Conclusions:

- No DLTs were observed in dose escalation cohorts and Japan LIC. Two patients in Cohort 2A had DLTs. The maximum tolerated dose (MTD) was not determined.

- PF-06747775 had a safety profile that was generally tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy in patients with advanced

CLINICAL STUDY REPORT SYNOPSIS

EGFRm NSCLC. No notable findings in laboratory parameters and electrocardiogram (ECG) data were reported.

- PF-06747775 provided clinically benefit for the total population as evidenced by Investigator-assessed ORR of 41.5% (90% CI: 31.2%, 52.5%) and median DOR of 11.09 (range: 2.70-34.57) months.

- Following single and multiple-dose administration, plasma PF-06747775 exposures based on geometric mean AUC_{tau}(dn) and C_{max}(dn) were generally proportional to dose over the range of 25 to 600 mg QD.

- In the Japan LIC following repeat oral administration for 11 days (Japan RP2D cohort) and 15 days (Japan PK cohort) in Cycle 1, plasma PF-06747775 exposures (based on AUC_{tau}[dn] and C_{max}[dn]) were similar between the 2 cohorts.

- Co-administration of multiple doses of PF-06747775 QD with a proton pump inhibitor (PPI) (esomeprazole), a strong CYP3A inhibitor (itraconazole), or a sensitive CYP3A substrate (sildenafil), were not associated with clinically meaningful DDIs.