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

Investigational Product Number:	PF-06939999
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	C3851001
Phase:	Phase 1

Short Title: A phase 1, open-label, dose escalation study of PF-06939999 in participants with selected advanced or metastatic solid tumors.

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amentment 3	11 June 2020	• Overarching rationale for Protocol Amendment 3: The C3851001 protocol is being amended to add Part 1B (PF-06939999 + docetaxel dose finding) and Part 2 (dose expansions) to the study to further evaluate the safety and tolerability of PF-06939999 monotherapy at RP2D as well as preliminary clinical efficacy in advanced or metastatic NSCLC, urothelial carcinoma (bladder cancer) and HNSCC, and PF-06939999 in combination with docetaxel in NSCLC. In addition, a food effect substudy has been added to assess the effect of food on the PK of PF-06939999. • Part 1B and Part 2 related changes and rationale: Provide study objectives, participant population (inclusion/exclusion criteria), study schema, protocol text, schedule of acitivies, PK/PD collection and statistical data analysis for Part 1B combination dose finding and Part 2 expansion cohorts. • Update to Overall Design – Protocol Summary, Overall Design, Sections 1.1, 1.2, 4.1, 4.1.1, 4.3.2, 9.2.1, 9.2.2, 10.9.2, and 10.9.3. • Added Schedule of Activities (SOA) tables (including ECG, pharmacokinetic [PK], and biomarker sampling schedules) Added separate tables for Part 1B and Part 2 [including food effect substudy]) Section 1.3.

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		• Added Objectives and Endpoints for Part 1B and Part 2 Dose Expansion (including food effect substudy), Sections 1.1, 3, 9.2.2, and 9.4.4.1.2. • Revised inclusion criteria to include details for participants in Part 1B and Part 2 (NSCLC, urothelial carcinoma, HNSCC). Section 5.1. • Revised exclusion criterion # 17 to exclude participatns with history of hypersensitivity reactions to docetaxel or drugs formulated with polysorbate 80. • Revised exlusion criterion # 18 indicating that Participants with HNSCC requiring drug administration via NG tube are eligible if they meet other criteria. • Added to text to Sections 8.5.1, and 8.5.2 to provide details for CCI [redacted] CCI and PF-06939999 urine PK. • Added details for food requirements for participants in the food effect sub-study to assess the effect of food on the PK of PF-06939999. Section 6.2.4.2. • Added patient reported outcomes as assessments in Part 2 for participants with NSCLC. Section 8.10. Rationale: To assess the impact of PRMT5 on lung cancer symptoms. • Updated sample size determination text. Section 9.2.

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		• Updated statistical analyses sections. Sections 9.4, 9.4.1, 9.4.2, 9.4.4.1.1, 9.4.4.1.2, 9.4.4.2. 9.4.4.3, 9.4.4.4, and Appendix 9.
		
		• Biomarker related changes and rationale: To optimize biomarker collection, timepoint and analysis to help clincial decision (PD biomarker) and potentially identify predictive biomarkers for patient selection; and remove suboptimal biomarker assay and anaylsis.
		
		• CCI [redacted]
		
		• Biomarker sample collection: Section 1.3 SoA, Table 2:
		
		  • Blood sample collection for RNAseq before starting treatment, while receiving treatment (Days 8 and 15 on Cycle 1, Cycle 2 Day 1), and end of treatment (EoT).
		  Rationale: For pharmacodynamic (PD) biomarker analysis.
		
		  • Remove plasma CCI [redacted] samples from 2 and 6 hour time points at Days 1 and 15; add EOT time point collection.
		  Rationale: Based on plasma CCI [redacted] data obtained from cohorts 1-5 during dose escalation study, there is no need to include those time

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		points. Added EOT time point to assess CCI rebound. • Added the strong recommendation for the collection of up to 5 on-treatment de novo biopsies in each arm for Part 2 dose expansion cohorts if state, local, and institutional policies allow. Rationale: To enable tumor PD biomarker analysis. • CCI [redacted] • Section 8.8.1. Revised first sentence by adding "and to assess PD activity of the tumor upon PF-06939999 treatment" after treatment with study drugs. • Section 8.8.2. Deleted serum from section title. • Section 8.9. Added clarifying language regarding who (investigators or qualified designees [Radiologist etc.]) will be evaluating tumor response. • Added bullet to Appendix 5 for the collection of whole blood samples for DNA sequencing.

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		• Protocol text and definition related changes and rationale: To provide details and clarifications on protocol language and definition and add protocol text for Part 1B combination dose finding and Part 2 expansion cohorts. • Updated Section 2. Summarized clinical data for PF-06939999 as of 17 October 2019. • Clarified specific details on the RP2D definition in Section 4.3.5. • Minor updates to last sentence of Section 4.2.6. • Updated end of study definition to increase clarity in Section 4.3.6. • Added details for study intervention administration. Section 6.1, 6.2, 6.2.1, 6.2.2. 6.2.3, 6.2.4, 6.2.4.1, 6.2.4.3. Rationale: To provide specific details for study treatment administration (PF-06939999 and docetaxel) for each study part including the administration of PF-0693999 via nasogastric tube for participants unable to swallow whole tablets. • Added details for allocation to investigational product for Part 2. Section 6.3.1. Rationale: To provide instructions for the sites for Part 2 allocation using IRT system. • Added text to allow for dexamethasone as a premedication for participants in

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		Part 1B and 2D receiving docetaxel. Section 6.5.1. Rationale: In order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions per docetaxel approved label (USPI). • Edited/added dose modification, interruption, and dose reduction text for Cohorts 1B and 2D and for Grade 3 toxicity (anemia) and thrombocytopenia (Table 14) Sections 6.6, 6.6.1, 6.6.2 and 6.6.3. Rationale: To provide details for Parts 1B and Part 2. To specify the reduction of 1 dose level and clarify instructions for dose modification for Grade 3 thrombocytopenia for recurrent toxicity. • To comply with protocol template updates May 2020, Section 7.1 was updated to provide examples of specific reasons for discontinuation of study intervention and added instructional text in the event of discontinuation of study intervention. • Appendix 2: Added RBC and MCV to hematology column and reticulocyte count and peripheral blood smear to serology column and included footnotes for each. Revised hepatitis B footnote (deleted non Hepatitis B text). • Updated adverse event, serious adverse event, medication error, and treatment of overdose language to align with the

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		May 2020 protocol template. The following were updated: • Section 8.3.1: Added paragraph describing SAE collection during the long-term follow-up period. Deleted "Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section". • Section 8.3.1.2: Added text to first and second paragraph clarifying the active collection period as beginning after informed consent is obtained and that the investigator is to to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant. • Section 8.4: Updated reporting timeframe for overdose from "immediately" to "within 24 hours". Updated item 2. Laboratory abnormalities are to be monitored for for at least 5 half-lives or 28 calendar days after the overdose of PF-06939999 (whichever is longer be detected systemically (at least 30 days). • Section 8.3.6: Updated the reporting timeframe for medication dosing erros from "immediately" to "within 24 hours". • Appendix 3. Section 10.3.2: Added text regarding suspected transmission

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		via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. Section 10.3.3: Added "All AEs/SAEs associated with exposure during pregnancy or breastfeeding" to the table in the recorded on the CRF column and 'Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure' in the Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness column • Section 10.3.4. Deleted non-applicable text regarding the reporting of serious adverse events (SAEs) using an electronic data collection tool. Appendix 3, Section 10.3.4. Rationale: A CT SAE Report Form is being used in this study, not an electronic data collection tool. • Added Section 10.13 Appendix 13 to provide guidance during public emergencies, including the COVID-19 pandemic. Added references to this appendix in Sections 5, 7.1.1, and 8.2. Incorporated language from Protocol Administrative Change Letter dated 26 March 2020. • Aligned Section 9.5.1 data monitoring committee language to align with added text in protocol summary. • Administrative changes or corrections including updates to list of

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		abbreviations and references as applicable. Sections: global.
Amendment 2	16 December 2019	• Changes to allow once a day (QD) dosing in the upcoming dose escalation cohorts: Section 1 protocol summary (1.1 synopsis, 1.2 study schema, 1.3 SoA), 4.1 overall design, 4.3 justification for dose. Rationale: To test additional dosing regimen (QD) for improving patient convenience and compliance. • Changes Pharmacokinetic (PK) sample collection timepoints to capture trough concentrations for QD and BID dosing regimens: section 1.3 SoA table 2 (add Day 16 PK sample collection for QD dosing; add PK sample collection 12 hours post dose on Day 1 and Day 15 for BID dosing). Rationale: To better characterize PK profiles for both QD and BID dosing regimens. • Change biomarker sample collection: section 1.3 SoA table 2: a. Delete whole blood for circulating tumor cell collection. Rationale: The circulating tumor cell analysis assay was not sensitive and informative. b. Add blood sample collection for RNAseq before starting treatment, while receiving treatment (day 8 on cycle 1, 2 and 3, SoA table 2), and post treatment.

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		Rationale: For splicing factor and biomarker analysisAdd 1 blood sample collection for plasma CCI . • Rationale: To further characterize plasma CCI profiles at steady state. • Optional on-treatment biopsies for Part 1 dose escalation.
Amendment 1	15 January 2019	• Change in starting dose and maximum percent dose escalation increment – Protocol Summary, Overall Design, Sections 1.1, 1.2, 1.3, 2.2.4, 4.1, 4.3, 6.2.5, 9.4.1 and 10.9.2. • Rationale – FDA request to change the starting dose to approximately 1/6 the HED of the HNSTD/NOAEL in dogs and a maximum dose escalation increment of 100%. • Update to Overall Design – Protocol Summary, Overall Design, Sections 1.1, 1.2, 4.1, 4.3.2, 9.2.1 and 10.9.2. • Rationale – Increased number of cohorts and participants resulting from change in starting dose and maximum dose escalation increment of 100%. • Update to Section 1.2, Table 1 SOA and Table 2 PK//Biomarker Sampling Schedule. Rationale – FDA request and other clarifications. • Removal of specific references to Part 2 (dose expansion) of the

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Document	**Version Date**	**Summary of Changes and Rationale**
		study -Protocol Summary, Overall Design, Sections 1.1, 1.2, and 4.1. Rationale – FDA request. • Include solubility data at different pH levels and no anticipated impact in absorption – Sections 2.2.3. and 6.5.5. Rationale – FDA request. • Updated safety margins – Sections 2.2.4 and 4.3.1. Rationale – New starting dose. • Update to neutropenia DLT and dose reduction DLT added – Sections 4.3.3 and 6.6.2. Rationale – FDA request. • Update to inclusion 2 – Section 5.1. Rationale – FDA request. • Exclusion of current use of strong P-gp or BCRP inhibitors and potential drug-drug interaction – Sections 5.2. and 6.5.1. Rationale – FDA request. • Update simulation of the BLRM model for new starting dose – Section 10.9.2. Rationale – FDA request. • Administrative changes or corrections.
Original protocol	12 November 2018	Not applicable (N/A)

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

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A phase 1, open-label, dose escalation study of PF-06939999 in participants with selected advanced or metastatic solid tumors.

Rationale: PF-06939999 is a potent and selective small molecule inhibitor of protein arginine methyltransferase 5 (PRMT5), which is overexpressed in hematologic malignancies and solid tumors. PRMT5 methylates multiple substrates with a variety of biological functions known to be dysregulated in cancer including transcription, cell signaling, messenger ribonucleic acid (mRNA) translation, deoxyribonucleic acid (DNA) damage, receptor trafficking, protein stability, and pre-mRNA splicing. Proliferation of multiple cancer cell lines was reduced in response to treatment with PF-06939999 and this translated to robust tumor growth inhibition in vivo as a single agent.

This is 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 maxium tolerable dose (MTD) and recommended dose for expansion (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.

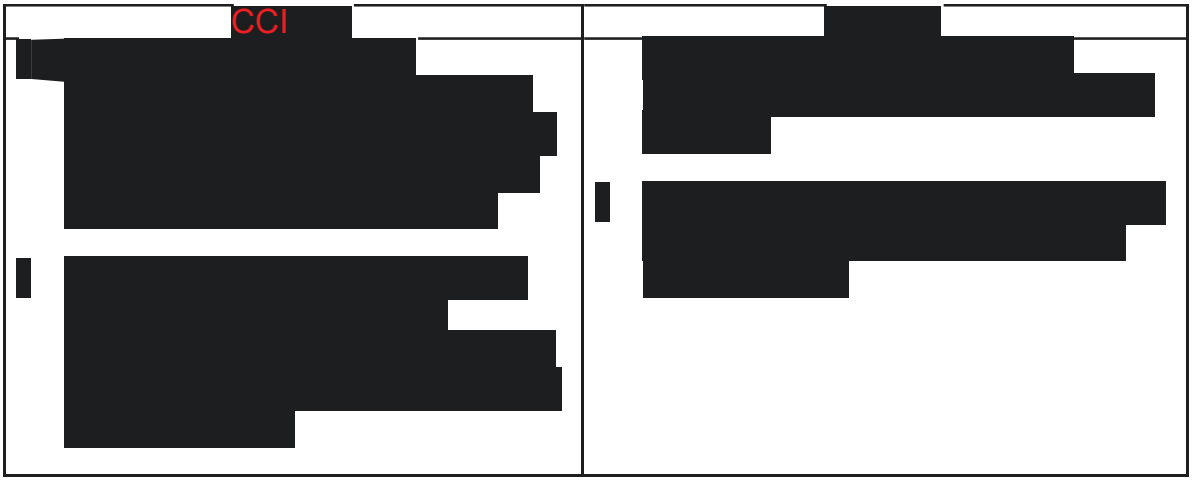
Part 1A Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• 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 or Maximum Administered Dose (MAD) and select the RP2D/schedule.	• Dose Limiting Toxicities (DLTs). • Adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [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.
Secondary:	**Secondary:**
• To characterize the single and multiple dose PK of PF-06939999 following oral administration. • To evaluate preliminary anti-tumor activity.	• PK parameters of PF-06939999: Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{1/2}$, AUC_{inf}, CL/F, and Vz/F. • PK parameters of PF-06939999: Multiple Dose (MD) – $C_{max,ss}$, $T_{max,ss}$, $AUC_{ss,\tau}$, and as data permit, CL/F, Vss/F, and Rac ($AUC_{ss,\tau}/AUC_{sd,\tau}$). • Tumor response: Objective response rate (ORR) and duration of response (DoR), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) Section 10.11.
• CCI [redacted]	[redacted]
[redacted]	[redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]

Part 1B Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• 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.
Secondary:	**Secondary:**
• To characterize the single and multiple dose PK of PF-06939999 when administered in combination with docetaxel. • To evaluate preliminary anti-tumor activity. • To evaluate overall survivial (OS).	• PK parameters of PF-06939999: SD - C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{1/2}$, AUC_{inf}, CL/F, and Vz/F. • PK parameters of PF-06939999: MD – $C_{max,ss}$, $T_{max,ss}$, $AUC_{ss,\tau}$, and as data permit, CL/F, Vss/F, and Rac ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$). • Tumor response: ORR,DoR, progression-free survival (PFS) and time to progression (TTP), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) Section 10.11. • OS, proportion of participants alive at 6 months, 1 year, and 2 years of PF-06939999 in combination with docetaxel.
• CCI [redacted]	[redacted]
[redacted]	[redacted]



Part 2 Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• 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.
• To estimate clinical efficacy by 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 the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) Section 10.11.
Secondary:	**Secondary:**
• To further evaluate the PK of PF-06939999 as a single agent and in combination with docetaxel at the respective RP2D.	• PK parameters of PF-06939999: C_{max}, T_{max} from single and multiple dose, and C_{trough} at selected timepoints.

Objectives	Endpoints
• To evaluate the effect of food on the PK of PF-06939999 (Part 2B). • 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. • To evaluate overall survival (OS).	• PK parameters of PF-06939999 given with and without food: C_{max}, T_{max}, and AUC_{last}. • Tumor response:Duration of response (DoR) progression free survival (PFS) and time to progression (TTP) as assessed by investigators using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) Section 10.11 of PF-06939999 monotherapy and in combination with docetaxel. • OS, proportion of participants alive at 6 months, 1 year, and 2 years of PF-06939999 monotherapy and in combination with docetaxel.
• CCI [redacted]	[redacted]
[redacted]	[redacted]

Overall Design:

The study is divided into 2 parts: dose escalation (Part 1) followed by dose expansion (Part 2). The overall study design is depicted in the schema (Section 1.2).

Part 1 dose escalation further divides into Part 1A and Part 1B. Part 1A contains dose escalation as a single agent in participants with locally advanced or metastatic head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), esophageal cancer, endometrial cancer, cervical cancer, or bladder cancer who are resistant or intolerant to standard therapy or for whom no standard therapy is available, to determine the MTD and RP2D. Part 1B contains dose finding of PF-06939999 in combination with docetaxel in locally advanced or metastatic NSCLC.

Part 1A (dose escalation) plans to enroll approximately 40 participants in different dose level cohorts. Bayesian Logistic Regression Model (BLRM) was used to determine the maximum tolerable dose (MTD). Participants have received escalating doses of PF-06939999 starting from 0.5 mg once daily. Dose limiting toxicities (DLT) were assessed during Cycle 1 (the first 28 days) to inform dose escalation and determine the MTD. Cohort size was approximately 3 participants, with at least 1 DLT-evaluable participant per cohort in the first 3 cohorts and at least 2 DLT evaluable participants per cohort in the remaining cohorts.

For Part 1A, PF-06939999 was administered as a single agent, orally QD for the first cohort then BID or QD in 28 day cycles for subsequent cohorts on a continuous basis until disease progression, participant refusal, or unacceptable toxicity. The estimated length of treatment is approximately 2 years. Any additional treatment with PF-06939999 beyond 2 years shall be discussed and approved by the Sponsor. The actual number of participants enrolled in Part 1A depends on the tolerability of PF-06939999 and the number of dose levels required to identify the MTD and and recommended dose for expansion (RP2D). RP2D definition is provided in Section 4.2.9. After the selecton of recommended dose for expansion (RP2D) for monotherapy, Part 2 (dose expansion) will evaluate the safety and antitumor activity of PF-06939999 monotherapy at the single agent RP2D. Part 2 dose expansion will consist of 3 monotherapy cohorts in locally advanced or metastatic NSCLC (Part 2A), urothelial cancinoma (Part 2B) and HNSCC (Part 2C) repspectively and 1 combination cohort with docetaxel in locally advanced or metastatic NSCLC (Part 2D). The participant population is briefly described below and detailed in the inclusion criteria (Section 5.1).

Monotherapy expansion cohorts Part 2A, 2B, and 2C:

- Part 2A: Participants with NSCLC (n=20) who have progressed after at least 1 line of checkpoint inhibitors and 1 line of platinum based chemotherapy (2L+).

- Part 2B: Participants with urothelial carcinoma (n=20) who have progressed after at least 1 line of standard of care systemic chemotherapy (cisplatin/carboplatin+ Gemcitabine; or methotrexate/vinblastine sulfate/doxorubicin hydrochloride/cisplatin [MVAC]) and checkpoint inhibitor (2L+).

- Part 2C: Participants with HNSCC (n=20) who have progressed after at least 1 line of standard of care systemic chemotherapy and 1 line of checkpoint inhibitor (2L+).

The collection of on-treatment biopsies in up to 5 participants per arm is strongly recommended if state, local, and institutional policies allow.

Combination expansion cohort Part 2D (PF-06939999 in combination with docetaxel):

- Part 2D: Participants with NSCLC (n=20) who have progressed after at least 1 line of checkpoint inhibitor and 1 line of platinum based chemotherapy (2L+).

