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SYNOPSIS

Study Title: A Phase 1 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Escalating Doses of PF-06939999 (PRMT5 Inhibitor) in Participants With Advanced or Metastatic Non-Small Cell Lung Cancer, Head and Neck Squamous Cell Carcinoma, Esophageal Cancer, Endometrial Cancer, Cervical Cancer and Bladder Cancer

Study Number: C3851001

Regulatory Agency or Public Disclosure Identifier Number: IND 140966, NCT03854227

Study Phase: 1

Name of Study Intervention: PF-06939999

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Final CSR (PCD Date) Version 1.0	26 October 2022

Number of Study Centers and Investigators:

A total of 54 participants were enrolled at 10 centers in the United States.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: Not applicable

Study Period:

Study Initiation (FPFV) Date: 14 March 2019

Study Completion (LPLV) Date: 27 April 2022

This study was terminated.

Rationale:

PF-06939999 is an orally available small molecule inhibitor of protein arginine methyltransferase 5 (PRMT5). PRMT5 over-expression in hematologic malignancies and solid tumors promotes methylation of protein substrates that activate a variety of biological functions known to be dysregulated in cancer. Inhibition of PRMT5 leads to growth arrest and cell death in tumors that harbor alterations in mRNA splicing pathways. PF-06939999

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has potent cellular effects as measured by its ability to reduce symmetric dimethylarginine (SDMA) levels of splicing regulators resulting in growth arrest in multiple hematologic and solid tumor cell lines. In this study, PF-06939999 was investigated in participants with advanced or metastatic head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), esophageal, endometrial, cervical and bladder cancer.

This was a first-in-human clinical study of PF-06939999. The study is divided into 2 parts: dose escalation (Part 1) followed by dose expansion (Part 2). The purpose of Part 1 (dose escalation) is to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of escalating doses of PF-06939999 in participants with advanced or metastatic HNSCC, NSCLC, esophageal, endometrial, cervical, and bladder cancer and determine the maximum tolerated dose (MTD) and Recommended Part 2 Dose (RP2D).

The purpose of Part 2 (dose expansion) is to further evaluate the safety and tolerability of PF-06939999 at RP2D as well as preliminary clinical efficacy in advanced or metastatic NSCLC, urothelial carcinoma (bladder cancer) and HNSCC.

The study was terminated in November 2021 based on a strategic evaluation following the review of clinical results within the current Pfizer oncology portfolio. This decision was not due to any safety concerns or requests from any regulatory authorities. The safety profile remains unchanged for PF-06939999 as a single agent.

Objectives, Endpoints, and Statistical Methods:

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Type	Objective	Endpoints
Primary		
Safety	Part 1A: To assess safety and tolerability at increasing dose levels of PF-06939999 in successive cohorts of participants with selected advanced or metastatic solid tumors in order to estimate MTD and select the RP2D/schedule.	• Dose limiting toxicities (DLTs). • Adverse events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 5.0), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.
	Part 1B: To assess safety and tolerability of PF-06939999 in combination with docetaxel in participants with locally advanced or metastatic NSCLC to determine MTD and select the RP2D/schedule for combination.	• DLTs. • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.
	Part 2: To assess safety and tolerability of PF-06939999 monotherapy in participants with locally advanced or metastatic NSCLC, urothelial carcinoma, or HNSCC and in combination with docetaxel in locally advanced or metastatic NSCLC.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.
Efficacy	Part 2: To estimate clinical efficacy by overall response rate (ORR) of PF-06939999 monotherapy in participants with NSCLC, urothelial carcinoma or HNSCC and in combination with docetaxel in NSCLC.	Best overall response (BOR) as assessed by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
Secondary		