Furthermore, the PF-06939999 in combination with docetaxel will be evaluated in locally advanced or metastatic NSCLC (Part 1B combination dose finding and Part 2D combination dose expansion). In Part 1B, the PF-06939999 in combination with docetaxel will be evaluated in participants with locally advanced or metastatic NSCLC who have progressed after at least 1 line of checkpoint inhibitor and platinum based chemotherapy (2L+). BLRM specifically designed for combinations and guided by EWOC principle will be used for dose finding. PF-06939999 may start at 1 dose level below single agent RP2D (RP2D-1) with fixed dose of docetaxel per standard of care. Dose limiting toxicities (DLT) will be assessed during the first 28 days to inform dose escalation and determine the MTD. Cohort size will be approximately 3 participants with at least 3 DLT-evaluable participants. In addition, depending on the safety findings in Part 1A, and whether significant overlapping toxicities are expected in combination, the starting dose of PF-06939999 may be further escalated or de-escalated but will not exceed the single agent RP2D. It is anticipated that Part 1B will enroll approximately 6-9 participants.

Once the RP2D for the combination has been determined, additional NSCLC participants will be enrolled under Part 2D combination expansion cohort until a total of 20 participants have been evaluated at the combination RP2D (Part 1B participants dosed at the combination RP2D will be counted towards the total of 20 participants). The collection of on-treatment biopsies in up to 5 participants is strongly recommended if state, local, and institutional policies allow.

Food effect will be assessed in at least 6 participants (but no more than 15 participants) from the urothelial carcinoma monotherapy cohort.

Approximately 80 participants are expected to be enrolled in Part 2.

All participants will undergo up to 28 days of screening prior to study entry. Eligible participants will then receive treatment with PF-06939999 for up to 2 years, or until disease progression, unacceptable toxicities, a decision by the participant (withdrawal of consent or no longer willing to participate), or investigator to discontinue treatment or study termination. Any additional treatment beyond 2 years shall be discussed and approved by the sponsor. At least 28 days and no more than 35 days after end of treatment all participants will complete a Safety follow up visit. Participants in Part 1B and Part 2 dose expansion

cohorts will be contacted by telephone every 12 weeks for survival data collection until end of trial (2 years from last participant first dose).

Data Monitoring Committee:

This is an open label non-randomized Phase 1 study. This study will not use a data monitoring committee (DMC).

Discussions between the investigators and the sponsor regarding safety will occur in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and determine if further participant enrollment is appropriate.

Statistical Methods:

Bayesian adaptive approach: The dose escalation in the Part 1A and Part 1B of the study will be guided by a Bayesian analysis of Cycle 1 dose limiting toxicity (DLT) data for PF-06939999. Toxicity is modelled using 2-parameter logistic regression in Part 1A and 5-parameter model specifically designed for combinations in Part 1B for the probability of a participant experiencing a DLT at the given dose.

Assessment of participant risk: After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-06939999 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0, 0.16]
Targeted dosing:	[0.16, 0.33]
Overdosing:	[0.33, 1]

The escalation with overdose control (EWOC) principle: Dosing decisions in both Part 1A and Part 1B are guided by the escalation with overdose control principal.[1] A dose may only be used for newly enrolled participants if the risk of over-dosing at that dose is less than 25%.

Prior distributions in Part 1A for BID regimen: Weekly informative prior distribution based on pre-clinical/expert opinion information will be chosen for the logistic parameters.

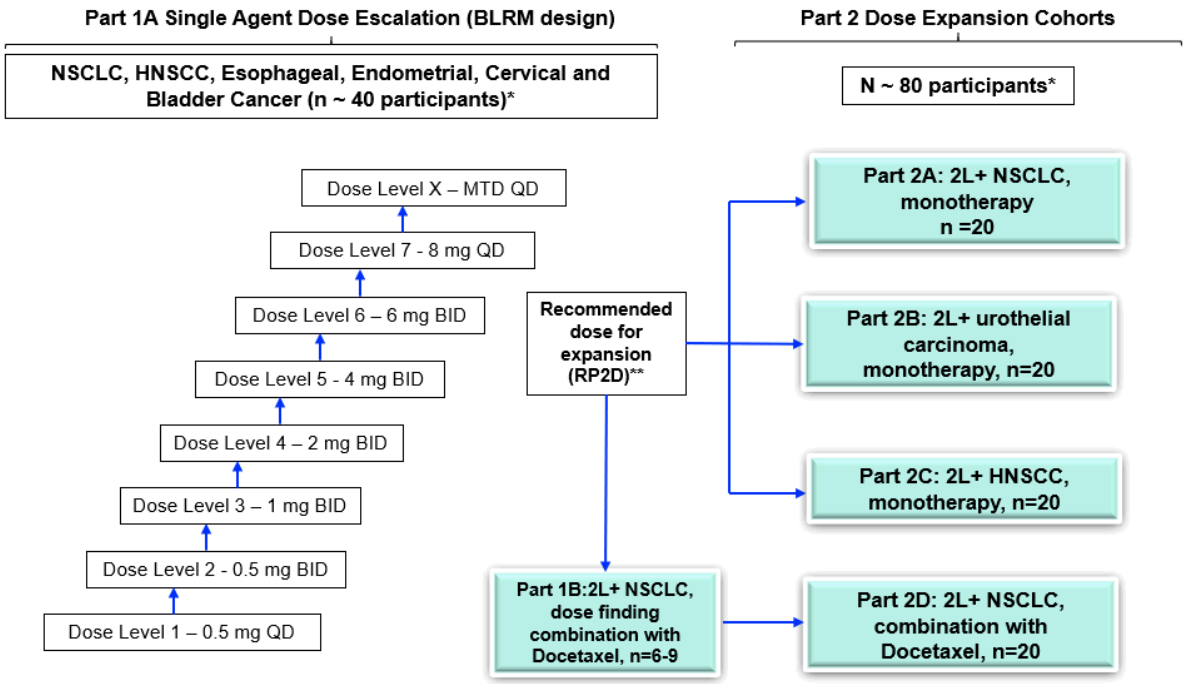
Prior distributions in Part 1A QD regimen: The data from BID regimen have been used to set up a meta-analystic prior (MAP) and a mixture of the MAP and weakly informative prior has been used for Part 1A QD regimen. Details are described in Appendix 10.9.

Prior distributions in Part 1B: A meta-analytic-predictive (MAP) approach will be used to derive the prior distribution for model parameters used in Part 1B based on the data collected in Part 1A and original dose escalation studies of docetaxel. A full description of the application of the MAP approach to derive the prior distributions of the model parameters is given in Technical Supplement to Appendix 10.9.

Efficacy analysis:

Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, dose on Day 1, tumor response at each visit, and best overall response. In addition, progression date, death date, date of first response and last tumor assessment date and date of last contact will be listed. Part 1B and Part 2: The Kaplan-Meier methods will be used to analyze all time to event endpoints. Proportion of participants alive at 6 months, 1 year, and 2 years will be also reported.

1.2. 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

1.3. Schedule of Activities (SoA)

Table 1provides an overview of the protocol visits and procedures for Part 1A (dose escalation PF-06939999 monotherapy).

Table 2 provides an overview of the protocol visits and procedures for Part 1B (dose finding PF-06939999 + docetaxel).

Table 3 provides and overview of the protocol visits and procedures for Parts 2A, 2B, and 2C (dose expansion, PF-06939999 monotherapy).

Table 4 provides and overview of the protocol visits and procedures for Part 2D, (dose expansion, PF-06939999 + docetaxel).

ECG, Pharmacokinetic (PK) and Biomarker Sampling Schedules

Table 5 provides an overview of the ECG, PK, and biomarker sampling schedule for Part 1A (dose escalation PF-06939999 monotherapy).

Table 6 provides an overview of the ECG, PK, and biomarker sampling schedule for Part 1B (dose finding, PF-06939999 + docetaxel).

Table 7 provides an overview of the ECG, PK, and biomarker sampling schedule for Parts 2A, 2B, and 2C (dose expansion PF-06939999 monotherapy) except for food effect sub-study.

Table 8 provides and overview of the ECG, PK, and biomarker sampling schedule for the food effect sub-study participants.

Table 9 provides and overview of the ECG, PK and biomarker sampling schedule for Part 2D (dose expansion PF-06939999 + docetaxel).

Refer to Section 8 of the protocol for detailed information on each assessment required for compliance with the protocol for each study part. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA tables, in order to conduct evaluations or assessments required to protect the well being of the participant.

Table 1. Study Related Procedures: Part 1A (dose escalation PF-06939999 monotherapy)

	Screen[1] (≤28 days)		Cycle 1 (28 days)					Subsequent Cycles (28 Days per cycle)		End of Treatment (EOT)[21]	Safety follow-Up visit[22]
Protocol Activity		Day 1	Day 2a	Day 8	Day 15	Day 16[a]	Day 22	Day 1	Day 15		
Visit Window				±2 day	±2 day		±2 day	±2 days	±2 day		
Informed Consent[2]	X										
Medical History[3]	X										
Physical Examination[4]	X	X		X	X			X	X	X	X
Baseline Signs and Symptoms5		X									
Height	X										
Weight	X	X						X		X	
Vital Signs[6]	X	X		X	X			X	X	X	X
ECOG Performance Status[7]	X	X						X		X	
Contraception check[8]	X	X						X		X	
12-lead ECG		See Table 6 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1A									
Laboratory Studies											
Hematology[9]	X	X		X	X		X	X	X	X	X
Blood Chemistry[10]	X	X		X	X		X	X	X	X	X
Coagulation[11]	X	X						X		X	X
Urinalysis[12]	X	X								X	X
Pregnancy Test[13]	X	X								X	X
Viral disease screen [Hepatitis B, C, and HIV tests][14]	X										
Registration and Treatments											
Registration[15]	X										
PF-06939999 Treatment[16]		Day 1 to Day 28						Day 1 to Day 28			
Tumor Assessments											
CT or MRI Scans[17]	X	Every 8 weeks for the first 6 months, then every 12 weeks. See footnote 17									

Table 1. Study Related Procedures: Part 1A (dose escalation PF-06939999 monotherapy)

	Screen[1] (≤28 days)	Cycle 1 (28 days)						Subsequent Cycles (28 Days per cycle)		End of Treatment (EOT)[21]	Safety follow-Up visit[22]
Protocol Activity		Day 1	Day 2a	Day 8	Day 15	Day 16[a]	Day 22	Day 1	Day 15		
Visit Window				±2 day	±2 day		±2 day	±2 days	±2 day		
Other Clinical Assessments											
Serious and Non-serious Adverse Event Monitoring[18]	X	→									
Concomitant Medications[19]	X	X	X	X	X		X	X	X	X	X
Archival or De Novo Tumor Biopsy[20]	X										
Other Laboratory Assessments											
Blood for Biomarker Analyses		See Table 6 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1A									
Plasma for PF-06939999 PK and CCI		See Table 6 ECG, ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1A									
Banked Biospecimen		See Table 6 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1A									
Serum for CA-125 [Cervical and Endometrial Cancer only]		X						X			
28- to 35-day Follow-up											X

Abbreviations: → ongoing/continuous event; C = Cycle; CT = computed tomography;CA-125 = cancer antigen 125 ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; CCI

Footnotes (Schedule of Activities)

a. Days 2 and 16 are Cycle 1 only to correspond with PK collection days for QD dosing regimen only. No clinical assessments required.
1. Screening: To be conducted within 28 days prior to treatment start.
2. Informed Consent: Must be obtained prior to undergoing any study specific procedures.
3. Medical History: To include date of diagnosis and information on prior anti-tumor treatments, surgeries, radiotherapy and recurrence date.
4. Physical Examination: Examination of major body systems including body weight. Height is measured at screening visit only.
5. Baseline Signs and Symptoms: Participants will be asked about any signs and symptoms experienced within 14 days prior to C1D1.
6. Vital Signs: Includes temperature, blood pressure (BP), and pulse rate (PR) to be recorded in the sitting position or semi-recumbent position (however the position should be maintainted throughout the study) after approximately 5 minutes of rest.
7. ECOG Performance Status: ECOG performance scale is available in Section 10.10 Appendix 10.

8. The participant will be informed of the need to use highly effective contraception consistently and correctly. The conversation and participant's affirmation will be documented in the participant's chart.
9. Hematology: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. The list of required laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
10. Blood Chemistry: All chemistry laboratory tests included in Section 10.2 Table 15) are required at every protocol chemistry required time point. No need to repeat full blood chemistry on C1D1 if screening assessment performed within 7 days prior to that date. During Cycle 1, liver function tests, creatinine and amylase/lipase must be checked on Days 8, 15 and 22 to assess for events qualifying as dose limiting toxicities (DLTs). For participants with treatment emergent Grade ≥3 AST/ALT, close clinical monitoring with an increased frequency of relevant blood testing should be undertaken, eg, every 2-3 days.
11. Coagulation: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. To be performed per the schedule of activities and as clinically indicated after baseline. The list of required laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
12. Urinalysis: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. To be performed as clinically indicated after baseline. The list of required urine laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
13. Pregnancy Test: Pregnancy tests (serum/urine) for female participants of childbearing potential. Test may also be repeated as per request of Institutional Review Board/Independent Ethics Committee (IRB/IECs), if required by local regulations. FSH will be done at Screening only in females who are amenorrheic for at least 12 consecutive months. See Section 8.2.5 Pregnancy Testing for further details.
14. Viral disease screening tests: Hepatitis B testing includes: Hepatitis B Surface Ag (HBsAg), Total Hepatitis B Core Ab (anti-HBc), Hepatitis B Surface Ab (anti-HBs) as clinically indicated IgM antibody to hepatitis B core antigen (IgM anti-HBc), HCV Ab, and HIV to be conducted by local laboratory where required by local regulations or if warranted by participant history.
15. Registration: Participant identification number and dose level allocation to be operated by the Sponsor (see Section 6.3.1 Allocation to Investigational Product). Allocation to Investigational Product).
16. PF-06939999 treatment: Initially PF-06939999 will be administered as a single agent, orally, once daily (QD) for the first cohort then twice a day (BID) or daily (QD) for all subsequent cohorts in 28 day cycles on a continuous basis. Additional dosing frequency may be considered in the study if supported by emerging clinical data. Treatment will continue until PD, unacceptable toxicity or participant refusal, whichever occurs first. If PD occurs during treatment, continuation of study drug may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor. The participant will be reminded not to take their morning dose at home on PK days, but to bring their bottle into clinic so that study drug may be administered after study visit assessments are completed, and PK samples have been collected.
17. Tumor Assessments: Tumor assessments will include all known or suspected disease sites (eg, including CT or MRI of neck with contrast for HNSCC). CT or MRI scans are to be performed every 8 weeks for the first 6 months, then every 12 weeks until the end of the safety follow up visit or participant withdrawal from the study. Efficacy assessments start on Cycle 2 Day 28. The allowable time window for disease assessments is ±7 days while on treatment and up to 7 days for screening (ie, the screening time window is up to 35 days prior to registration). Brain CT or MRI scan for participants with known or suspected brain metastases; bone scan and/or bone X-rays for participants with known or suspected bone metastases. Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation. When the study treatment is discontinued for reasons other than disease progression or participant refusal, participants will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) participant refusal or (c) start of another anti-cancer treatment, whichever occurs first. Tumor assessments should be fixed according to the calendar, regardless of treatment delays.

18. Adverse Events: The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product. For participants who are screen failures, the active collection period ends when screen failure status is determined. See Section 8.3.1.
19. Concomitant Medications: Concomitant medications and treatments must be recorded on the CRF.
20. Archival or de novo Tumor Biopsy: Tumor biospecimens from archival and/or de novo biopsies will be required at study entry. Post-treatment biopsies are not required for Part 1. A summary of planned analysis for core needle biopsies is provided in Section 8.8.1.
21. End of Treatment or for early discontinuation: Obtain these assessments if not completed in the last week. Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation.
22. Safety follow up visit: At least 28 days, and no more than 35 days after discontinuation of treatment, participants will return to undergo review of concomitant medications and assessment for resolution of any treatment related toxicity. Participants continuing to experience toxicity 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. When the study treatment is discontinued for reasons other than disease progression or participant refusal, participants will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) participant refusal or (c) start of another anti-cancer treatment, (whichever occurred first).

Table 2. Study Related Procedures: Part 1B (dose finding PF-06939999 + docetaxel)

	Screen[1] (≤28 days)	Cycle 1 (21 days)					Cycle 2 (21 days)		Subsequent Cycles (21 Days per cycle)	End of Treatment (EOT)[21]	Safety Follow-Up Visit[22]	Long-Term Survival Follow-up[23]
Protocol Activity		Day 1	Day 2	Day 8	Day 15	Day 16	Day 1	Day 8	Day 1			
Visit Window				±2 days	±2 days	±2 days	±2 days	±2 days	±2 days			
Informed Consent[2]	X											
Medical History[3]	X											
Physical Examination[4]	X	X		X	X		X	X	X	X	X	
Baseline Signs and Symptoms[5]		X										
Height	X											
Weight	X	X					X		X	X		
Vital Signs[6]	X	X		X	X		X	X	X	X	X	
ECOG Performance Status[7]	X	X					X		X	X		
Contraception check[8]	X	X					X		X	X		
12-lead ECG		See Table 6 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1B										
Laboratory Studies												
Hematology[9]	X	X		X	X		X	X	X	X	X	
Reticulocyte count[9]		X					X		X			
Blood Chemistry[10]	X	X		X	X		X	X	X	X	X	
Coagulation[11]	X	X					X		X	X	X	
Urinalysis[11]	X	X								X	X	
Pregnancy Test[12]	X	X								X	X	
Viral disease screen Hepatitis B, C, and HIV tests][13]	X											
Registration and Treatments												
Registration[14]	X											

Table 2. Study Related Procedures: Part 1B (dose finding PF-06939999 + docetaxel)

	Screen[1] (≤28 days)	Cycle 1 (21 days)					Cycle 2 (21 days)		Subsequent Cycles (21 Days per cycle)	End of Treatment (EOT)[21]	Safety Follow-Up Visit[22]	Long-Term Survival Follow-up[23]
Protocol Activity		Day 1	Day 2	Day 8	Day 15	Day 16	Day 1	Day 8	Day 1			
Visit Window				±2 days	±2 days	±2 days	±2 days	±2 days	±2 days			
Docetaxel treatment[15]		X					X		X			
PF-06939999 Treatment[16]		Day 1 to Day 21					Day 1 to Day 21		Day 1 to Day 21			
Tumor Assessments												
CT or MRI Scans[17]	X	Every 6 weeks for the first 9 months, then every 12 weeks. See footnote 17										
Other Clinical Assessments												
Serious and Non-serious Adverse Event Monitoring[18]	X	→										
Concomitant Medications[19]	X	X		X	X		X	X	X	X		
Archival or De Novo Tumor Biopsy[20]	X								X (C3 only, optional)			
Other Laboratory Assessments												
Blood for Biomarker Analyses		See Table 6 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1B										
Plasma for PF-06939999 PK and [redacted]		See Table 6 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1B										
Banked Biospecimen		See Table 6 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1B										
Other Assessments												
28- to 35-day Follow-up											X	
Overall Survival												X

Footnotes (Schedule of Activities)
1. Screening: To be conducted within 28 days prior to treatment start.
2. Informed Consent: Must be obtained prior to undergoing any study specific procedures.