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Type	Objective	Endpoints
PK	Part 1A: To characterize the single and multiple dose PK of PF-06939999 following oral administration.	• PK parameters of PF-06939999: single dose (sd) - maximum observed plasma concentration (C_{max}), time for C_{max} (T_{max}), area under the serum concentration-time profile from time zero to the time of last quantifiable concentration (AUC_{last}), and as data permitted, terminal elimination half-life ($t_{½}$), area under the serum concentration-time profile from time zero extrapolated to infinity (AUC_{inf}), apparent clearance (CL/F), and volume of distribution (V_z/F). • PK parameters of PF-06939999: multiple dose (md) - steady state C_{max} ($C_{max,ss}$), time for steady state C_{max} ($T_{max,ss}$), area under the serum concentration-time profile within 1 dose interval ($AUC_{ss,\tau}$), and as data permitted, CL/F, V_{ss}/F, and observed accumulation ratio based on AUC_{tau} (R_{ac}) ($AUC_{ss,\tau}$/ single-dose area under the serum concentration-time profile within 1 dose interval [$AUC_{sd,\tau}$]).
	Part 1B: To characterize the single and multiple dose PK of PF-06939999 when administered in combination with docetaxel.	• PK parameters of PF-06939999: sd - C_{max}, T_{max}, AUC_{last}, and as data permitted, $t_{½}$, AUC_{inf}, CL/F, and V_z/F. • PK parameters of PF-06939999: md - $C_{max,ss}$, $T_{max,ss}$, $AUC_{ss,\tau}$, and as data permitted, CL/F, V_{ss}/F, and R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$).
	Part 2: • To further evaluate the PK of PF-06939999 as a single agent and in combination with docetaxel at the respective RP2D. • To evaluate the effect of food on the PK of PF-06939999 (Part 2B).	• PK parameters of PF-06939999: C_{max}, T_{max} from single and multiple dose, and C_{trough} at selected timepoints. • PK parameters of PF-06939999 given with and without food: C_{max}, T_{max}, and AUC_{last}.

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Type	Objective	Endpoints
Efficacy	Part 1A: To evaluate preliminary anti-tumor activity.	• Tumor response: ORR and duration of response (DoR), as assessed using RECIST, version 1.1.
	Part 1B: • To evaluate preliminary anti-tumor activity.	• Tumor response: ORR, DoR, progression free survival (PFS) and time to progression (TTP), as assessed using RECIST, version 1.1.
	• To evaluate OS.	• Overall survival (OS), proportion of participants alive at 6 months, 1 year, and 2 years of PF-06939999 in combination with docetaxel.
	Part 2: • To evaluate anti-tumor activity of PF-06939999 monotherapy in participants with locally advanced or metastatic NSCLC, urothelial carcinoma, or HNSCC and in combination with docetaxel in locally advanced or metastatic NSCLC.	• Tumor response: DoR, PFS, and TTP as assessed by investigators using the RECIST version 1.1 of PF-06939999 monotherapy and in combination with docetaxel.
	• To evaluate OS.	• OS, proportion of participants alive at 6 months, 1 year, and 2 years of PF-06939999 monotherapy and in combination with docetaxel.
Exploratory*		

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Type	Objective	Endpoints
Pharmacodynamics (PD)	Part 1A: • To explore the PD effect of PF-06939999 treatment and PRMT5 pathway modulation in tumor biopsies or blood of participants with selected advanced metastatic solid tumors.	• Change in SDMA levels in tumor biopsy or blood and change in abundance of RNA transcripts and alternatively spliced gene patterns post PF-06939999 treatment.
	• To evaluate mutations, dysregulated expression of splicing factors, alternative splicing patterns, and RNA gene signatures as potential participant response markers.	• Alteration status (wild type vs mutated), alternative splicing patterns, and RNA gene signatures.
	Part 1B: • To explore the PD effect of PF-06939999 treatment and PRMT5 pathway modulation in tumor biopsies or blood of participants with selected advanced metastatic solid tumors.	• Change in SDMA levels in tumor biopsy or blood and change in abundance of RNA transcripts and alternatively spliced gene patterns post PF-06939999 treatment.
	• To evaluate mutations, dysregulated expression of splicing factors, alternative splicing patterns, and RNA gene signatures as potential participant response markers.	• Alteration status (wild type vs mutated), alternative splicing patterns and RNA gene signatures.
	Part 2: • To explore the PD effect of PF-06939999 treatment and PRMT5 pathway modulation in tumor biopsies or blood of participants with selected advanced metastatic solid tumors.	• Change in SDMA levels in tumor biopsy or blood and change in abundance of RNA transcripts and alternatively spliced gene patterns post PF-06939999 treatment.
	• To evaluate mutations, dysregulated expression of splicing factors, alternative splicing patterns, and RNA gene signatures as potential participant response markers.	• Alteration status (wild type vs. mutated), alternative splicing patterns and RNA gene signatures.