3. Medical History: To include smoking, alcohol abuse (ETOH) and human papilloma virus (HPV) status, date of diagnosis or primary disease and information on prior anti-tumor treatments, surgeries, radiotherapy and recurrence date as as well as prior tumor genomic testing resport if available.
4. Physical Examination: Examination of major body systems including body weight. Height is measured at screening visit only.
5. Baseline Signs and Symptoms: Participants will be asked about any signs and symptoms experienced within 14 days prior to C1D1.
6. Vital Signs: Includes temperature, blood pressure (BP), and pulse rate (PR) to be recorded in the sitting position or semi-recumbent position (however the position should be maintainted throughout the study) after approximately 5 minutes of rest.
7. ECOG Performance Status: ECOG performance scale is available in Section 10.10 Appendix 10.
8. The participant will be informed of the need to use highly effective contraception consistently and correctly. The conversation and participant's affirmation will be documented in the participant's chart.
9. Hematology: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Grade ≥3 thrombocytopenia should trigger a blood smear for differential. Reticulocyte count should be performed per schedule of acitivity. In addition, Grade≥3 anemia should trigger a recticulcyte count if not done within 7 days. The list of required laboratory tests is provided in Section 10.2 Appendix 2.
10. Blood Chemistry: All chemistry laboratory tests included in Section 10.2 Appendix 2 are required at every protocol chemistry required time point. No need to repeat full blood chemistry on C1D1 if screening assessment performed within 7 days prior to that date. Liver function tests, creatinine and amylase/lipase must be checked on Cycle 1 Days 8 and,15 and on Cycle2 Days 1 and 8 to assess for events qualifying as dose limiting toxicities (DLTs). For participants with treatment emergent Grade ≥3 AST/ALT, close clinical monitoring with an increased frequency of relevant blood testing should be undertaken, eg, every 2-3 days. Coagulation: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. To be performed per the schedule of activities and as clinically indicated after baseline. The list of required laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
11. Urinalysis: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. To be performed as clinically indicated after baseline. The list of required urine laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
12. Pregnancy Test: Pregnancy tests (serum/urine) for female participants of childbearing potential. Test may also be repeated as per request of Institutional Review Board/Independent Ethics Committee (IRB/IECs), if required by local regulations. FSH will be done at Screening only in females who are amenorrheic for at least 12 consecutive months. See Section 8.2.5 Pregnancy Testing for further details.
13. Viral disease screening tests: Hepatitis B testing includes: Hepatitis B Surface Ag (HBsAg), Total Hepatitis B Core Ab (anti-HBc), Hepatitis B Surface Ab (anti-HBs) as clinically indicated IgM antibody to hepatitis B core antigen (IgM anti-HBc), HCV Ab, and HIV to be conducted by local laboratory where required by local regulations or if warranted by participant history.
14. Registration: Participant identification number and dose level allocation to be operated by the Sponsor (see Section 6.3.1 Allocation to Investigational Product).
15. Docetaxel will be administered at 75 mg/m2 intravenously over 1 hour on Day 1 of each 21 day cycle until disease progression unacceptable toxicity or participant refusal, whichever occurs first, All participants should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (eg, 8 mg BID) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Participants should be observed closely for hypersensitivity reactions, especially during the first and second infusions.
16. PF-06939999 treatment: Initially PF-06939999 will be administered as a single agent, orally, once daily (QD) or twice a day (BID) in 21 day cycles on a continuous basis. Treatment will continue until PD, unacceptable toxicity or participant refusal, whichever occurs first. If PD occurs during treatment, continuation of study drug may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor. The participant will be reminded not to take their morning dose at home on PK days, but to bring their bottle into clinic so that study drug may be administered after study visit assessments are completed, and PK samples have been collected.

17. Tumor Assessments: Tumor assessments will include all known or suspected disease sites (eg, including CT or MRI of neck with contrast for HNSCC). CT or MRI scans are to be performed every 6 weeks for the first 9 months, then every 12 weeks until the end of safety follow up visit or participant withdrawal from the study. Efficacy assessments start on Cycle 2 Day 21. The allowable time window for disease assessments is ±7 days while on treatment and up to 7 days for screening (ie, the screening time window is up to 35 days prior to registration). Brain CT or MRI scan for participants with known or suspected brain metastases; bone scan and/or bone X-rays for participants with known or suspected bone metastases. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. When the study treatment is discontinued for reasons other than disease progression or participant refusal, participants will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) participant refusal or (c) start of another anti-cancer treatment, whichever occurs first. Tumor assessments should be fixed according to the calendar, regardless of treatment delays.
18. Adverse Events: The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product. For participants who are screen failures, the active collection period ends when screen failure status is determined. See Section 8.3.1.
19. Concomitant Medications: Concomitant medications and treatments must be recorded on the CRF.
20. Archival or de novo Tumor Biopsy: Tumor biospecimens from archival and/or de novo biopsies will be required at study entry. Post-treatment biopsies are not required for Part 1B. A summary of planned analysis for core needle biopsies is provided in Section 8.8.1.
21. End of Treatment or for early discontinuation: Obtain these assessments if not completed in the last week. Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation.
22. Follow up: At least 28 days, and no more than 35 days after discontinuation of treatment, participants will return to undergo review of concomitant medications and assessment for resolution of any treatment related toxicity. Participants continuing to experience toxicity 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. When the study treatment is discontinued for reasons other than disease progression or participant refusal, participants will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) participant refusal or (c) start of another anti-cancer treatment, (whichever occurred first).
23. Long term survival follow up: Participants in Part 2 dose expansion cohorts will be contacted by telephone every 12 weeks for survival data collection until end of trial (2 years from last participant's first dose).

Table 3. Study Related Procedures: Part 2A, 2B, and 2C (dose expansion, monotherapy)

	Screen[1] (≤28 days)	Cycle 1 (28 days)						Subsequent Cycles (28 Days per cycle)		End of Treatment (EOT)[22]	Safety Follow-Up Visit[23]	Long-Term Survival Follow-up[24]
Protocol Activity		Day 1	Day 8	Day 15	Day 16[a]	Day 17[a]	Day 22	Day 1	Day 15			
Visit Window			±2 days	±2 days			±2 days	±2 days	±2 days			
Informed Consent[2]	X											
Medical History[3]	X											
Physical Examination[4]	X	X	X	X				X	X	X	X	
Baseline Signs and Symptoms[5]		X										
Height	X											
Weight	X	X						X		X		
Vital Signs[6]	X	X	X	X				X	X	X	X	
ECOG Performance Status[7]	X	X						X		X		
NSCLC-SAQ and PGIS[8]		X	X					X(C2D1, and C4D1 only)		X		
Contraception check[9]	X	X						X		X		
12-lead ECG		See Table 7 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule See Table 8 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Parts 2A and 2B participants in the food effect assessment										
Laboratory Studies												
Hematology[10]	X	X	X	X			X	X	X	X	X	
Reticulocyte count[10]		X						X				
Blood Chemistry[11]	X	X	X	X			X	X	X	X	X	
Coagulation[12]	X	X						X		X	X	
Urinalysis[13]	X	X								X	X	
Pregnancy Test[14]	X	X								X	X	
Viral disease screen Hepatitis B, C, and HIV tests][15]	X											
Registration and Treatments												

Table 3. Study Related Procedures: Part 2A, 2B, and 2C (dose expansion, monotherapy)

	Screen[1] (≤28 days)	Cycle 1 (28 days)						Subsequent Cycles (28 Days per cycle)		End of Treatment (EOT)[22]	Safety Follow-Up Visit[23]	Long-Term Survival Follow-up[24]
Protocol Activity		Day 1	Day 8	Day 15	Day 16[a]	Day 17[a]	Day 22	Day 1	Day 15			
Visit Window			±2 days	±2 days			±2 days	±2 days	±2 days			
Registration[16]	X											
PF-06939999 Treatment[17]		Day 1 to Day 28						Day 1 to Day 28				
Tumor Assessments												
CT or MRI Scans[18]	X	Every 8 weeks for the first 12 months, then every 12 weeks. See footnote 18									X	
Other Clinical Assessments												
Serious and Non-serious Adverse Event Monitoring[19]	X	→										
Concomitant Medications[20]	X	X	X	X	X	X	X	X	X	X	X	
Archival or De Novo Tumor Biopsy[21]	X							X (C3 only from 5 participants/ arm)				
Other Laboratory Assessments												
Blood for Biomarker Analyses		See Table 7 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule See Table 8 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Parts 2A and 2B participants in the food effect assessment										
Plasma for PF-06939999 PK and [redacted]		See Table 7 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule See Table 8 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Parts 2A and 2B participants in the food effect assessment										
Banked Biospecimen		See Table 7 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule See Table 8 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Parts2A and 3B participants in the food effect assessment										
Other Assessments												
28- to 35-day Follow-up											X	
Overal Survival												X

Table 3. Study Related Procedures: Part 2A, 2B, and 2C (dose expansion, monotherapy)

	Screen[1] (≤28 days)	Cycle 1 (28 days)						Subsequent Cycles (28 Days per cycle)		End of Treatment (EOT)[22]	Safety Follow-Up Visit[23]	Long-Term Survival Follow-up[24]
Protocol Activity		Day 1	Day 8	Day 15	Day 16[a]	Day 17[a]	Day 22	Day 1	Day 15			
Visit Window			±2 days	±2 days			±2 days	±2 days	±2 days			

Abbreviations: → ongoing/continuous event; C = Cycle; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; CCI [redacted]

Footnotes (Schedule of Activities)

a. Days 16 and 17 are displayed in the table for Cycle 1 only to correspond with PK collection days for participants in the food effect cohort only. No clinical assessments required.

1. Screening: To be conducted within 28 days prior to treatment start.
2. Informed Consent: Must be obtained prior to undergoing any study specific procedures.
3. Medical History: To include smoking, alcohol abuse (ETOH) and human papilloma virus (HPV) status, date of diagnosis or primary disease and information on prior anti-tumor treatments, surgeries, radiotherapy and recurrence date as as well as prior tumor genomic testing resport if available.
4. Physical Examination: Examination of major body systems including body weight. Height is measured at screening visit only.
5. Baseline Signs and Symptoms: Participants will be asked about any signs and symptoms experienced within 14 days prior to C1D1.
6. Vital Signs: Includes temperature, blood pressure (BP), and pulse rate (PR) to be recorded in the sitting position or semi-recumbent position (however the position should be maintainted throughout the study) after approximately 5 minutes of rest.
7. ECOG Performance Status: ECOG performance scale is available in Section 10.10 Appendix 10.
8. PROs: Only NSCLC participants (Parts 2A and, 2D) will complete the NSCLC-SAQ and the patient global impression of severity (PGIS).
9. Hematology: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Grade ≥3 thrombocytopenia should trigger a blood smear for differential. Reticulocyte count should be performed per schedule of acitivity. In addition, Grade ≥3 anemia should trigger a recticulcyte count if not done within 7 days. The list of required laboratory tests is provided in Section 10.2 Appendix 2 (Table 15).
10. Blood Chemistry: All chemistry laboratory tests included in Section 10.2 Appendix 2 (Table 15) are required at every protocol chemistry required time point. No need to repeat full blood chemistry on C1D1 if screening assessment performed within 7 days prior to that date. Liver function tests, creatinine and amylase/lipase must be checked on Cycle 1 Days 8 and,15 and on Cycle2 Days 1 and 8 to assess for events qualifying as dose limiting toxicities (DLTs). For participants with treatment emergent Grade ≥3 AST/ALT, close clinical monitoring with an increased frequency of relevant blood testing should be undertaken, eg, every 2-3 days.
11. Blood Chemistry: All chemistry laboratory tests included in Section 10.2 Appendix 2: Clinical Laboratory Tests (Table 15) are required at every protocol chemistry required time point. No need to repeat full blood chemistry on C1D1 if screening assessment performed within 7 days prior to that date. During Cycle 1, liver function tests, creatinine and amylase/lipase must be checked on Days 8, 15 and 22 to assess for events qualifying as dose limiting toxicities (DLTs). For participants with treatment emergent Grade ≥3 AST/ALT, close clinical monitoring with an increased frequency of relevant blood testing should be undertaken, eg, every 2-3 days.

12. Coagulation: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. To be performed per the schedule of activities and as clinically indicated after baseline. The list of required laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
13. Urinalysis: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. To be performed as clinically indicated after baseline. The list of required urine laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
14. Pregnancy Test: Pregnancy tests (serum/urine) for female participants of childbearing potential. Test may also be repeated as per request of Institutional Review Board/Independent Ethics Committee (IRB/IECs), if required by local regulations. FSH will be done at Screening only in females who are amenorrheic for at least 12 consecutive months. Section 10.2 Appendix 2 Pregnancy Testing for further details.
15. Viral disease screening tests: Hepatitis B testing includes: Hepatitis B Surface Ag (HBsAg), Total Hepatitis B Core Ab (anti-HBc), Hepatitis B Surface Ab (anti-HBs) as clinically indicated IgM antibody to hepatitis B core antigen (IgM anti-HBc), HCV Ab, and HIV to be conducted by local laboratory where required by local regulations or if warranted by participant history.
16. Registration: Participant identification number and dose level allocation to be operated by the Sponsor (see Section 6.3.1 Allocation to Investigational Product).
17. PF-06939999 treatment: Initially PF-06939999 will be administered as a single agent, orally, once daily (QD) or twice a day (BID) in 28 day cycles on a continuous basis. Treatment will continue until PD, unacceptable toxicity or participant refusal, whichever occurs first. If PD occurs during treatment, continuation of study drug may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor. The participant will be reminded not to take their morning dose at home on PK days, but to bring their bottle into clinic so that study drug may be administered after study visit assessments are completed, and PK samples have been collected.
18. Tumor Assessments: Tumor assessments will include all known or suspected disease sites (eg, including CT or MRI of neck with contrast for HNSCC). CT or MRI scans are to be performed every 8 weeks for the first 12 months, then every 12 weeks until the end of safety follow up visit or participant withdrawal from the study. Efficacy assessments start on Cycle 2 Day 28. The allowable time window for disease assessments is ±7 days while on treatment and up to 7 days for screening (ie, the screening time window is up to 35 days prior to registration). Brain CT or MRI scan for participants with known or suspected brain metastases; bone scan and/or bone X-rays for participants with known or suspected bone metastases. Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation. When the study treatment is discontinued for reasons other than disease progression or participant refusal, participants will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) participant refusal or (c) start of another anti-cancer treatment, whichever occurs first. Tumor assessments should be fixed according to the calendar, regardless of treatment delays.
19. Adverse Events: The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product. For participants who are screen failures, the active collection period ends when screen failure status is determined. See Section 8.3.1.
20. Concomitant Medications: Concomitant medications and treatments must be recorded on the CRF.
21. Archival or de novo Tumor Biopsy: Tumor biospecimens from archival and/or de novo biopsies will be required at study entry. Post-treatment biopsies are not required for Part 2 but up to 5 participants from each study arm will be strongly recommended to provide de novo post-treatment tumor biopsies at cycle 3 day 1 if state, local, and institutional policies allow. A summary of planned analysis for core needle biopsies is provided in Section 8.8.1.
22. End of Treatment or for early discontinuation: Obtain these assessments if not completed in the last week. Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation.

23. Follow up: At least 28 days, and no more than 35 days after discontinuation of treatment, participants will return to undergo review of concomitant medications and assessment for resolution of any treatment related toxicity. Participants continuing to experience toxicity 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. When the study treatment is discontinued for reasons other than disease progression or participant refusal, participants will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) participant refusal or (c) start of another anti-cancer treatment, (whichever occurred first).
24. Long term survival follow up: Participants in Part 2 dose expansion cohorts will be contacted by telephone every 12 weeks for survival data collection until end of trial (2 years from last participant's first dose).

Table 4. Study Related Procedures: Part 2D (dose expansion, PF-06939999 + docetaxel)

	Screen[1] (≤28 days)	Cycle 1 (21 days)			Subsequent Cycles (21 Days per cycle)	End of Treatment (EOT)[23]	Follow-up[24]	Long-Term Survival Follow-up[25]
Protocol Activity		**Day 1**	**Day 8**	**Day 15**	**Day 1**			
Visit Window			**±2 day**	**±2 day**	**±2 days**			
Informed Consent[2]	X							
Medical History[3]	X							
Physical Examination[4]	X	X	X	X	X	X	X	
Baseline Signs and Symptoms[5]		X						
Height	X							
Weight	X	X			X	X		
Vital Signs[6]	X	X	X	X	X	X	X	
ECOG Performance Status[7]	X	X			X	X		
NSCLC-SAQ and PGIS[8]		X	X		X(C2D1, and C4D1 only)	X		
Contraception check[9]	X	X			X	X		
12-lead ECG		See Table 9 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 2D						
Laboratory Studies								
Hematology[10]	X	X	X	X	X	X	X	
Reticulocyte count[10]		X			X			
Blood Chemistry[11]	X	X	X	X	X	X	X	
Coagulation[12]	X	X			X	X	X	
Urinalysis[13]	X	X				X	X	
Pregnancy Test[14]	X	X				X	X	
Viral disease screen [Hepatitis B, C, and HIV tests][15]	X							
Registration and Treatments								
Registration[16]	X							
PF-06939999 Treatment[17]		Day 1 to Day 21			Day 1 to Day 21			
Docetaxel treatment[18]		X			X			

Table 4. Study Related Procedures: Part 2D (dose expansion, PF-06939999 + docetaxel)

	Screen[1] (≤28 days)	Cycle 1 (21 days)			Subsequent Cycles (21 Days per cycle)	End of Treatment (EOT)[23]	Follow-up[24]	Long-Term Survival Follow-up[25]
Protocol Activity		**Day 1**	**Day 8**	**Day 15**	**Day 1**			
Visit Window			**±2 day**	**±2 day**	**±2 days**			
Tumor Assessments								
CT or MRI Scans[19]		Every 6 weeks for the first 9 months, then every 12 weeks. See footnote						
Other Clinical Assessments								
Serious and Non-serious Adverse Event Monitoring[20]		→						→
Concomitant Medications[21]	X	X	X	X	X	X	X	
Archival or De Novo Tumor Biopsy[22]	X				X (C3 only)			
Other Laboratory Assessments								
Blood for Biomarker Analyses		See Table 9 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 2D						
Plasma for PF-06939999 PK and [redacted]		See Table 9 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 2D						
Banked Biospecimen		See Table 9 ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 2D						
Other Assessments								
28- to 35-day Follow-up							X	
Overal Survival								X

Abbreviations: → ongoing/continuous event; C = Cycle; CT = computed tomography;CA-125 = cancer antigen 125 ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; [redacted]

Footnotes (Schedule of Activities)

1. Screening: To be conducted within 28 days prior to treatment start.
2. Informed Consent: Must be obtained prior to undergoing any study specific procedures.
3. Medical History: To include date of diagnosis and information on prior anti-tumor treatments, surgeries, radiotherapy and recurrence date as as well as prior tumor genomic testing resport if available.
4. Physical Examination: Examination of major body systems including body weight. Height is measured at screening visit only.
5. Baseline Signs and Symptoms: Participants will be asked about any signs and symptoms experienced within 14 days prior to C1D1.
6. Vital Signs: Includes temperature, blood pressure (BP), and pulse rate (PR) to be recorded in the sitting position or semi-recumbent position (however the position should be maintainted throughout the study) after approximately 5 minutes of rest.

7. ECOG Performance Status: ECOG performance scale is available in Section 10.10 Appendix 10.
8. PROs: Only NSCLC participants (cohorts 2A, 2D) will complete the NSCLC-SAQ and the patient global impression of severity (PGIS).
9. The participant will be informed of the need to use highly effective contraception consistently and correctly. The conversation and participant's affirmation will be documented in the participant's chart.
10. Hematology: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Grade ≥ 3 thrombocytopenia should trigger a blood smear for differential. Reticulocyte count should be performed per schedule of acitivity. In addition, Grade≥ 3 anemia should trigger a recticulcyte count if not done within 7 days.The list of required laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
11. Blood Chemistry: All chemistry laboratory tests included in Section 10.2 Table 15) are required at every protocol chemistry required time point. No need to repeat full blood chemistry on C1D1 if screening assessment performed within 7 days prior to that date. Liver function tests, creatinine and amylase/lipase must be checked on Cycle 1 Days 8 and 15, and on Cycle2 Days 1 and 8 to assess assess for events qualifying as dose limiting toxicities (DLTs). For participants with treatment emergent Grade ≥3 AST/ALT, close clinical monitoring with an increased frequency of relevant blood testing should be undertaken, eg, every 2-3 days.
12. Coagulation: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. To be performed per the schedule of activities and as clinically indicated after baseline. The list of required laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
13. Urinalysis: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. To be performed as clinically indicated after baseline. The list of required urine laboratory tests is provided in Section 10.2 Appendix 2: Clinical Laboratory Tests.
14. Pregnancy Test: Pregnancy tests (serum/urine) for female participants of childbearing potential. Test may also be repeated as per request of Institutional Review Board/Independent Ethics Committee (IRB/IECs), if required by local regulations. FSH will be done at Screening only in females who are amenorrheic for at least 12 consecutive months. See Section 8.2.5 Pregnancy Testing for further details.
15. Viral disease screening tests: Hepatitis B testing includes: Hepatitis B Surface Ag (HBsAg), Total Hepatitis B Core Ab (anti-HBc), Hepatitis B Surface Ab (anti-HBs) as clinically indicated IgM antibody to hepatitis B core antigen (IgM anti-HBc), HCV Ab, and HIV to be conducted by local laboratory where required by local regulations or if warranted by participant history.
16. Registration: Participant identification number and dose level allocation to be operated by the Sponsor (see Section 6.3.1 Allocation to Investigational Product).
17. PF-06939999 treatment: Initially PF-06939999 will be administered as a single agent, orally, once daily (QD) or twice a day (BID) in 21 day cycles on a continuous basis. Treatment will continue until PD, unacceptable toxicity or participant refusal, whichever occurs first. If PD occurs during treatment, continuation of study drug may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor. The participant will be reminded not to take their morning dose at home on PK days, but to bring their bottle into clinic so that study drug may be administered after study visit assessments are completed, and PK samples have been collected.
18. Docetaxel will be administered at 75 mg/m^2 intravenously over 1 hour on Day 1 of each 21 day cycle until disease progression, unacceptable toxicity or participant refusal, whichever occurs first. All participants should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (eg, 8 mg BID) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Participants should be observed closely for hypersensitivity reactions, especially during the first and second infusions.

19. Tumor Assessments: Tumor assessments will include all known or suspected disease sites (eg, including CT or MRI of neck with contrast for HNSCC). CT or MRI scans are to be performed every 6 weeks for the first 9 months, then every 12 weeks until the end of safety follow up visit or participant withdrawal from the study. Efficacy assessments start on Cycle 2 Day 21. The allowable time window for disease assessments is ±7 days while on treatment and up to 7 days for screening (ie, the screening time window is up to 35 days prior to registration). Brain CT or MRI scan for participants with known or suspected brain metastases; bone scan and/or bone X-rays for participants with known or suspected bone metastases. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. When the study treatment is discontinued for reasons other than disease progression or participant refusal, participants will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) participant refusal or (c) start of another anti-cancer treatment, whichever occurs first. Tumor assessments should be fixed according to the calendar, regardless of treatment delays.
20. Adverse Events: The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product. For participants who are screen failures, the active collection period ends when screen failure status is determined. See Section 8.3.1.
21. Concomitant Medications: Concomitant medications and treatments must be recorded on the CRF.
22. Archival or de novo Tumor Biopsy: Tumor biospecimens from archival and/or de novo biopsies will be required at study entry. Post-treatment biopsies are not required but up to 5 participants will be strongly recommended to provide on-treatment de novo tumor biopsy samples if state, local, and institutional policies allow. A summary of planned analysis for core needle biopsies is provided in Section 8.8.1.
23. End of Treatment or for early discontinuation: Obtain these assessments if not completed in the last week. Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation.
24. Follow up: At least 28 days, and no more than 35 days after discontinuation of treatment, participants will return to undergo review of concomitant medications and assessment for resolution of any treatment related toxicity. Participants continuing to experience toxicity 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. When the study treatment is discontinued for reasons other than disease progression or participant refusal, participants will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) participant refusal or (c) start of another anti-cancer treatment, (whichever occurred first).
25. Long term follow up: Participants in Part 2 dose expansion cohorts will be contacted by telephone every 12 weeks for survival data collection until end of trial (2 years from last participant's first dose).

Table 5. ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 1A (dose escalation, PF-06939999 monotherapy)

	Screen (≤28 days)	Cycle 1 (28 days)																		Subsequent Cycles (28 Days per cycle)	EOT
Protocol Activity		Day 1							Day 2	Day 8	Day 15							Day 16	Day 22	Day 1	
Hours post dose*		Pre-dose§	0.5	1	2	4	6	12	Pre-dose	Pre-dose§	Pre-dose§	0.5	1	2	4	6	12	Pre-dose	Pre-dose§	Pre-dose§	
Sample collection window†			±3 min	±6 min	±12 min	±24 min	±36 min	±3h				±3 min	±6 min	±12 min	±24 min	±36 min	±3h				
Plasma for PF-06939999 PK[1]		X	X	X	X	X	X	X[2]		X	X	X	X	X	X	X	X[3]		X	X	X
CCI		[redacted]			[redacted]		[redacted]	[redacted]		[redacted]	[redacted]			[redacted]		[redacted]			[redacted]	[redacted] only)	
Triplicate ECGs[5]	X	X			X	X					X			X	X					(C2 and C3 Day 1; and anytime if clinically indicated)	X
Whole Blood for RNA Sequencing Analysis[6]		X								X										X (C2 and C3 only)	X
Whole Blood for Germline mutation[7]	X																				
Archival or De Novo Tumor Biopsy[8]	X																			C3 only (optional)	
Banked Biospecimen[9]		X																			

*Collection Time: Sampling times are related to morning dose.
†Sample collection windows: All sampling should be within the protocol specified window in the table above.
§Pre-dose sample collection: Within 3 hours prior to the morning dose of PF-06939999.

Footnotes (Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part 1A).

1. Pharmacokinetics: Blood samples for determination of plasma PF-06939999 drug concentrations will be collected at the time points specified (NOTE: PK sampling time points may change, pending PK data from early dose levels, but the total number of samples will remain the same). Additional PK blood samples may be collected at time of occurrence of unexpected or serious adverse events. On days when participants require predose PK sampling assessments, the morning dose of PF-06939999 should be held (NOT taken) prior to the study visit. On those days, the PF-06939999 morning dose can then be taken after the predose PK sampling is obtained.
2. Trough sample after single dosing: Only one sample will be collected. The sample will be collected on Day 1 (within 12±3 h from the Day 1 first dose and prior to Day 1 second dose) for BID dosing regimen or Day 2 (within 24±3 h from the Day 1 dose and prior to Day 2 dose) for QD dosing regimen.
3. Trough sample after multiple dosing: Only one sample will be collected. The sample will be collected on Day 15 (within 12±3 h from the Day 15 first dose and prior to Day 15 second dose) for BID dosing regimen or Day 16 (within 24±3 h from the Day 15 dose and prior to Day 16 dose) for QD dosing regimen.
4. CCI [redacted].
5. Triplicate 12 lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc and QRS intervals. During Cycles 2 and 3, ECGs will be performed on Day 1. After Cycle 3, ECGs can be performed as clinically indicated and will be required at the EOT visit. All ECG collection time points are with respect to PF-06939999 morning dosing. 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. If the mean QTc is prolonged (value of >480 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation; further guidance is provided in Section 8.2.3.
6. Whole blood will be collected for whole transcriptome RNA sequencing analysis according to the Laboratory/Study Manual.
7. Whole Blood for Germline mutation will be collected for whole genome sequencing.
8. Archival or de novo tumor tissue biopsy: Required for assessing splicing factors, alternative RNA splicing patterns and/or immunohistochemistry (IHC). Blood DNA needed as normal reference. Post-treatment Archival or de novo tumor tissue biopsy samples are optional but not required for Part 1. Archival tumor tissue samples less than 6 months old are preferred but also accept older samples.
9. Banked Biospecimen: Blood samples for banked biospecimens Prep D1 (4 mL K2 EDTA whole blood collection optimized for DNA analysis) will be collected at C1D1 (Pre-dose) as described in the Central Laboratory Manual. Participants will be asked to indicate on the consent form whether they will allow this sample to be also used for the Optional Pharmacogenomic Research as described in the Section 10.5, Appendix 5.

Table 6. ECG, Pharmacokinetic (PK) and Biomarker Sampling Schedule for Part 1B (dose finding, PF-06939999 + docetaxel)

	Screen (≤28 days)	Cycle 1 (21 days)															Cycle 2 (21 days)		Subsequent Cycles (21 Days per cycle)	EOT
Protocol Activity		Day 1						Day 2	Day 8	Day 15						Day 16	Day 1		Day 1	
Hours post dose*		Pre-dose[1]	0.5	1	2	4	6	Pre-dose	Pre-dose[1]	Pre-dose[1]	0.5	1	2	4	6	Pre-dose	Pre-dose[1]	1	Pre-dose	
Sample collection window†			±3 min	±6 min	±12 min	±24 min	±36 min				±3 min	±6 min	±12 min	±24 min	±36 min			-5 min		
Plasma for PF-06939999 PK[2]		X	X	X	X	X	X	X[3]	X	X	X	X	X	X	X	X[4]	X		X	X
CCI [redacted]		X															X	X[5]		
CCI [redacted]		[redacted]						[redacted]	[redacted]	[redacted]							[redacted]		[redacted]	
Triplicate ECGs[7]	X	X			X					X			X				X		(C3 Day 1; and anytime if clinically indicated)	X
Whole Blood for RNA Sequencing Analysis[8]		X							X								X		X (C3 only)	X
Whole Blood for Germline mutation[9]	X																			
Archival or De Novo Tumor Biopsy[10]	X																		C3 only (optional)	
Banked Biospecimen[11]		X																		

*Collection Time: Sampling times are related to morning dose.
†Sample collection windows: All sampling should be within the protocol specified window in the table above.

Footnotes (Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part 1B).

1. Pre-dose sample collection: Within 3 hours prior to the morning dose of PF-06939999 (for PF-06939999 PK) or within 6 hours prior to the start of docetaxel infusion (for CCI [redacted]
2. Pharmacokinetics: Blood samples for determination of plasma PF-06939999 drug concentrations will be collected at the time points specified (NOTE: PK sampling time points may change, pending PK data from early dose levels, but the total number of samples will remain the same). Additional PK blood samples may be collected at time of occurrence of unexpected or serious adverse events. On days when participants require predose PK sampling assessments, the morning dose of PF-06939999 should be held (NOT taken) prior to the study visit. On those days, the PF-06939999 morning dose can then be taken after the predose PK sampling is obtained.

3. Trough sample after single dosing: The sample will be collected on Day 2 (within 24±3 h from the Day 1 dose and prior to Day 2 dose) for QD dosing regimen.
4. Trough sample after multiple dosing: The sample will be collected on Day 16 (within 24±3 h from the Day 15 dose and prior to Day 16 dose) for QD dosing regimen.
5. The 1 hour sample for CCI should be collected from the contra-lateral arm of docetaxel infusion within 5 minutes prior to the end of infusion.
6. Blood for CCI : Blood samples for determination of free CCI concentration will be measured at the time points specified.
7. Triplicate 12 lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc and QRS intervals. During Cycles 2 and 3, ECGs will be performed on Day 1. After Cycle 3, ECGs can be performed as clinically indicated and will be required at the EOT visit. All ECG collection time points are with respect to PF-06939999 morning dosing. 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. If the mean QTc is prolonged (value of >480 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation; further guidance is provided in Section 8.2.3.
8. Whole blood will be collected for whole transcriptome CCI according to the Laboratory/Study Manual.
9. Whole Blood for Germline mutation will be collected for whole genome sequencing.
10. Archival or de novo tumor tissue biopsy: Required for assessing splicing factors, alternative CCI and/or immunohistochemistry (IHC). Blood DNA needed as normal reference. Post-treatment Archival or de novo tumor tissue biopsy samples are optional but not required for Part 1B. Archival tumor tissue samples less than 6 months old are preferred but also accept older samples.
11. Banked Biospecimen: Blood samples for banked biospecimens Prep D1 (4 mL K2 EDTA whole blood collection optimized for DNA analysis) will be collected at C1D1 (Pre-dose) as described in the Central Laboratory Manual. Participants will be asked to indicate on the consent form whether they will allow this sample to be also used for the Optional Pharmacogenomic Research as described in the Section 10.5, Appendix 5.

Table 7. ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 2A, Part 2B, and Part 2C (dose expansion, PF-06939999 monotherapy) (except for food effect sub-study)

	Screen (≤28 days)	Cycle 1 (28 days)											Subsequent Cycles (28 Days per cycle)	EOT
Protocol Activity		Day 1					Day 8	Day 15				Day 22	Day 1	
Hours post dose*		Pre-dose[1]	0.5	1	2	4	Pre-dose[1]	Pre-dose[1]	0.5	1	2	4	Pre-dose[1]	Pre-dose[1]	
Sample collection window†			±3 min	±6 min	±12 min	±24 min			±3 min	±6 min	±12 min	±24 min			
Plasma for PF-06939999 PK[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine for PF-06939999 PK								Optional: See Section 8.5.2							
CCI		[redacted]					[redacted]	[redacted]					[redacted]	[redacted]	[redacted]
Triplicate ECGs[4]	X	X			X			X			X			(C2 and C3 Day 1; and anytime if clinically indicated)	X
CCI [redacted]		X					X	X						X (C2 only)	X
Whole Blood for Germline mutation[6]	X														
Archival or De Novo Tumor Biopsy[7]	X													X (C3 only from 5 participants/arm)	
Banked Biospecimen[8]		X													

*Collection Time: Sampling times are related to morning dose.
†Sample collection windows: All sampling should be within the protocol specified window in the table above.

Footnotes (Pharmacokinetic and Pharmacodynamic Sampling Schedule).

1. Pre-dose sample collection: Within 3 hours prior to the morning dose of PF-06939999.
2. Pharmacokinetics: Blood samples for determination of plasma PF-06939999 drug concentrations will be collected at the time points specified (NOTE: PK sampling time points may change, pending PK data from early dose levels, but the total number of samples will remain the same). Additional PK blood samples may be collected at time of occurrence of unexpected or serious adverse events. On days when participants require predose PK sampling assessments, the morning dose of PF-06939999 should be held (NOT taken) prior to the study visit. On those days, the PF-06939999 morning dose can then be taken after the predose PK sampling is obtained.
3. Blood for CCI : Blood samples for determination of free CCI concentration will be measured at the time points specified.

4. Triplicate 12 lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc and QRS intervals. During Cycles 2 and 3, ECGs will be performed on Day 1. After Cycle 3, ECGs can be performed as clinically indicated and will be required at the EOT visit. All ECG collection time points are with respect to PF-06939999 morning dosing. 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. If the mean QTc is prolonged (value of >480 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation; further guidance is provided in Section 8.2.3.
5. Whole blood will be collected for whole transcriptome RNA sequencing analysis according to the Laboratory/Study Manual.
6. Whole Blood for Germline mutation will be collected for whole genome sequencing.
7. Archival or de novo tumor tissue biopsy: Required for assessing mutations in splicing factor genes, alternative RNA splicing patterns and/or immunohistochemistry (IHC) analysis. Blood DNA needed as normal reference. Post-treatment Archival or de novo tumor tissue biopsy samples are not required but up to 5 participants from each study arm will be strongly recommended to provide de novo post-treatment tumor biopsies at cycle 3 day 1 if state, local, and institutional policies allow. Archival tumor tissue samples less than 6 months old are preferred but also accept older samples.
8. Banked Biospecimen: Blood samples for banked biospecimens Prep D1 (4 mL K2 EDTA whole blood collection optimized for DNA analysis) will be collected at C1D1 (Pre-dose) as described in the Central Laboratory Manual. Participants will be asked to indicate on the consent form whether they will allow this sample to be also used for the Optional Pharmacogenomic Research as described in the Section 10.5, Appendix 5.

Table 8. Food Effect Sub-study Participants: ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule

	Screen (≤28 days)	Cycle 1 (28 days)																		Subsequent Cycles (28 Days per cycle)	EOT
Protocol Activity		Day 1	Day 8	Day 15							Day 16							Day 17	Day 22	Day 1	
Hours post dose*		Pre-dose[1]	Pre-dose[1]	Pre-dose[1]	0.5	1	2	4	6	12	Pre-dose[1]	0.5	1	2	4	6	12	Pre-dose	Pre-dose[1]	Pre-dose[1]	
Sample collection window†					±3 min	±6 min	±12 min	±24 min	±36 min	±3h		±3 min	±6 min	±12 min	±24 min	±36 min	±3h				
Plasma for PF-06939999 PK[2]		X	X	X	X	X	X	X	X	X[3]	X	X	X	X	X	X	X[4]		X	X	X
CCI																					
Triplicate ECGs[6]	X	X		X			X				X			X						(C2 and C3 Day 1; and anytime if clinically indicated)	X
CCI		X	X	X																X (C2 only)	X
Whole Blood for Germline mutation[8]	X																				
Archival or De Novo Tumor Biopsy[9]	X																			X (C3 only from 5 participants	
Banked Biospecimen[10]		X		X							X										

*Collection Time: Sampling times are related to morning dose.
†Sample collection windows: All sampling should be within the protocol specified window in the table above.

Footnotes (Pharmacokinetic and Pharmacodynamic Sampling Schedule)

1. Pre-dose sample collection: Within 3 hours prior to the morning dose of PF-06939999.
2. Pharmacokinetics: Blood samples for determination of plasma PF-06939999 drug concentrations will be collected at the time points specified. Additional PK blood samples may be collected at time of occurrence of unexpected or serious adverse events. On days when participants require predose PK sampling assessments, the dose of PF-06939999 should be held (NOT taken) prior to the study visit. On those days, the PF-06939999 dose will be taken after the predose PK sampling is obtained.
3. For BID dosing regimen only: The trough sample will be collected on Day 15 (within 12±3 h from the Day 15 first dose and prior to Day 15 second dose) for BID dosing regimen.
4. Trough sample after Day 16 dosing: Only one sample will be collected. The sample will be collected on Day 16 (within 12±3 h from the Day 16 first dose and prior to Day 16 second dose) for BID dosing regimen or Day 17 (within 24±3 h from the Day 16 dose and prior to Day 17 dose) for QD dosing regimen.
5. Blood for CCI : Blood samples for determination of free CCI concentration will be measured at the time points specified.
6. Triplicate 12 lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc and QRS intervals. During Cycles 2 and 3, ECGs will be performed on Day 1. After Cycle 3, ECGs can be performed as clinically indicated and will be required at the EOT visit. All ECG collection time points are with respect to PF-06939999 morning dosing. 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. If the mean QTc is prolonged (value of >480 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation; further guidance is provided in Section 8.2.3.
7. Whole blood will be collected for whole transcriptome CCI according to the Laboratory/Study Manual.
8. Whole Blood for Germline mutation will be collected for whole genome sequencing.
9. Archival or de novo tumor tissue biopsy: Required for assessing mutations in splicing factor genes, alternative CCI and/or immunohistochemistry (IHC) analysis. Blood DNA needed as normal reference. Post-treatment archival or de novo tumor tissue biopsy samples are not required but up to 5 participants will be strongly recommended to provide de novo post-treatment tumor biopsies at cycle 3 day 1 if state, local, and institutional policies allow. Archival tumor tissue samples less than 6 months old are preferred but older samples will also be accepted.
10. Banked Biospecimen: Blood samples for banked biospecimens Prep D1 (4 mL K2 EDTA whole blood collection optimized for DNA analysis) will be collected at C1D1 (Pre-dose) as described in the Central Laboratory Manual. Participants will be asked to indicate on the consent form whether they will allow this sample to be also used for the Optional Pharmacogenomic Research as described in the Section 10.5, Appendix 5.