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Type	Objective	Endpoints
PK	Part 1B: To evaluate the PK of docetaxel when administered with PF-06939999. Part 2: To evaluate the PK of docetaxel when administered with PF-06939999 (Part 2D only).	• PK parameter of docetaxel: C_{max}. • PK parameter of docetaxel: C_{max}.
Patient reported outcomes (PROs)	Part 2: To assess PROs in participants with NSCLC (Parts 2A and 2D) receiving PF-06939999 monotherapy and in combination with docetaxel.	• Change from baseline in NSCLC-Symptom Assessment Questionnaire. • Patient global impression of severity (PGIS) to assess meaningful change in lung cancer symptoms.

*These exploratory evaluations were not included for this terminated study.

Methodology:

This was a Phase 1, open-label, multi-center, dose escalation and dose expansion study to assess the safety, PK, PD, and anti-tumor activity of PF-06939999 as a single agent and in combination in participants with locally advanced or metastatic selected solid tumor indications.

The overall study design was depicted in the schema below (Figure 1). The study was divided into 2 parts, dose escalation (Part 1) followed by dose expansion (Part 2).

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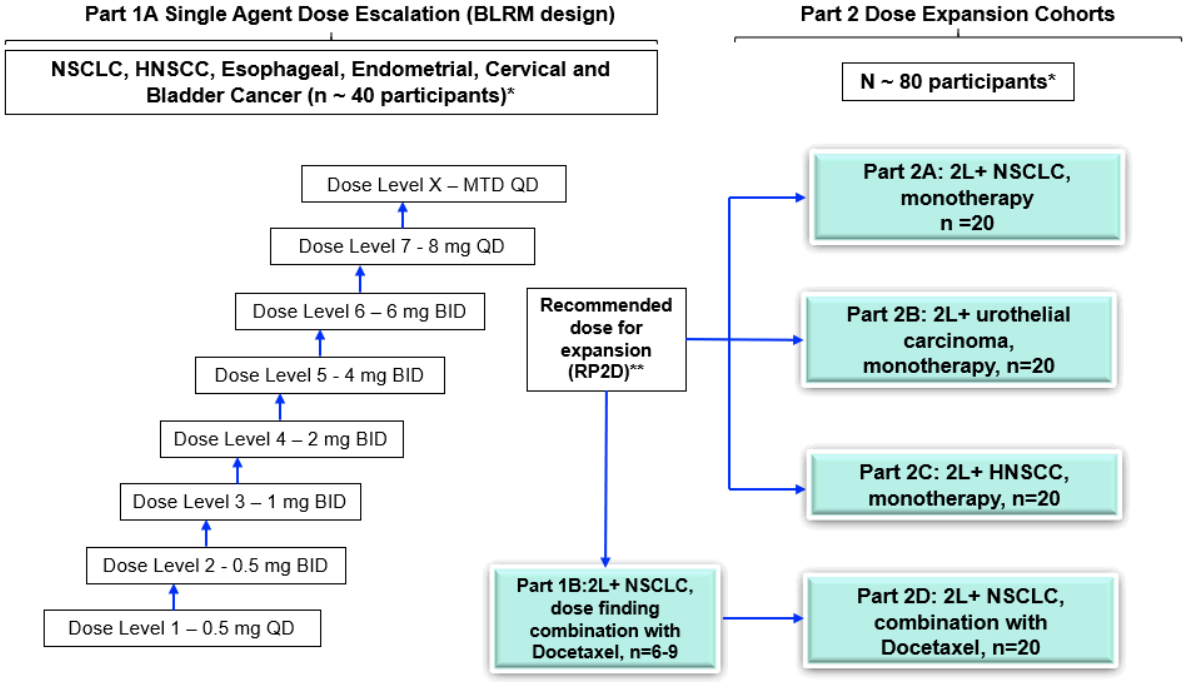
Figure 1. Study Schema



* 119 splicing factor mutations will be analyzed retrospectively on Part 1 and Part 2
** RP2D definition is provided in section 4.3.5

Number of Participants (planned and analyzed):

Planned: The overall sample size for Part 1A would be approximately 40 participants. Part 1B was expected to have 6-9 participants enrolled.

Each of the Parts 2A, 2B, 2C, and 2D would enroll approximately 20 participants.

Analyzed: A total of 54 participants were assigned to treatment and treated. Twenty-eight participants enrolled in Part 1A and 26 participants enrolled in Part 2.

All participants discontinued the treatment of PF-06939999. Thirty-five (64.8%) participants discontinued the follow-up phase.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Adult participants with selected advanced or metastatic solid tumors were enrolled.

Study Interventions, Dose, Mode of Administration, and Batch Numbers:

Participants enrolled in Parts 1A, 2A, 2B, and 2C received PF-06939999 orally daily on a continuous basis as monotherapy in 28-day cycles.

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The manufacturing lot numbers for the study intervention(s) dispensed in this study are provided in Table S1.

Table S1. Study Intervention Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
PF-06939999-09 0.5 mg Diamond White to Off-White Tablet	N/A	18-002322	0.5 mg	Tablet
PF-06939999-09 1 mg Round White to Off-White Tablet	19-DP-00046	19-002626	1 mg	Tablet
PF-06939999-09 1 mg Round White to Off-White Tablet	20-DP-00166	20-001683	1 mg	Tablet
PF-06939999-09 1 mg Round White to Off-White Tablet	N/A	18-002323	1 mg	Tablet
PF-06939999-09 5 mg Hexagonal White to Off-White Tablet	20-DP-00167	20-001684	5 mg	Tablet
PF-06939999-09 5 mg Hexagonal White to Off-White Tablet	N/A	18-002324	5 mg	Tablet

Duration of Study Intervention:

Participants enrolled in Parts 1A, 2A, 2B, and 2C would receive PF-06939999 orally daily on a continuous basis as monotherapy in 28-day cycles.

Summary of Results:

Demographic and Other Baseline Characteristics:

There were 31 male and 23 female participants; the mean (standard deviation [SD]) age of all participants was 63.35 (10.61) years. The majority of participants were White.

Exposure:

The median duration of treatment for all participants was 57.00 days (range: 12.00, 337.00). The majority of participants received treatment for more than 29 days.

Efficacy Results:

A total of 3 (6.8%) participants achieved objective response (all partial responses [PRs]); 2 in Part 1A (1 on PF-06939999 2 mg twice daily [BID] with HNSCC and 1 on PF-06939999

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4 mg BID with NSCLC) and 1 in Part 2A (2L + NSCLC, PF-06939999 6 mg once daily [QD]).

A total of 22 (50.0%) participants achieved disease control (complete response [CR] + PR + stable disease [SD] + Non-CR/Non- progressive disease [PD]). No clear trend of dose response relationship was observed.

The DoRs for the 2 confirmed responders in Part 1A were 4.3 and 4.7 months, respectively. The participant in Part 2A was censored due to start of new anti-cancer therapy

Safety Results:

Of the 462 all-causality treatment emergent adverse events (TEAEs) reported in 54 (100%) participants, 176 were considered to be treatment-related. All participants had at least 1 TEAE, whereas 45 (83.3%) participants had treatment-related AEs. Five (9.3%) participants discontinued study drug due to AEs. Thirty (55.6%) participants had maximum Grade 3-4 TEAEs. Twenty-two (40.7%) participants had SAEs, of whom, 3 (5.6%) participants had treatment-related SAEs. Nine (16.7%) participants had maximum Grade 5 TEAEs.

The most frequently reported all-causality TEAEs (≥30% of participants) were anaemia (44.4%), fatigue (42.6%), nausea (40.7%), and decreased appetite (31.5%).

A total of 39 (72.2%) participants had maximum CTCAE Grade ≥3 TEAEs. The most frequently reported Grade ≥3 TEAEs (≥10% of participants) were anaemia (31.5%), thrombocytopenia (14.8%) and disease progression (11.1%).