Table 9. ECG, Pharmacokinetic (PK), and Biomarker Sampling Schedule for Part 2D (dose expansion, PF-06939999 + docetaxel)

	Screen (≤28 days)	Cycle 1 (21 days)											Cycle 2 (21 days)		Subsequent Cycles (21 Days per cycle)	EOT
Protocol Activity		Day 1					Day 8	Day 15					Day 1		Day 1	
Hours post dose*		Pre-dose[1]	0.5	1	2	4	Pre-dose[1]	Pre-dose[1]	0.5	1	2	4	Pre-dose[1]	1	Pre-dose[1]	
Sample collection window†			±3 min	±6 min	±12 min	±24 min			±3 min	±6 min	±12 min	±24 min		-5 min		
Plasma for PF-06939999 PK[2]		X	X	X	X	X	X	X	X	X	X	X	X		X	X
CCI		X											X	X[3]		
CCI		[redacted]					[redacted]	[redacted]					[redacted]		[redacted]	[redacted]
Triplicate ECGs[5]	X	X			X			X			X		X		(C3 Day 1; and anytime if clinically indicated)	X
CCI		X					X	X					X			X
Whole Blood for Germline mutation[7]	X															
Archival or De Novo Tumor Biopsy[8]	X														X (C3 only from 5 participants)	
Banked Biospecimen[9]		X														

*Collection Time: Sampling times are related to morning dose.
†Sample collection windows: All sampling should be within the protocol specified window in the table above.

Footnotes (Pharmacokinetic and Pharmacodynamic Sampling Schedule).

1. Pre-dose sample collection: Within 3 hours prior to the morning dose of PF-06939999 (for PF-06939999 PK) or within 6 hours prior to the start of CCI [redacted].
2. Pharmacokinetics: Blood samples for determination of plasma PF-06939999 drug concentrations will be collected at the time points specified (NOTE: PK sampling time points may change, pending PK data from early dose levels, but the total number of samples will remain the same). Additional PK blood samples may be collected at time of occurrence of unexpected or serious adverse events. On days when participants require predose PK sampling assessments, the morning dose of PF-06939999 should be held (NOT taken) prior to the study visit. On those days, the PF-06939999 morning dose can then be taken after the predose PK sampling is obtained.
3. The 1 hour sample for CCI [redacted] should be collected from the contra-lateral arm of docetaxel infusion within 5 minutes prior to the end of infusion.
4. Blood for CCI [redacted]: Blood samples for determination of free CCI [redacted] concentration will be measured at the time points specified.
5. Triplicate 12 lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc and QRS intervals. During Cycles 2 and 3, ECGs will be performed on Day 1. After Cycle 3, ECGs can be performed as clinically indicated and will be required at the EOT visit. All ECG collection time points are with respect to PF-06939999 morning dosing. 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. If the mean QTc is prolonged (value of >480 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation; further guidance is provided in Section 8.2.3.
6. Whole blood will be collected for whole transcriptome RNA sequencing analysis according to the Laboratory/Study Manual.
7. Whole Blood for Germline mutation will be collected for whole genome sequencing.
8. Archival or de novo tumor tissue biopsy: Required for assessing mutations in splicing factor genes, alternative RNA splicing patterns and/or immunohistochemistry (IHC) analysis. Blood DNA needed as normal reference. Post-treatment Archival or de novo tumor tissue biopsy samples are not required but up to 5 participants will be strongly recommended to provide de novo post-treatment tumor biopsies at cycle 3 day 1 if state, local, and institutional policies allow. Archival tumor tissue samples less than 6 months old are preferred but also accept older samples.
9. Banked Biospecimen: Blood samples for banked biospecimens Prep D1 (4 mL K2 EDTA whole blood collection optimized for DNA analysis) will be collected at C1D1 (Pre-dose) as described in the Central Laboratory Manual. Participants will be asked to indicate on the consent form whether they will allow this sample to be also used for the Optional Pharmacogenomic Research as described in the Section 10.5, Appendix 5.

2. INTRODUCTION

PF-06939999 is an orally available small molecule inhibitor of protein arginine methyltransferase 5 (PRMT5) that is 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.

2.1. Study Rationale

This is 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, and pharmacodynamics of escalating doses of PF-06939999 in participants with advanced or metastatic HNSCC, NSCLC, esophageal, endometrial, cervical, and bladder cancer and determine the maxium tolerable dose (MTD) and recommended dose for expansion (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.

2.2. Background

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 has potent cellular effects as measured by its ability to reduce CCI [redacted] levels of splicing regulators resulting in growth arrest in multiple hematologic and solid tumor cell lines. In this study PF-06939999 is being investigated in participants with advanced or metastatic HNSCC, NSCLC, esophageal, endometrial, cervical and bladder cancer.

2.2.1. Protein Arginine Methyltransferase 5 (PRMT5)

2.2.1.1. Cellular Functions

PRMT5 and binding partner MEP50 form the methylosome complex that utilizes S-adenosylmethionine to transfer methyl groups to arginine, catalyzing both mono- and symmetric di-methylation on substrate residues. PRMT5 methylates multiple protein substrates involved in transcription, cell signaling, mRNA translation, DNA damage, receptor trafficking, protein stability, and pre-mRNA splicing.[2]

The most well studied of the PRMT5 substrates are the spliceosomal assembly proteins that regulate pre-mRNA splicing. Mutations in splice sites, splicing factor mutations, and changes in splicing activity have been linked to cancer development and progression.[3] PRMT5 symmetrically di-methylates proteins that regulate pre-mRNA splicing including spliceosomal proteins, SmD1, SmD3 and SmB/B.[4] This methylation increases the affinity of

the Sm proteins for the tudor domain of the SMN1 protein, facilitating assembly of small nuclear ribonucleoprotein (snRNP) complexes for proper splice site recognition and recruitment of additional splicing factors. This is shown in Figure 1. A conditional PRMT5 knockout in mouse neural stem/progenitor cells (NPCs) highlights that PRMT5 function is necessary for proper splice site selection.[5] PRMT5 genetic inhibition leads to increased intron retention and exon skipping in pre-mRNAs resulting in mRNA non-sense mediated decay or alteratively spliced mRNAs. These splicing alterations can reduce expression of proteins or generate alternative protein isoforms that function in cell cycle regulation, DNA replication and repair, and metabolism.[5,6,7]

Figure 1. PRMT5 methylosome complex regulates snRNP assembly

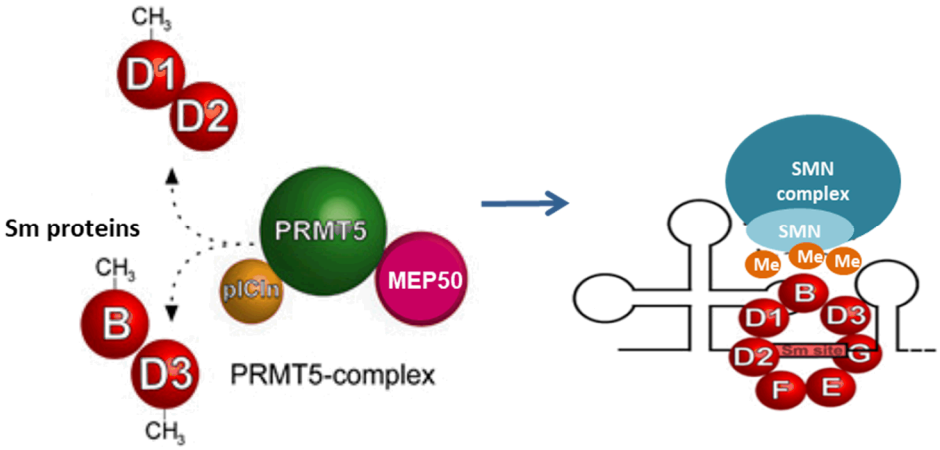


Figure modified from (Neuenkirchen N 2008)[8] to show PRMT5 complex methylates core spliceosomal proteins (SmD1, SmD3 and SmB) and aids in formation of mature U snRNPs through recruitment of the SMN complex.

2.2.1.2. PRMT5 Dysregulation in Cancer

Epigenetic dysregulation of cancer cell growth and survival pathways is a hallmark of both hematologic malignancies and solid tumors. PRMT5 is an epigenetic regulator that is overexpressed in hematologic malignancies and solid tumors which has been associated with decreased patient survival.[2,6] PRMT5 over-expression increases protein methylation on multiple substrates performing a variety of biological functions known to be dysregulated in cancer including transcription, cell signaling, mRNA translation, DNA damage, receptor trafficking, protein stability, and pre-mRNA splicing. Cancer cells are dependent on PRMT5 enzymatic activity for growth as genetic inhibition or catalytic inhibition of PRMT5 blocks cancer cell proliferation.[9]

PRMT5 methylation of splicing proteins, including Sm proteins, leads to splicing changes in oncogenes and tumor suppressor genes that regulate cancer cell proliferation and survival. Loss of PRMT5 activity induces alternative splicing changes with significant increases in levels of intron retention and exon skipping, primarily at sites with weak 5' exon-intron junctions.[5,7] These alternative splice variants may reduce expression of proteins or generate alternative protein isoforms with altered cellular functions. One example of an alternative

splicing event induced by PRMT5 loss is skipping of exon 6 in the MDM4 gene, causing the transcript to go through nonsense mediated decay, leading to a decrease in MDM4 protein, and subsequent activiation of the p53 pathway. In p53 wild-type lymphoma models, exon 6 skipping in MDM4 was linked to the anti-proliferative activity of PRMT5 inhibitors.[10] Other examples of alternative splicing events induced by PRMT5 loss or inhibition include genes involved in proliferation of cancer cells, such as: DVL1, MINK1, EP400, DDX51, ATR, RAC1 and CDC25B.[6]

2.2.1.3. Splicing Changes in Cancer

Recent high-throughput sequencing of human tumor tissue has identified that perturbations in mRNA splicing represent a common feature of tumorigenesis. Tumors have up to 30% more alternative splicing events than normal samples, including cancer specific exon-exon junctions, and there are associations between somatic variants of splicing factors and alternative splicing events.[12] The Cancer Genome Atlas (TCGA) identified recurrent somatic mutations and copy number alterations in 119 splicing factor genes, including genes encoding the splicing factors SF3B1, U2AF1, SRSF2, FUBP1, ZRSR2, and RBM10[17] in hematologic malignancies and solid tumors such as NSCLC, bladder, endometrial, esophageal, cervical, and HNSCC. Stratification of 119 genes with recurrent mutations with known roles in RNA splicing, including known PRMT5 substrates, and those important in snRNP assembly and branch point recognition, enriches the incidence of splicing factor mutations in these tumor types to over 42% of the total participants. RNA sequencing data from participant samples harboring these somatic mutations has revealed that cancers demonstrate transcriptome-wide splicing alterations, including splicing of regulators of proliferation, angiogenesis and cell death.[3]

2.2.1.4. PRMT5 Inhibitor Activity in Splicing Factor Mutated Leukemia

Splicing factor SF3B1 is frequently mutated in leukemia and hotspot mutations in the HEAT domain are classified as gain of function. Hotspot mutations in SF3B1 induce aberrant 3' splice site selection by utilizing an alternative branch point to generate an increased number of mRNAs targeted for nonsense mediated decay.[13] One example of these transcripts is ABCB7, a heme transporter and mediator of erythroid growth. ABCB7 is down-regulated in refractory anemia with ring sideroblasts (RARS), a subtype of myelodyplastic syndrome (MDS) with over 80-90% incidence of SF3B1 hotspot mutations.[13] A hematopoietic conditional heterozygous knock-in of $SF3B1^{K700E}$ in mice demonstrated impaired blood cell differentiation leading to anemia and myelodysplasia.[14] HSPCs isolated from $SF3B1^{+/K700E}$ mice also demonstrated increased sensitivity to spliceosome inhibitor, E7107, compared to wild–type cells.[14] To assess whether splicing dysregulation caused by splicing factor mutations would lead to increased sensitivity to PRMT5 inhibitors, anti-proliferative activity of PF-06939999 was tested in heterozygous $SF3B1^{+/H662Q}$ NALM-6 leukemia cells. Increased potency of PF-06939999 was observed in NALM-6 cells harboring the $SF3B1^{+/H662Q}$ mutation compared to the wild-type isogenic parental cell line with IC_{50} values of 4.05 nM and 13.41 nM respectively. PF-06939999 also demonstrated strong anti-proliferative activity in SF3B1 mutant MOLT-4 cells (IC_{50} = 0.381 nM), which translated to in vivo efficacy of 96% tumor growth inhibition at 10 mg/kg once daily, at a C_{av}

free = 23 nM and a 79 % reduction of the CCI biomarker. PRMT5 inhibitors have also demonstrated increased sensitivity in leukemia mouse models with splicing factor $SRSF2^{P95H}$ mutation compared to wild-type.[15] CCI [redacted]

2.2.1.5. PRMT5 and NSCLC

PRMT5 is highly expressed in lung cancer cells where it has been identified to promote lung cancer cell growth and accelerated metastasis. NSCLC is dependent on PRMT5 enzymatic function for growth as both genetic inhibiton and small molecule inhibitors block proliferation of lung cancer cells.[11] Splicing dysregulation has been well characterized as a molecular feature of NSCLC.[3,17,19] Using analysis of TCGA data, the incidence of mutations in 119 splicing factors analyzed in 5171 NSCLC samples was 46%, one of highest percentages of all tumor types. A panel of NSCLC cell lines (50% containing splicing factor mutations) were tested for anti-proliferative activity in response to PF-06939999. IC50 values for the splicing mutant cell lines were 50nM or lower, suggesting splicing dysregulation may increase sensitivity to PRMT5 inhibitors. There exists a necessity to identify novel therapeutic modalities that target previously unrecognized molecular events that drive the aggressiveness of lung cancer. These data highlight the potential for PF-06939999 as an attractive therapeutic in NSCLC.

2.2.1.6. Role of PRMT5 in Additional Solid Tumor Types

Additional solid tumors with increased splicing dysregulation due to higher percentages of splicing factor mutations include: head and neck squamous cell carcinoma, cervical cancer, endometrial cancer, esophageal cancer, and bladder cancer. Using analysis of TCGA data, the incidence of mutations in the 119 splicing factors described above were determined. In bladder cancer, the incidence of splicing factor mutations was 51% in 1857 patients, 38% of 1638 endometrial cancer patients, 42% of 604 cervical cancer patients, 44% of 1662 esophageal cancer patients and 51% of 1587 head and neck cancer patients. These identified mutations may permit enhanced sensitivity to a PRMT5 inhibitor.

2.2.1.7. PRMT5 Inhibitors in Treatment Resistant Disease

Development of drug resistance is a reality for many patients being treated with targeted agents. Initial clinical response is strong, but development of resistance to these drugs is common, with relapse occurring as early as 2 months of treatment.[16] Mechanisms tumors use to evade targeted therapies involve bypassing the targeted pathways by utilizing alternative signaling pathways, regulating gene expression and acquiring DNA mutations in oncogenic drivers. PF-06939999 targets a unique PRMT5-driven cellular process, alternative splicing, which remains a vulnerability in cancer cells where resistance has emerged to chemotherapy, oncogenic driver mutation therapies, cell cycle inhibitors and immunotherapy. PF-06939999 demonstrated efficacy in several drug resistant cell lines, suggesting combinations or later line therapy options in the clinic may be effective in multiple cancer indications. This provides the rationale for developing PF-06939999 in participants with advanced or metastatic cancers including HNSCC, NSCLC, esophageal cancer, endometrial cancer,

cervical cancer, and bladder cancer that are resistant to standard therapy or for whom no standard of therapy is available.

2.2.2. Nonclinical Pharmacology

PF-06939999 is a potent and selective small molecule inhibitor with demonstrated biochemical and cellular activity against PRMT5. The biochemical potency was assessed using enzymatic assays performed using human full length PRMT5/MEP50 complex and peptides based on the C-terminal GR rich region of SmD3. The Ki value (concentration required to produce half maximum enzyme inhibition) is <50 pM, which is below the lower limits of quantitation for the assay. Selectivity of PF-06939999 at 10 μM was assessed in both protein methyltransferase and kinase selectivity panels and showed no activity above 20% inhibition for all enzymes in both enzyme panels.

Cellular activity of PF-06939999 was measured by the reduction of its direct biomarker, CCI [redacted] and anti-proliferative activity in cancer cells. PF-06939999 displayed potent inhibition of cellular activity in an CCI [redacted] ELISA assay with an IC_{50} value of 0.417 nM. Breadth of efficacy studies were done to assess anti-proliferative activity of PF-06939999 in cell lines representing multiple solid tumor indications with increased incidence of splicing dysregulation. Anti-proliferative responses with differential sensitivity to PF-06939999 were observed in NSCLC, esophageal, endometrial, cervical, bladder and leukemia cell lines treated for 7 days. In NSCLC, potency ranged from IC_{50} = 1.3 nM to 79.2 nM with many sensitive cell models harboring mutations in splicing factors or demonstrating significant differences in alternative splicing patterns. Additionally, PC-9 (an EGFR mutant NSCLC line) was evaluated for anti-proliferative effects, comparing the sensitivity of the parental cell line to one that had developed acquired resistant to specific EGFR inhibitors. PF-06939999 demonstrated similar efficacy in parental (IC_{50} = 12.2 nM) and resistant cells (IC_{50} = 15.4 nM). In bladder cancer cell lines, potency ranged from IC_{50} = 1 nM to 92 nM for anti-proliferation. Esophageal cancer cell lines demonstrated a similar range of potency to other solid tumor cell lines with a potency range from IC_{50} = 8.96 nM to 131 nM. Leukemia cell lines also had strong anti-proliferative activity in response to PF-06939999 treatment with IC_{50} values ranging from 0.6 nM to 116 nM and induction of apoptosis in several cell lines.

In vivo, PF-06939999 demonstrated significant tumor growth inhibition (TGI) relative to vehicle in xenograft studies representing NSCLC, bladder and esophageal cancer as a monotherapy. PF-06939999 showed significant tumor suppression as an orally administered single agent in the 2 splicing factor mutant NSCLC (A427 and NCI-H441) xenograft models. In the NCI-H441 ($U2AF1^{S34F}$) model, PF-06939999 demonstrated dose dependent tumor growth inhibition (TGI) of 55.5% at 5 mg/kg BID, 14.9% at 3 mg/kg once daily, 46.6% at 10 mg/kg once daily and 87.2% at 30 mg/kg once daily doses. Modulation of CCI [redacted] in the tumors was evaluated via ELISA at end of study with reductions compared to control from 70.6% to 85.9% for the once daily doses. PF-06939999 also demonstrated dose dependent TGI in the A427 ($RBM10^{I348N}$) model, of 94.5% at 5 mg/kg BID, 32.4% at 3 mg/kg once daily, 76.2% at 10 mg/kg once daily and 102.3% at 30 mg/kg once daily doses. Patient derived xenografts of bladder and esophageal cancer were evaluated for tumor growth

inhibition at 10 mg/kg or 30 mg/kg QD. Significant tumor growth inhibition was observed in 6/7 bladder cancer xenografts and 7/13 esophageal cancer xenografts. Body weight was maintained over the course of dosing. Based on these data, there is pre-clinical rationale for the use of PF-06939999 as a single agent in the clinic for NSCLC, bladder cancer, esophageal cancer, and leukemia indications.

2.2.3. Nonclinical Pharmacokinetics and Projection of Human Pharmacokinetics

Details of the nonclinical ADME properties of PF-06939999 are provided in the Investigator's Brochure. Briefly, PF-06939999 is predicted to have a human plasma clearance of 3.1 mL/min/kg, a steady-state volume of distribution of 1.6 L/kg, and a half-life of approximately 6 hours. The oral bioavailability is predicted to be 50%. Stomach pH is not anticipated to impact oral absorption in the planned clinical dose range. Since PF-06939999 is a substrate for efflux transporters, there is the potential to observe variable nonlinear pharmacokinetics with over-proportional increases in exposure across doses due to saturation of efflux transporters. Minimal accumulation (≤3x) was observed in rats and dogs after 15 weeks of once daily dosing. PF-06939999 showed moderate plasma protein binding with unbound fractions in plasma of 0.1 to 0.2 across the species evaluated and partitioning of PF-06939999 into blood cells was modest with blood-to-plasma ratios of ≤1.4. Brain penetration of PF-06939999 was limited in mice, with unbound brain to plasma concentration ratios of ≤0.1. Preliminary in vitro metabolism evaluation of PF-06939999 showed similar oxidative metabolite profiles across species with no evidence of human specific oxidative metabolites. PF-06939999 is expected to be primarily metabolized by cytochrome P450 (CYP) 3A4/5 (~70% of hepatic metabolism), with minor contributions from CYP1A2, CYP2C9, and CYP2D6. Physiologically-based pharmacokinetic (PBPK) modeling suggested that the oral exposure of PF-06939999 at the predicted pharmacologically active dose (PAD) of 50 mg twice daily (BID) could increase by 2 to 3-fold with coadministration of a strong CYP3A inhibitor and decrease by 50% to 70% with coadministration of a strong CYP3A inducer. Based on the cumulative in vitro drug-drug interaction (DDI) data and projected total steady-state maximum systemic concentration ($C_{max,ss}$) of 458 nM (53 nM unbound) in humans at the dose of 50 mg BID, PF-06939999 has a low risk to cause pharmacokinetic DDIs with compounds for which CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15 mediated metabolism constitutes the primary mechanism of clearance. PF-06939999 has a low potential to inhibit BCRP (systemic), MDR1/P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and MATE1 in humans at the dose of 50 mg BID. However, PF-06939999 may have the potential to inhibit CYP2D6, BCRP (intestinal), and OCT1 at clinically relevant concentrations. PBPK modeling suggested that PF-06939999, at the predicted PAD of 50 mg BID, could increase the oral exposure of 30 mg dextromethorphan (CYP2D6 substrate) by ~1.4-fold.

2.2.4. Nonclinical Safety

The nonclinical safety profile of PF-06939999 was evaluated in vitro (off-target binding, hERG, genetic toxicity) and in vivo following oral administration of PF-06939999 to rats and dogs in nonpivotal and pivotal Good Laboratory Practice (GLP) toxicity studies of up to 1-month in duration. PF-06939999 was developed as a brain restricted compound. The oral route of exposure with a continuous once daily dosing regimen was selected for in vivo studies since it is the intended route of administration in participants.

In vitro assays with PF-06939999 suggest minimal risk of off-target pharmacology or direct effects on ion channels or cardiac tissues at clinically relevant exposures. PF-06939999 was not mutagenic in the in vitro bacterial reverse mutation assay and not clastogenic or aneugenic in an in vitro micronucleus assay in human lymphoblastoid TK6 cells. PF-06939999 may have potential risk for phototoxicity based on its UV absorption within the 290-400 nm range, with a calculated molar extinction coefficient (MEC) >1000 Lmol-1cm-1. PF-06939999 will be evaluated for phototoxicity during exploratory development prior to any large-enrollment clinical trials (Phase 3). Developmental and reproductive toxicity studies have not been conducted with PF-06939999, the effects of PF-06939999 on sperm, a pregnancy, a fetus, or a nursing child are not known. Adverse effects on sperm, a pregnancy, a fetus, or a nursing child are common with oncology therapeutics and may result from exposure to PF-06939999.

In repeat dose 1-month GLP toxicity studies in rats and dogs, administration of PF-06939999 was not tolerated at the high doses of 30 and 0.3 mg/kg/day, respectively, with the declining clinical condition in both species being primarily ascribed to extensive and persistent adverse gastrointestinal effects. The primary target organs identified in the pivotal toxicity studies in rats and dogs included:

Significant Non-Clinical Toxicities:

- Gastrointestinal (GI): clinical signs including liquid feces, dehydration, decreased body weight and food consumption, emesis (dog) and severely decreased activity. Microscopically GI findings were characterized by minimal to moderate degeneration of crypt epithelium with regeneration throughout the entire GI tract. GI findings were observed at the high doses of 30 mg/kg in rats (margin vs predicted exposure at the start dose is 1859x) and 0.3 mg/kg in dogs (margin vs predicted exposure at the start dose is 41.4x). GI findings in the dog defined the highest non-severely toxic dose (HNSTD). Reversibility was established for the PF-06939999-related GI changes in rats and dogs following a 1-month recovery period. The rat STD_{10} exposure equates to approximately 116 mg BID doses in humans, which is not anticipated to be explored in the clinic. Note: the PAD (pharmacologically active dose) is predicted to be 50mg BID. The GI toxicity observed may be anticipated to commence at human dose of approximately 3.5mg BID.

- Bone Marrow: hematopoietic/myelosuppressive effects characterized by decreased red blood cell mass, platelets and WBCs; and microscopically evidenced by moderate to marked decreased cellularity of bone marrow was observed. Bone marrow findings at ≥10 mg/kg (mid dose) in rats and were considered non-adverse until 30mg/kg (exposure margin vs. predicted start dose is 1859x) and for dogs findings were non-adverse even at the highest dose level (at 0.3mg/kg exposure margin vs. predicted start dose is 41.4x). Reversibility was established for PF-06939999-related bone marrow changes in rats and dogs following a 1-month recovery period. The rat STD_{10} exposure equates to approximately 116 mg BID doses in humans, which is not anticipated to be explored in the clinic. Note: the PAD (pharmacologically active dose) is predicted to be 50mg BID. The bone marrow toxicity observed may be anticipated to commence at human dose of approximately 10mg BID.

- Pancreatic: microscopic observations included moderate pancreas acinar cell necrosis and mild atrophy, inflammation/necrosis of pancreatic and peripancreatic adipose tissue with associated clinical pathology such as increases in amylase and lipase. Findings were observed in only one dog at the highest dose of 0.3mg/kg and in rats at doses ≥10mg/kg (adverse in both species, margins vs exposure at the start dose is 41.4x in dogs, 464x in rats). The pancreatic effects in dogs also contributed to the HNSTD. Reversibility was established for the PF-06939999-related pancreatic changes in rats and dogs following a 1-month recovery period. The rat STD_{10} exposure equates to approximately 116 mg BID doses in humans, which is not anticipated to be explored in the clinic. Note: the PAD (pharmacologically active dose) is predicted to be 50mg BID. The pancreatic toxicity observed may be anticipated to commence at a human dose of approximately 10mg BID.

Non-Significant Non-Clinical Toxicities:

- Male reproductive: in the testis minimal to marked degeneration of seminiferous tubules; ≥10 mg/kg (mid dose); and epididymis minimal to moderate cell debris at ≥0.3 mg/kg (high dose, dog only) and moderate reduced sperm count and single cell necrosis at 30 mg/kg (high dose, rat only). PF-06939999-related male reproductive changes did not recover following a 1-month recovery period. These were considered clinically non-significant for an oncology subject population.

- Additional target organs identified in the rat only included: bone (moderate to marked decreased trabecular bone/necrosis in the metaphysis, osteoblast degeneration, increased osteoclasts; ≥10 mg/kg) and pituitary (minimal to mild single cell necrosis, pars anterior (distalis); ≥10 mg/kg). Reversibility was established for the PF-06939999-related bone and pituitary findings in rats following a 1-month recovery period. Bone effects on the open epiphyseal plate in rats would not be considered to represent a risk to adult participants with a closed growth plate. Changes in the pituitary gland were minimal and nonadverse and only observed in a single species and were not associated with any functional alterations, thus the relationship of this finding to humans is unknown but likely minimal. These were considered clinically non-significant.

The dog was identified as the most sensitive species to PRMT5-related toxicities. The HNSTD (highest nonseverely toxic dose) in the pivotal 1-month toxicity study in dogs was 0.1 mg/kg/day (total C_{max} of 15 ng/mL and AUC24 of 175 ng*hr/mL,and unbound C_{ave} of 2.9 nM and C_{max} of 5.9 nM). The STD_{10} (severely toxic dose in 10% of rodents) in the pivotal 1-month toxicity study in rats was 10 mg/kg/day (total C_{max} of 437 ng/mL and AUC_{24} of 4824 ng*hr/mL, and unbound C_{ave} of 95 nM and C_{max} of 206 nM). At the HNSTD/NOAEL in the dog, safety margins over the unbound projected exposure at the 0.5 mg QD human starting dose for C_{ave} and C_{max} are approximately 14.5 and 15.1, respectively. At STD_{10} in rat, safety margins over the unbound projected exposure at the 0.5 mg QD human starting dose for C_{ave} and C_{max} are approximately 475-x and 528-x. This justifies the starting dose of 0.5 mg QD which is one sixth the HNSTD/NOAEL in dogs.

The nonclinical safety findings related to oral administration of PF-06939999 represent toxicities that can be monitored and/or are considered clinically manageable or acceptable risks in the intended advanced cancer participant population. Additional details of the nonclinical safety program and a complete list of all toxicity findings are provided in the current Investigator's Brochure.

2.2.5. Clinical Overview

As of 17 October 2019, 7 participants were enrolled and dosed at 4 dose levels (0.5 mg QD, 0.5 mg BID, 1 mg BID and 2 mg BID) in this study. Five of 7 particpants experienced at least 1 treatment-emergent adverse event (TEAE). Most TEAEs were CTCAE Grade 1 or 2. One participant dosed at 1 mg BID experienced 2 CTCAE Grade 3 TEAEs of anemia and hypomagnesemia, resulting in a dose reduction to 0.5 mg BID.

Treatment related AEs include CTCAE Grade 3 anemia, and Grade 1 blood creatinine increased, dysgeusia, and hypomagneseamia (n=1 each).

As of 17 October 2019, 1 participant experienced a treatment-emergent serious adverse event (SAE) of pneumonia, which was assessed as not related to PF-06939999. No particpants experienced treatment related SAEs. No participants were discontinued due to an AE. No participants experienced dose limiting toxicities (DLTs) or CTCAE Grade 4 or 5 TEAEs.

2.3. Benefit/Risk Assessment

This is the first-in-human clinical trial to evaluate PF-06939999. As of the data cut-off date of 17 October 2019, 7 participants have been enrolled and dosed in clinical study C3851001.

Treatment related AEs include CTCAE Grade 3 Anemia, and Grade 1 blood creatinine increased, dysgeusia and hypomagneseamia (n=1 each). No particpants experienced treatment related SAEs. No participants were discontinued due to an AE. No participants experienced dose limiting toxicities (DLTs) or CTCAE Grade 4 or 5 TEAEs.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06939999 may be found in the investigator's brochure, which is the single reference safety document (SRSD) for this study.

The SRSD for docetaxel is the Taxotere® USPI.[17]

3. OBJECTIVES AND ENDPOINTS

Part 1A Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• 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 or Maximum Administered Dose (MAD) and select the RP2D/schedule.	• Dose Limiting Toxicities (DLTs). • Adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [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.
Secondary:	**Secondary:**
• To characterize the single and multiple dose PK of PF-06939999 following oral administration. • To evaluate preliminary anti-tumor activity.	• PK parameters of PF-06939999: Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{1/2}$, AUC_{inf}, CL/F, and Vz/F. • PK parameters of PF-06939999: Multiple Dose (MD) - $C_{max,ss}$, $T_{max,ss}$, $AUCss,_{\tau}$, and as data permit, CL/F, Vss/F, and Rac ($AUC_{ss,\tau}/AUC_{sd,\tau}$). • Tumor response: Objective response rate (ORR) and duration of response (DoR), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) Section 10.11.

Part 1B Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• 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.
Secondary:	**Secondary:**
• 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 permit, $t_{1/2}$, AUC_{inf}, CL/F, and Vz/F. • PK parameters of PF-06939999: MD - $C_{max,ss}$, $T_{max,ss}$, $AUC_{ss,\tau}$, and as data

Objectives	Endpoints
• To evaluate preliminary anti-tumor activity. • To evaluate overall survivial (OS).	permit, CL/F, Vss/F, and Rac ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$). • Tumor response: ORR,DoR, progression-free survival (PFS) and time to progression TTP, as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) Section 10.11. • OS, proportion of participants alive at 6 months, 1 year, and 2 years of PF-06939999 in combination with docetaxel.
• CCI [redacted]	[redacted]
[redacted]	[redacted]

Part 2 Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• 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.
• To estimate clinical efficacy by 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 the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) Section 10.11.
Secondary:	**Secondary:**
• 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). • 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. • To evaluate overall survival (OS).	• 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}. • Tumor response:Duration of response (DoR) progression free survival (PFS) and time to progression (TTP) as assessed by investigators using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) Section 10.11 of PF-06939999 monotherapy and in combination with docetaxel. • OS, proportion of participants alive at 6 months, 1 year, and 2 years of PF-06939999 monotherapy and in combination with docetaxel.

Objectives	Endpoints
• CCI	

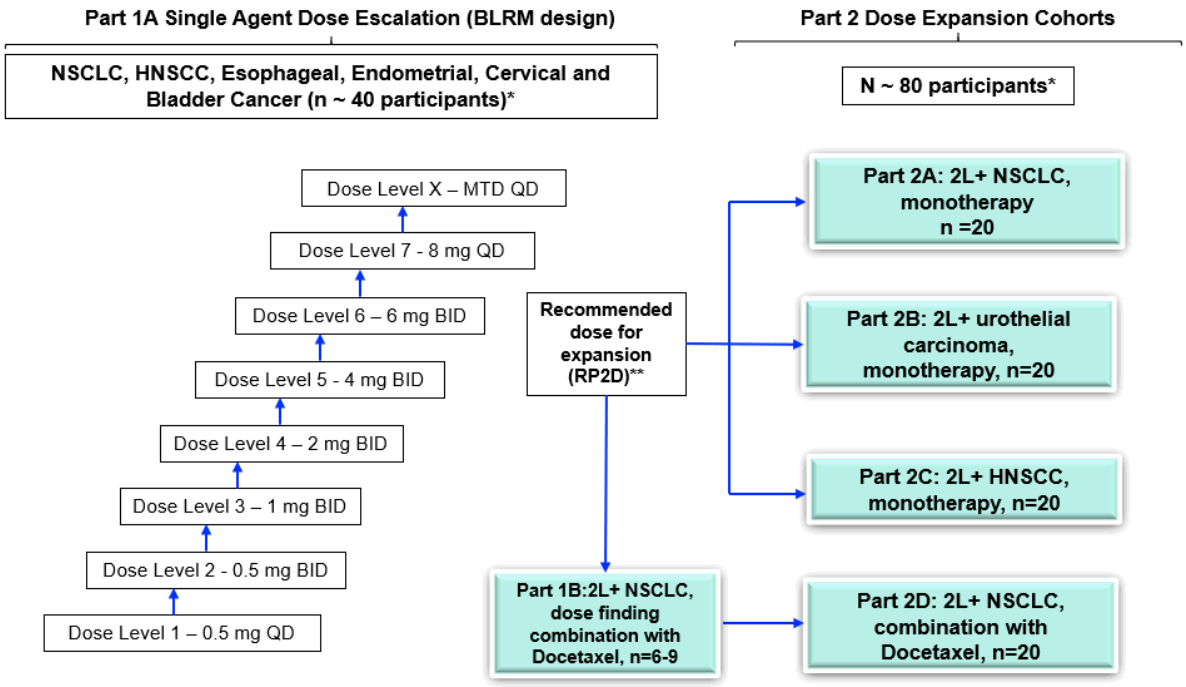
4. STUDY DESIGN

4.1. Overall Design

This is 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 is depicted in the schema below. The study is divided into 2 parts, dose escalation (Part 1) followed by dose expansion (Part 2). Part 1 dose escalation further divides into Part 1A and 1B. Part 1A contains dose escalation as a single agent in participants with locally advanced or metastatic head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), esophageal cancer, endometrial cancer, cervical cancer, or bladder cancer who are resistant or intolerant to standard therapy or for whom no standard therapy is available, to determine the MTD and RP2D. Part 1B contains

dose finding of PF-06939999 in combination with docetaxel in locally advanced or metastatic NSCLC.



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

Part 1A (dose escalation) is anticipated to have approximately 9 cohorts and expected to enroll approximately 40 participants. A Bayesian Logistic Regression Model (BLRM) was used to determine the MTD. Participants received escalating doses of PF-06939999 starting from 0.5 mg QD. Dose limiting toxicities (DLT) were assessed at the end of Cycle 1 (28 days) to inform dose escalation and determine the MTD. Cohort size was approximately 3 participants, with at least 1 DLT-evaluable participant per cohort at the first 3 dose levels and at least 2 DLT-evaluable participants per cohort in the remaining cohorts. PF-06939999 was administered as a single agent, orally, once daily during the first cohort, twice a day (BID) or once a day (QD) for subsequent cohorts in 28 day cycles on a continuous basis until disease progression, participant refusal, or unacceptable toxicity. If the clinical PK and pharmacodynamic data support the feasibility of QD dosing regimen, QD will be tested for better participant compliance and convenience. Other dosing regimens (eg, a regimen with dose interruptions to allow recovery from certain adverse events) may be considered in the study if further supported by emerging clinical data. The estimated length of treatment is approximately 2 years. Any additional treatment beyond 2 years shall be discussed and approved by the Sponsor. The proposed treatment schedule(s) and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data. The actual number of participants enrolled will depend on the tolerability of PF-06939999 and the number of dose levels required to identify the MTD and recommended dose for expansion (RP2D). RP2D definition is provided in Section 4.3.5.

After the selection of recommended dose for expansion (RP2D) for monotherapy, Part 2 (dose expansion) will evaluate the safety and antitumor activity of PF-06939999 monotherapy at the single agent RP2D in 3 expansion cohorts: locally advanced or metastatic NSCLC (Part 2A, 20 participants), urothelial carcinoma (Part 2B, 20 participants) and HNSCC (Part 2C, 20 participants). The collection of on-treatment biopsies in up to 5 participants per arm is strongly recommended if state, local, and institutional policies allow.

Furthermore, the PF-06939999 in combination with docetaxel will be evaluated in locally advanced or metastatic NSCLC (Part 1B combination dose finding and Part 2D combination dose expansion). In part 1B, the PF-06939999 in combination with docetaxel will be evaluated in participants with locally advanced or metastatic NSCLC who have progressed after at least 1 line of checkpoint inhibitor and platinum based chemotherapy (2L+). BLRM specifically designed for combinations guided by EWOC principle will be used for dose finding. PF-06939999 may start at 1 dose level below single agent RP2D (RP2D-1) with fixed dose of docetaxel per standard of care. In addition, depending on the safety findings in Part 1A, and whether significant overlapping toxicities are expected in combination, the starting dose of PF-06939999 may be further escalated or de-escalated but will not exceed the single agent RP2D. Participants will be enrolled in cohorts of approximately 3 paticipants of whom at least 3 will be DLT evaluable. It is anticipated that approximately 6-9 participants will be enrolled in Part 1B.