The most frequently reported treatment-related TEAEs (≥20% of participants) were anaemia (42.6%), nausea (31.5%), fatigue (27.8%), thrombocytopenia (27.8%), decreased appetite (24.1%) and dysgeusia (22.2%).

A total of 23 (42.6%) participants had maximum CTCAE Grade ≥3 treatment-related TEAEs. The most frequently reported Grade ≥3 treatment-related TEAEs (≥5% of participants) were anaemia (27.8%), thrombocytopenia (14.8%), platelet count decreased (7.4%) and fatigue (5.6%).

A total of 16 (29.6%) participants died. The main reason was disease under study (14 [25.9%] participants).

In Part 1, a total of 4 (16.7%) participants had DLTs reported. Two participants in PF-06939999 6 mg BID cohort had DLTs; One participant had Grade 4 thrombocytopenia and the other participant had Grade 3 thrombocytopenia. One participant in PF-06939999 8 mg QD cohort had 2 episodes of Grade 3 anaemia. One participant in PF-06939999 6 mg QD cohort had Grade 3 neutropenia.

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Three (5.7%) participants reported Grade 4 lymphocyte count decreased and 2 (3.8%) participants reported Grade 4 platelet count decreased, all of whom had grade increased compared to baseline.

Grade 4 creatinine increased, hypercalcemia and hypomagnesemia, were all reported in single participant, all of whom had grade increased compared to baseline.

Pharmacokinetic Results:

Single Dose Pharmacokinetics - Cycle 1 Day 1

Following single oral doses of 0.5 mg to 8 mg, PF-06939999 was absorbed rapidly with median T_{max} of 0.9 to 2.0 hours. In general, AUC_{last} and C_{max} appeared to increase in a dose-related manner. The PK parameters observed in Part 2 were consistent with the observation in Part 1 (6 mg QD). Variability in PF-06939999 exposure based on geometric coefficient of variation (CV)% ranged from 15% to 94% for AUC_{last} and 13% to 93% for $C_{max.}$ Due to limited PK data in the elimination phase, $t_{½}$ and CL/F could not be calculated.

Multiple Dose Pharmacokinetics - Cycle 1 Day 15

Following daily oral doses of 0.5 mg to 8 mg, PF-06939999 was absorbed rapidly with median T_{max} of 0.5 to 2.1 hours. Both AUC_{tau} and C_{max} appeared to increase in a dose-related manner. The R_{ac} ranged between 2.39 to 35.6. Variability in PF-06939999 exposure based on geometric CV% ranged from 31% to 98% for AUC_{tau} and 26% to 99% for $C_{max.}$ The PK parameters observed in Part 2 were consistent with the observation in Part 1 (6 mg QD).

Conclusions:

Overall, 28 participants received PF-06939999 at doses from 0.5 mg to 12 mg daily (QD or BID) during the dose escalation part (Part 1A). Twenty-four out of 28 participants were evaluable for DLTs, and 4/24 (17%) participants had DLTs including 2 with thrombocytopenia at 6 mg BID, 1 with anaemia at 8 mg QD and 1 with neutropenia at 6 mg QD.

Based on Part 1A safety, efficacy and clinical PK data of PF-06939999, 6 mg QD was chosen as the recommended dose for Part 2 monotherapy dose expansion cohorts.

The most frequently reported Grade ≥3 treatment-related TEAEs were anaemia (27.8%), thrombocytopenia (14.8%), platelet count decreased (7.4%) and fatigue (5.6%). Hematological toxicities are treatment-related, dose dependent and can be managed by dose interruption and reduction.

Following both single and multiple oral dosing, exposures of PF-06939999 based on AUC_{last} or AUC_{tau} and C_{max} appeared to increase with dose. The PK parameters observed in Part 2 were consistent with the observation in Part 1 (6 mg QD).

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Confirmed PRs were observed in 3 participants including 2 participants with NSCLC and 1 participant with HNSCC.

PF-06939999 was generally well-tolerated. The Phase 1 study C3851001 was terminated based on a business strategic decision.