Once the RP2D for the combination has been determined, additional NSCLC participants will be enrolled under Part 2D combination expansion cohort until a total of 20 participants have been evaluated at the combination RP2D (Part 1B participants dosed at the combination RP2D will be counted towards the total of 20 participants). The collection of on-treatment biopsies in up to 5 participants per arm is strongly recommended if state, local, and institutional policies allow.

Approximately 80 participants are expected to be enrolled in Part 2. The participant population is briefly described below and detailed in inclusion criteria (Section 5).
Monotherapy expansion cohorts Parts 2A, 2B, and 2C:

- Part 2A: Participants with NSCLC (n=20) who have progressed after at least 1 line of checkpoint inhibitors and 1 line of platinum based chemotherapy (2L+).

- Part 2B: Participants with urothelial carcinoma (n=20) who have progressed after at least 1 line of standard of care systemic chemotherapy (cisplatin/carboplatin+ Gemcitabine; or methotrexate/vinblastine sulfate/doxorubicin hydrochloride/cisplatin [MVAC]) and checkpoint inhibitor (2L+).

- Part 2C: Participants with HNSCC (n=20) who have progressed after at least 1 line of standard of care systemic chemotherapy and 1 line of checkpoint inhibitor (2L+).

Combination expansion cohort Part 2D (PF-06939999 in combination with docetaxel):

- Part 2D: Participants with NSCLC (n=20) who have progressed after at least 1 line of checkpoint inhibitor and 1 line of platinum based chemotherapy (2L+).

- All participants in Part 1 and Part 2:

- Will undergo up to 28 days of screening prior to study entry.

- Will receive doses of PF-06939999, administered orally continuously on 28 day cycles up to 2 years (for combination with docetaxel, 21 day cycle is used to be consistent with docetaxel dosing schedule). Any additional treatment with PF-06939999 beyond 2 years shall be discussed and approved by the Sponsor.

- Treatment with investigational product (IP) will continue until disease progression, a decision by the participant (withdrawal of consent or no longer willing to participate), or investigator , or unacceptable toxicity, whichever occurs first.

- Will undergo a Safety follow up visit at least 28 days but no more than 35 days after end of treatment.

- In addition, participants in Part 1B and Part 2 dose expansion cohorts will be contacted by telephone every 12 weeks for survival data collection until end of trial (2 years from last participant first dose).

- A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the schedule of activities, including overall survial (OS). OS follow up should not continue after end of the study (Section 4.3.6).

4.1.1. Food-Effect Substudy

The effect of food on the PK of PF-06939999 at the recommended Phase 2 dose and regimen (BID or QD) will be assessed in at least 6 participants (but no more than 15 participants) from Part 2B, to inform whether PF-06939999 can be administered without food restriction in subsequent clinical trials. A fixed sequence one-way cross-over design will be utilized to assess the PK of PF-06939999 under the fasted and fed conditions on Cycle 1 Day 15 and Day 16, respectively, following repeated dosing under empty stomach condition (no food or liquids other than water will be consumed for 2 hours before and 1 hour following each dose).

With the exception of the study visits for food effect assessment (Cycle 1 Day 15 and Day 16), participants will receive continuous oral doses of PF-06939999 (QD or BID) under an empty stomach condition (ie, no food or liquids other than water will be consumed for 2 hours before and 1 hour following each dose). On Cycle 1 Day 15, participants will receive an oral dose of PF-06939999 under the fasted condition (overnight fasting of at least

10 hours; water permitted). On Cycle 1 Day 16, participants will receive another oral dose of PF-06939999 with a high-fat, high-calorie meal (breakfast) following 10-hour overnight fasting (water permitted). Serial PK samples will be collected after each dose on Day 15 and Day 16 per the Schedule of Activities. Subsequently, participants will receive the remaining drug treatment under an empty stomach condition. Participants who have had a gastrectomy or have dietary or other restrictions that preclude a 10- hour overnight fast (water permitted) or consumption of the high fat, high calorie meal will not be required to participate in this assessment.

Details regarding PF-06939999 administration and food requirements for participants in the the food-effect assessment are provided in Section 6.2.4.2.2.

4.2. Scientific Rationale for Study Design

4.2.1. Non-Small Cell Lung Cancer (NSCLC)

About 80-85% of lung cancers are histologically classified as NSCLC, which includes 2 major sub-types: 1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma (rare), and other cell types) and 2) squamous cell (epidermoid) carcinoma.[22] The 5-year survival rate of metastatic NSCLC is 4%.[23]

For the majority of participants diagnosed with advanced-stage NSCLC without targetable genetic aberrations, platinum-based doublet chemotherapy (ChTx) has been the standard of care (SOC) for over 30 years. With the exception of bevacizumab,[24,25] and despite extensive study of multiple targeted and cytotoxic agents, addition of a third agent to platinum-doublet chemotherapy has not been shown to improve progression-free survival (PFS) or overall survival (OS) over platinum-doublet chemotherapy alone in randomized studies.[26] Targeting driver mutations responsible for tumor progression (EGFR receptor and the EML4-ALK receptor) is modestly effective; however resistance to these therapies inevitably ensues.[27,28,29] Checkpoint inhibitors including anti-PD-1 and anti-PD-L1 have recently approved as 1L and 2L treatment regimens in metastatic NSCLC.[30,31,32] Unfortunately, only a sub-group of these participants responds and shows long-term survival to these therapies indicating that a significant unmet medical need exists for NSCLC participants as the majority do not respond to checkpoint inhibitors.

PRMT5 is highly expressed in lung cancer cells, where it has been identified to promote lung cancer growth and also accelerate metastasis. NSCLC is dependent on PRMT5 enzymatic function for growth as both genetic inhibiton and small molecule inhibitors block proliferation of lung cancer cells. NSCLC models have demonstrated strong anti-tumor responses to PF-06939999. Splicing dysregulation has been well characterized as a molecular feature of NSCLC.[3,17,19] Computational analysis identified specific splicing factor mutations enriched in NSCLC cell lines sensitive to PF-06939999, including RBM10 mutation or loss and U2AF1 mutations. Based on the rationale in Section 2.2.1.5 this tumor type is selected for Part 1 (Dose Escalation) and Part 2 (Dose Expansion).

4.2.2. Head and Neck Squamous Cell Carcinoma (HNSCC)

Head and neck squamous cell carcinoma (HNSCC) represents a heterogenous disease entity, which encompasses a variety of tumors originating in the lip/oral cavity, hypopharynx, nasopharynx or larynx with differences in epidemiology, etiology and therapeutic approach. It is the sixth most common malignancy worldwide, accounting for approximately 6% of all cases and is responsible for an estimated 1-2% of all cancer deaths.[20] HNSCC has been historically associated with tobacco and alcohol use; however, in the past decade, infection with high-risk human papillomaviruses (HPV) and especially type 16 has been implicated in the pathogenesis of a subset of HNSCCs, mainly those arising from the oropharynx.[20,21] For recurrent/metastatic disease (R/M), cytotoxic-based chemotherapy remains the standard therapeutic option and median survival of participants with palliative chemotherapy alone ranges from 6-10 months. Checkpoint inhibitors pembrolizumab and nivolumab are also established in the treatment paradigm for metastatic disease.[20,21] However, limited overall survival and toxicities with standard of care agents highlight the unmet medical need for enhanced treatment options in HNSCC. PRMT5 is frequently expressed in this disease and analysis of TCGA data uncovered an incidence of splicing factor mutations of 51% (119 genes analyzed), hence HNSCC was selected for Part 1 (Dose Escalation) and Part 2 (Dose Expansion) of this study since these tumors may be sensitive to PRMT5 inhibition.[17]

4.2.3. Esophageal Cancer

Esophageal carcinoma is the eighth most common cancer and the sixth most common cause of cancer related deaths worldwide.[33,34] Despite many advances in diagnosis and treatment, the 5-year survival rate for all participants diagnosed with esophageal cancer ranges from 15-20%.[35] The 2 most common histological types of esophageal carcinoma include squamous cell carcinomas and adenocarcinoma. Current treatment options include multimodality therapy -mainstays of current treatment include surgery, radiation and chemotherapy. With increasing clinical experience, biomarker analyses, and improvements in preclinical models, the potential role of immunotherapy in esophageal cancers is emerging with checkpoint inhibitors such as CTLA-4, PD-1 and PD-L1 which are currently underway.[36] However, advanced esophageal cancers carry a poor prognosis with limited therapeutic options, and few major therapeutic advances. PRMT5 is overexpressed in esophageal cancer. Using TCGA analysis, the incidence of mutation in 119 splicing factors analyzed in esophageal cancer samples was 44%, hence this tumor type was selected for Part 1 (dose escalation) of the study.

4.2.4. Endometrial Cancer

Endometrial cancer is the most common gynecologic malignancy in the developed world. In 2016, 60,050 women were diagnosed with endometrial cancer in the US and there were over 10,000 deaths due to this disease.[37] Endometrial cancer is a heterogenous malignancy with very different prognoses: Endometroid cancer (type 1 endometrial cancer) accounts for 85% of all endometrial cancers and has a good prognosis. Serous carcinomas and clear cell carcinomas (CCC) are traditionally designated nonendometrioid carcinomas (type II endometrial cancers) and are very aggressive tumors.[37] At the time of diagnosis, 67% of women have disease confined to the uterus and an associated 5-year survival rate of 95%. In

contrast, the 8% of participants with distant metastases at the time of diagnosis have a 5-year survival rate of 17% and face cytotoxic chemotherapy (primarily taxanes, anthracyclines and platinum drugs) with limited responses. A triplet regimen of paclitaxel, doxorubicin and cisplatin (TAP) in participants with advanced and recurrent endometrial cancers has an ORR of 57% and median OS of 15.3 months and is associated with chemotherapy related toxicities.[38] Hormonal therapy is better tolerated but results in response rates between 18% and 34%. With taxanes alone showing response rates of greater than 20% in select participants (taxane-naïve) with recurrent disease, effective second line therpaeutic approaches are warranted in this participant population.[38] Phase I trials testing immunotherapy agents in endometrial cancer are ongoing and have demonstrated encouraging immunologic responses but few clinical responses in heavily pretreated participants with advanced disease, making this an area of high unmet medical need.[38] PRMT5 is expressed in endometrial cancer. Using TCGA analysis, the incidence of mutation in 119 splicing factors analyzed in endometrial cancer samples was 38%, hence this tumor type was selected for the Part 1 (dose escalation) portion of the study.

4.2.5. Cervical Cancer

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death among females in less developed countries. Early-stage cervical cancer can be cured with surgery, while concurrent chemoradiation is the treatment of choice for locally advanced stages. Participants with recurrent or metastatic cancers have limited treatment options: the use of cisplatin-based chemotherapy regimens is the first-line treatment for advanced cervical cancer. However, it has low response rates (20%), short median PFS (2.8-3.2 months) and OS (6.2-8.0 months).[39] Recently, bevacizumab has been approved in combination with chemotherapy as first-line therapy, with a statistically significant OS improvement as compared with chemotherapy alone.[40] No validated treatment options exist beyond first-line treatment regimens. Chemotherapy is associated with substantial toxicity and poor efficacy with a median overall survival of 7 months. New effective treatment options are therefore needed in this setting. PRMT5 is expressed in cervical cancer. Using TCGA analysis, the incidence of mutation in 119 splicing factors analyzed in cervical cancer samples was 42%, hence this tumor type was selected in Part 1 (dose escalation) of the study.

4.2.6. Urothelial Carcinoma

Urothelial carcinoma (bladder cancer) is the second most common genitourinary malignant disease in the USA. Risk factors include genetic and molecular abnormalities, chemical or environmental exposures and chronic irritation. More than 90% of bladder cancers are transitional cell carcinomas, 5% are squamous cell carcinomas, and less than 2% are adenocarcinomas.[41] Cisplatin-based chemotherapies have been the SOC for metastatic bladder cancer for over 30 years and is the first-line treatment for advanced tumors sensitive to platinum salts however, long-term responses are rare and relapses often occur within 3 months of the end of chemotherapy. Additionally, almost half of the participants are not eligible for first-line cisplatin-containing chemotherapy, with no clear SOC, but carboplatin-based regimens (gemcitabine-carboplatin) or single agent therapies are considered acceptable. As second-line therapy, only vinflunine is approved in Europe with a

overall survival (OS) of 6.9 months and taxanes are used in the U.S.(paclitaxel response rates 5-10% with median OS of 6.5-7.2 months).[42] Better response rates (15-60%) but higher toxicity rates with multidrug combinations including taxanes are available in the U.S. Recently, clinical trials are evaluating checkpoint inhibitors as frontline therapy for cisplatin eiligible and ineligible participants. However, a large majority of participants do not respond to anti-PD(L)1 drugs as monotherapy making this an area of high unmet medical need for combination IO treatments and novel therapeutic options such as PF-06939999.[42,43] PRMT5 is expressed in this disease, and bladder cancer models have demonstrated strong anti-tumor responses to PF-06939999. Using TCGA analysis, the incidence of mutation in 119 splicing factors analyzed in bladder cancer samples was 51%, hence this tumor type was selected for Part 1 (dose escalation) and Part 2 (dose expansion) of the study.

4.2.7. Drug Resistance

Development of drug resistance is a reality for many participants being treated with targeted agents. Initial clinical response is strong, but development of resistance to these drugs is common, with relapse occurring as early as 2 months of treatment.[16] Mechanisms tumors use to evade targeted therapies involve bypass of the targeted pathways by utilizing alternative signaling pathways, regulating gene expression and acquiring DNA mutations in oncogenic drivers. PF-06939999 targets a unique PRMT5-driven cellular process, alternative splicing, which remains a vulnerability in cancer cells where resistance has emerged to chemotherapy, oncogenic driver mutation therapies, cell cycle inhibitors and immunotherapy. PF-06939999 demonstrated efficacy in several drug resistant cell lines, suggesting combinations or later line therapy options in the clinic may be effective in multiple cancer indications. This provides additional rationale for developing PF-06939999 in participants with advanced or metastatic HNSCC, NSCLC, esophageal, endometrial, cervical and bladder cancer that are resistant to standard therapy or for whom no standard of therapy is available in Part 1.

4.2.8. Background of Biomarker Assessments

The objectives of the biomarker assessments is to (1) provide insight into the pharmacological effects of PF-06939999 by measuring CCI levels on target proteins such as SmD1, SmD3 and SmB/B' prior to treatment, during treatment, and upon progression when appropriate samples are available; and (2) test the hypothesis of a participant selection strategy by retrospectively assessing mutations in splicing factor genes, aberrant splicing patterns and CCI PRMT5 inhibitor activity on the pharmacodynamic (PD) biomarker was originally assessed by measuring decreases in CCI level detected by an in-cell ELISA and more recently by a flow-based assay utilizing a pan-CCI antibody (CST #13222), but will be replaced by a plasma-based liquid chromatography-mass spectrometry (LC/MS) assay. The biomarker assessments may contribute to confirming target exposure/engagement, determining PD effects and identifying those participants who are most likely to benefit from treatment.

Since cancer types included in Part 1 Dose Escalation of this study are solid tumors, an immunohistochemistry (IHC) assay for CCI will be developed for participants who provide both pre- and post-treatment tumor samples. Easily accessible biomarkers such as those which can be detected in peripheral blood are always desirable options if available. Recent cell culture and mouse tumor model studies indicated that PF-06939999 could reduce more than 50% of supernatant and plasma free CCI respectively; whereas no change in the relevant control asymmetric dimethyl arginine (ADMA) level was detected, manifesting the specificity of PF-06939999. Furthermore, a correlation was observed between plasma CCI and the tumor volume in a mouse tumor model (data not shown), raising the possibility of utilizing free plasma CCI concentration as a PD and even a response predictive biomarker. A measurement of free CCI or plasma by an aforementioned LC/MS[44] assay has been developed to enable PD biomarker analysis in a non-invasive way with the possibility of monitoring pre- and post-treatment samples at multiple time points. Since PRMT5 activity was shown to be associated with both adaptive and innate immune responses, peripheral blood RNA profiling will be performed for identifying potential PD biomarkers and for additional CCI purposes such as MoA (eg activation of CD8 T cell activity) or/and safety analysis (eg, identification of any toxicity-related gene signature).

As previously stated, cancer cell lines carrying splicing factor mutations are more sensitive to PRMT5 inhibitors; for example, NSCLC cell lines with hotspot splicing factor mutations are more sensitive to PF-06939999 than those without mutation, and a participant stratification strategy based on these observations was therefore proposed accordingly. Splicing factor mutations will be assessed by using either a targeted sequencing approach or by whole exome sequencing (WES) focusing on the recently identified 119 splicing factor genes.[45] A recent TCGA publication reported that tumors have up to 30% more alternative splicing events than normal tissue, and there are associations between somatic variants of splicing factors and alternative splicing events.[12] Therefore an effort will be made to identify common splicing variant events from tumor cell line data and to look for landmark splice variants in TCGA data with the expectation that a small set of alternatively spliced variants only detectable in PRMT5 sensitive tumors may be found to serve as predictive biomarkers.

The results may help in the future development of PF-06939999 as a single agent, or in combination with other compounds, and may provide information on specific participant populations that may respond to the Investigational Product.

4.2.9. Scientific Rationale for Biomarker Studies

Biomarker studies will be used to help understand the in vivo mechanism of action of the agent(s) in this trial as well as identify potential mechanisms of resistance.

Splicing factor mutations in archived or fresh biopsied tumor tissues will be analyzed retrospectively. In addition, this study will also evaluate and attempt to identify predictive molecular targets/signatures in vivo. Sample collection details for these studies can be found in the SoA.

4.3. Justification for Dose

4.3.1. Starting Dose

The rationale for the starting dose in this study is based on all available nonclinical data including PK, pharmacodynamics, efficacy in xenograft mouse models, and toxicity observed in rat and dog. The goals of selecting the starting dose were: to identify a dose that is expected to have pharmacologic effects and is reasonably safe to use; and to minimize exposure to subtherapeutic doses.

As described in Section 2.2.3, predicted CLp and Vss of PF-06939999 in humans were 3.1 mL/min/kg and 1.6 L/kg, respectively. The projected human effective half-life is approximately 6 hours, which was the rationale for the intial evaluation of the twice daily (BID) dose regimen following the first cohort receiving a once daily (QD) dose regimen. Preliminary data (PK, PD, safety) from early cohorts of the study suggested that a QD dose regimen may also be feasible and will be evaluated for better participant compliance and convenience in subsequent dose escalation cohorts.

Based on the PK/PD modeling in xenograft models with Pfeiffer (lymphoma) and SW1990 (pancreatic cancer) cell lines, the pharmacologically active dose (PAD) was predicted to be 50 mg BID, and corresponds to the tumor stasis concentration in these models and approximately 90% inhibition of CCI in the tumor. Using the MOLT4 (leukemia) xenograft model as representing sensitization to PRMT5 inhibition in a tumor with splicing factor mutation, the tumor stasis concentration was approximately 10-fold lower, suggesting the PAD may be lower in tumor indications with increased incidence of splicing dysregulation.

In the pivotal study the HNSTD and NOAEL of PF-06939999 in dog was 0.1 mg/kg/day, based on GI and hematologic toxicities. The toxicities which led to the determination of HNSTD are considered to be reversible and monitorable in humans. Similar GI toxicities occurred in rats at the highest dose of 30 mg/kg/day, and the middle dose of 10 mg/kg/day was determined to be the STD_{10}.

Using a body surface area scaling approach, the human equivalent dose (HED) for the HNSTD/NOAEL (0.1 mg/kg once daily) dose in dog is approximately 3.2 mg/day (assuming a body weight of 60 kg). The HED for STD_{10} in rat is approximately 100 mg/day. Therefore, the dog is considered the most sensitive species and is used for setting the starting dose in humans. Based on the lowest available tablet strength (0.5 mg), the proposed starting dose is 0.5 mg po once daily (QD), or approximately one sixth the HED of the HNSTD/NOAEL in dogs. This starting dose is projected to result in less than 20% CCI inhibition based on translational PK/PD modeling and is considered reasonably safe given the predicted toxicities described above.

The human unbound steady-state C_{ave} and C_{max} of PF-06939999 at the starting dose is projected to be 0.2 nM and 0.39 nM, respectively, resulting in an approximate 14.5-x and 15.1-x margin relative to the observed unbound C_{ave} (2.9 nM) and C_{max} (5.9 nM) at HNSTD/NOAEL in dog, (po 0.1 mg/kg/day), and approximately 475-x and 528-x relative to the unbound C_{ave} (95 nM) and C_{max} (206 nM) at STD_{10} in rat. The projected exposures at the starting dose could be considered a conservative estimate as they do not incorporate impact of efflux by P-gp and BCRP, which could result in exposures lower than predicted, thereby leading to a larger margin relative to HNSTD.

The starting dose will be 0.5 mg given orally QD on a continuous basis in 28 day cycles. Subsequent cohorts will utilize a BID or QD dosing regimen on a continuous basis. Other dosing regimens, eg, intermittent dosing (such as 3 weeks on 1 week off), may also be considered in the study if supported by emerging clinical data.

4.3.2. Criteria for Dose Escalation

A 2-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used in dose escalation in Part 1A and 5-parameter model specifically developed for combinations will be used for Part 1B dose finding. See 10.9 for more details on the model used in Part 1A and Technical Supplement to Section 10.9 for more details of the model used in Part 1B. Using DLT data at all tested dose levels and pre-specified prior distribution of model parameters, posterior probabilities of probability of having a DLT falling into 3 dosing intervals (underdosing, target dosing, overdosing) will be calculated for all dose levels. A dose may only be used for newly enrolled participants in Part 1A and Part 1B if the risk of excessive toxicity (toxicity higher than 0.33 at that dose is less than 25%).

If intermediate dose levels are used, all the dose levels selected for administration will satisfy EWOC principle, ie, risk of over-dosing at this dose is predicted to be less than 25%.

Final selection of the dose for the next cohort will be made based on all the available toxicity information (including adverse events which are not DLTs), PK, PD, and other relevant data as well as predictions of toxicity levels using BLRM.

The provisional dose levels to be evaluated are listed in Table 10.

Table 10. Provisional Dose Levels in Dose Escalation

Cohort	Total Daily Dose (mg)	Regimen	Maximal % increase[a]
DL1 (starting dose)	0.5	QD (0.5 mg)	-
DL2	1	BID (0.5 mg)	100%
DL3	2	BID (1 mg)	100%
DL4	4	BID (2 mg)	100%
DL5	8	BID (4 mg)	100%
DL6	16	BID (8 mg)	100%
DL7	<32	QD or BID (TBD[b])	100%
DL8 and beyond	TBD[b]	QD or BID (TBD[b])	100%

a. Calculated based on total daily dose (mg/day).
b. To be determined.
Note: Alternative dosing may be evaluated based on evolving PK and safety data.

A maximum of 100% increment may be used in both Part 1A and Part 1B, given that the predicted human toxicities based on toxicities observed in both animal species are considered monitorable and reversible; however a smaller increment may be used based on review of data available from prior cohorts. Dose escalation cohorts may remain with the same regimen (QD or BID) or proceed to a different dosing regimen (eg, from BID to QD) compared to that for the previous dose level. However, within a given cohort, all participants should be tested either QD or BID but not both. The maximal dose increment will be calculated based on total daily dose regardless of the dosing regimen. The decision for testing a different dosing regimen in subsequent cohorts will be based on evaluation of available PK, PD, and safety data. Dose escalation utilizing continuous dosing will stop when stopping criteria are met (see Section 9.4.1). For individual participants, interchanging QD and BID dosing regimen during treatment is not allowed.

If warranted, an intermittent dosing schedule may be used to mitigate toxicities observed in this first in human study. In such case, participants may for example receive PF-06939999 administered orally BID or QD for 21 days on followed by 7 days off. The intermittent dose escalation schedule will begin at the MTD based on escalation using a continuous dosing regimen, and will proceed towards determination of MTD of the intermittent schedule (see Table 11).

Table 11. Provisional Dose Levels in Dose Escalation with Intermittent Dosing Regimen

Cohort	Dose [mg/BID]	Maximal % increase
Starting dose (DL1)	X	-
DL2	≤2x	100%
DL3	≤4x	100%
DL4*	≤8x	100%

*Higher dose levels might be tested if warranted. Abbreviations: DL = dose level; x = the maximum tolerated dose determined from the escalation under continuous dosing regimen.

Intrapatient dose escalation will not be allowed in any regimen.

4.3.3. Dose Limiting Toxicity Definition

Participants who discontinue treatment before completing Cycle 1 or receive less than 75% of the planned doses for reasons other than treatment-related toxicity (eg, missed appointments, misplaced investigational product supplies, development of rapidly progressing disease) might be replaced.

For the purpose of dose escalation, the DLT observation period will be the first cycle of treatment (within 28 days of the first dose) in each participant including the Day 29 laboratory assessments (for example, for PF-06939999 monotherapy with 28-day cycle, day 29 laboratory assessments should be Cycle 2 Day 1 laboratory assessments). Significant adverse events considered to be related to the investigational product or treatment under investigation that occurs after the DLT observation period will be reviewed in context of all safety data available. That review may result in re-evaluation of the dosing level or regimen.

Severity of adverse events (AEs) will be graded according to CTCAE version 5.0.

Hematologic Dose-Limiting Toxicities:

Any Grade 4 hematologic AE is a DLT with the following clarifications:

1. Grade 4 neutropenia regardless of intervention is a DLT.

2. Febrile neutropenia (defined as absolute neutrophil count $<1000/mm^3$ with a single temperature of >38.5°C [101.3°F] or a temperature of ≥38°C [100.4°F] sustained for more than 1 hour) is a DLT.

3. Grade 3 neutropenia with infection is a DLT.

4. Grade 3 thrombocytopenia with ≥ Grade 2 clinically significant bleeding (defined as hospitalization or urgent medical intervention for atypical bleeding sites) is a DLT.

5. Grade 3 anemia requiring blood transfusion is a DLT.

Non Hematologic Dose-Limiting Toxicities:

Any Grade ≥3 non-hematologic adverse events (AEs) is a DLTs with the following clarifications:

1. Grade 3 nausea/vomiting or diarrhea lasting ≥4 days after treatment with adequate antiemetics or other supportive care is a DLT.

2. Confirmed drug induced liver injury (DILI) meeting Hy's law criteria is a DLT.

3. For participants with Grade 2 hepatic transaminase or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis, a hepatic transaminase or alkaline phosphatase level >10 times the upper limit of normal will be considered a DLT.

4. Clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by Pfizer and the investigators. All DLTs need to represent a clinically significant shift from baseline.

Any toxicity causing greater than 2 weeks of dose delay is a DLT. Note: Participants deriving clinical benefit from study treatment who experience a DLT may continue on study at a reduced dose following recovery of the AE to Grade 1 or baseline, only after discussion between the Investigator and Sponsor.

Any dose reduction due to an adverse event (per protocol) during the first cycle will be qualified as the participant experiencing DLT.

The following AEs will not be adjudicated as DLTs:

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

4.3.4. Maximum Tolerated Dose Definition

Maximum tolerated dose (MTD) is defined as a dose with probability of a DLT from the target toxicity interval. The target interval for the DLT rate is defined as (0.16,0.33).

For any given participant that is on-treatment at dose levels that are subsequently considered to be above the MTD, the option to dose reduce will be discussed. If a participant tolerated the above MTD dose level well and is benefiting from therapy, continuation of treatment at the above MTD dose level will require re-consenting.

4.3.5. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further investigation based on Phase 1 dose escalation and expansion study results. Based on the safety, tolerability and PK/PD data from Part 1A dose escalation, the single agent recommended dose for expansion will be selected as an estimate of monotherapy RP2D. After expansion cohorts with larger sample size and sufficient data, the final RP2D will be made by sponsor based on the recommendation from investigators and study team. The determination of RP2D will be based on safety, tolerability, and early sign of clinical efficacy and benefit. Based on the safety, tolerability, and PK/PD data from Part 1B combination dose finding, the combination recommended dose for expansion will be selected as an estimate of combination RP2D. Similarly, the final combination RP2D will be determined after combination expansion cohort. Combination RP2D may be different from monotherapy RP2D due to potential overlap toxicity or drug-drug interaction.

4.3.6. End of Study Definition

The end of the study is defined as two years after last participant first visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

During COVID-19 pandemic, please refer to Appendix 13 (Section 10.13) for additional eligibilities.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Females and/or male participants age ≥18 years.

   - Refer to Section 10.4 Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

2. For Part 1 dose escalation participants must have histological or cytological diagnosis of a solid tumor that is advanced/metastatic, participants are intolerant to standard treatment or resistant to standard therapy* for the following tumor types:

   - NSCLC;
   - HNSCC;
   - Esophageal;
   - Endometrial;
   - Cervical;
   - Bladder.
   - *Intolerance or progression on prior therapies must be documented for study enrollment.

3. For Part 2 single agent dose expansion, NSCLC participants:

    - Histologically or cytologically confirmed, locally advanced or metastatic NSCLC including squamous cell carcinoma or adenocarcinoma;

    - For NSCLC without available 1L targeted therapies (EGFR, ALK, ROS1, BRAF and NTRK negative), 2L+ NSCLC who have progressed after at least 1 line of checkpoint inhibitors (CPI) and 1 line of platinum based chemotherapy regimen given together or sequentially in the metastatic setting;

    - For NSCLC with available 1L targeted therapies (EGFR, ALK, ROS1, BRAF or NTRK posivite), 2L+ NSCLC who have progressed after at least 1 line of targeted therapies;

    - Should receive no more than 3 lines of systemic therapies in metastatic setting;

    - Radiographic progression during or after the most recent treatment.

4. For Part 2 combination with docetaxel expansion, NSCLC participants:

    - Histologically or cytologically confirmed, locally advanced or metastatic NSCLC including both squamous cell carcinoma and adenocarcinoma;

    - For NSCLC without available 1L targeted therapies (EGFR, ALK, ROS1, BRAF and NTRK negative), 2L+ NSCLC who have progressed after at least 1 line of checkpoint inhibitors (CPI) and 1 line of platinum based chemotherapy regimen given together or sequentially in the metastatic setting;

    - For NSCLC with available 1L targeted therapies (EGFR, ALK, ROS1, BRAF or NTRK posivite), 2L+ NSCLC who have progressed after at least 1 line of targeted therapies;

    - Have not been treated with taxane chemotherapy (docetaxel or palclitaxel) in locally advanced or metastatic setting;

    - Should receive no more than 2 lines of systemic therapies in metastatic setting;

    - Radiographic progression during or after the most recent treatment.

5. For Part 2 urothelial carcinoma participants:

    - Histologically or cytologically confirmed, locally advanced or metastatic urothelial carcinoma of the bladder, renal pelvis, ureter or urethra;

- 2L+ urothelial cancinoma who have progressed after at least 1 line of standard of care chemotherapy (cisplatin/carboplatin+ Gemcitabine; or MVAC) and 1 line of checkpoint inhibitor in the metastatic setting;
- Should receive no more than 3 lines of systemic therapies in metastatic setting;
- Radiographic progression during or after the most recent treatment.

6. For Part 2 HNSCC participants:
   - Histologically or cytologically confirmed locally advanced or metastatic HNSCC;
   - 2L+ HNSCC who have progressed after at least 1 line of standard of care systemic chemotherapy and one line of checkpoint inhibitors in the metastatic setting;
   - Should receive no more than 3 lines of systemic therapies in metastatic setting;
   - Radiographic progression during or after the most recent treatment.
7. A mandatory archived formalin fixed- paraffin embedded (FFPE) tumor tissue block must be provided. If an archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample should be obtained in accordance with local institutional practice for tumor biopsies.
8. Participants must have at least 1 measurable lesion (not previously irradiated) as defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1, Section 10.11) that has not been previously irradiated.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
10. Adequate Bone Marrow Function, including:
    a. Absolute Neutrophil Count (ANC) $\geq$1,500/mm^3 or $\geq$1.5 x 10^9/L;
    b. Platelets $\geq$100,000/mm^3 or $\geq$100 x 10^9/L;
    c. Hemoglobin $\geq$9 g/dL. Limited transfusions to reach this value are allowed, after discussion with the sponsor's medical monitor. There should not be a chronic need for transfusions in the recent (approximately 3 month) past.

11. Adequate Renal Function, including:

    a. 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. In equivocal cases, a 24-hour urine collection test can be used to estimate the creatinine clearance more accurately;

    b. Estimated creatinine clearance ≥40 mL/min for participants with urothelial carcinoma.

12. Adequate Liver Function, including:

    For Part 1A, 2A, 2B and 2C monotherapy

    a. Total serum bilirubin ≤1.5 x upper limit of normal (ULN) for PF-06939999 monotherapy (unless the partipant has documented Gilbert syndrome);

    b. Aspartate and Alanine aminotransferase (AST and ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor) for PF-06939999 monotherapy; AST and ALT ≤1.5 x ULN for PF-06939999 in combination with docetaxel;

    For Part 1B and 2D in combination with Docetaxel

    c. Total bilirubin ≤ ULN for PF-06939999 in combination with docetaxel;

    d. Aspartate and Alanine aminotransferase (AST and ALT) ≤1.5 x ULN; alkaline phosphatase (ALP) ≤2.5 x ULN for PF-06939999 in combination with docetaxel.

13. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment. Participants with hypothyroidism of hypopituitarism resulting from immunotherapy on stable hormone replacement therapy and participants with adrenal insufficiency receiving doses <15 mg/day of prednisone equivalents are eligible.

14. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

15. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Part 1 – Dose Escalation Monotherapy

1. Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Participants with a history of CNS metastases or cord compression are eligible if they have been definitively treated (eg, radiotherapy, stereotactic surgery), have discontinued corticosteroid treatment (except for adrenal replacement therapy) for these metastases for at least 4 weeks, and are clinically stable for 3 months (requires MRI confirmation) with no evidence of progression at time of study enrollment.

2. Participants with advanced/metastatic, symptomatic, visceral spread, that are at risk of life threatening complications in the short term (including participants with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement). Note: Participants with indwelling catheter for drainage, or requirement for drainage no more frequently than monthly will be allowed.

3. Participants with any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.

4. Major surgery within 4 weeks prior to study entry.

5. Radiation therapy within 4 weeks prior to study entry.

6. Systemic anti-cancer therapy within 4 weeks prior to study entry (6 weeks for mitomycin C or nitrosoureas). If the last immediate anti-cancer treatment contained an antibody based agent(s) (approved or investigational), then an interval of 28 days or 5 half lives (whichever is shorter) of the agent(s) prior to receive the investigational product treatment is required.

7. Prior irradiation to >25% of the bone marrow (see Section 10.12 Appendix 12: Bone Marrow Reserve in Adults).

8. Participants with active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness. HIV seropositive subjects who are healthy and low risk for -AIDS related outcomes could be considered eligible. Eligibility criteria for -HIV positive- subjects should be evaluated and discussed with sponsor's medical monitor, and will be based on current and past CD4 and Tcell counts, history (if any) of -AIDS defining- conditions (eg, opportunistic infections), and status of HIV treatment. Also the potential for drug drug interactions will be taken into consideration. In equivocal cases, with positive serology, those participants with a negative viral load are potentially eligible provided the other entry criteria are met. Note: Inclusion of participants with well controlled HIV, HBV or HCV can be discussed with the sponsor on a case by case basis.

9. Bleeding esophageal or gastric varices <2 months prior to informed consent document (ICD) date.

10. Unmanageable ascites (limited medical treatment to control ascites is permitted, but all participants with ascites require review by the sponsor's medical monitor).

11. Baseline 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT [QTc] interval >470 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of active myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >470 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. The average of the triplicate QTc or QRS values should be used to determine the participant's eligibility. If the average QTc exceeds 470 msec, or the average QRS exceeds 120 msec, the participant is not eligible. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants. Cases must be discussed in detail with the sponsor's medical monitor to judge eligibility.

12. Therapeutic anticoagulation. However, low molecular weight heparin, vitamin K antagonists or factor Xa inhibitors may be allowed following discussion with the Sponsor.

13. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsade de Pointes, clinically significant arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), left anterior hemiblock, bifascicular block, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF, New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism or other clinical significant episode of thrombo embolic disease.

Ongoing cardiac dysrhythmias of National Cancer Institute (NCI) CTCAE Grade ≥2, atrial fibrillation of any grade (Grade ≥2 in the case of asymptomatic lone atrial fibrillation). Subjects with cardiac rhythm device/pacemaker must be discussed in detail with sponsor's medical monitor to judge eligibility.

14. Hypertension that cannot be controlled by medications (>150/90 mmHg despite optimal medical therapy) or requiring more than 2 medications for adequate control.

15. Participants with intolerance to or who have had a severe (Grade 3) allergic or anaphylactic reaction to any of the substances included in the investigational product (excluding excipients).

16. Participation in other studies involving investigational drug(s) within 28 days prior to first dosing. Note: Participation in long term follow up of other studies is allowed if no procedures which may interfere with the interpretation of study results will be performed.

17. Known or suspected hypersensitivity to PF-06939999. For PF-06939999 in combination with docetaxel, history of hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80 is also excluded.

18. Inability to consume or absorb study drug, including but not limited to: Active inflammatory gastrointestinal (GI) disease, known diverticulitis or previous gastric resection or lap-band surgery. Impairment of gastro-intestinal function or GI disease that may significantly alter the absorption of PF-06939999 tablets, such as history of GI surgery with may result in intestinal blind loops and participants with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhea of CTCAE Grade >1. Participants with HNSCC requiring drug administration via NG tube are eligible if they meet other criteria.

19. Current use or anticipated need for food or drugs that are known strong and/or moderate CYP3A4/5 inhibitors, including their administration within 10 days or 5 half lives of the CYP3A4/5 inhibitor, whichever is longer prior to first dose of investigational product (Strong CYP3A4/5 inhibitors: eg, 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; Moderate CYP3A4/5 inhibitors: eg, erythromycin, verapamil, atazanavir, delavirdine, fluconazole, darunavir, diltiazem, aprepitant, imatinib, tofisopam, ciprofloxacin, and cimetidine).

20. Current use or anticipated need for drugs that are known strong/moderate CYP3A4/5 inducers, including their administration within 10 days or 5 half lives of the CYP3A4/5 inducer, whichever is longer prior to the first dose of investigational product (Strong CYP3A4/5 inducers: eg, phenobarbital, rifampin, phenytoin,

carbamazepine, rifabutin, rifapentin, clevidipine, St. John's Wort; Moderate CYP3A4/5 inducers: eg, bosentan, efavirenz, etravirine, modafinil, nafcillin).

21. Current use or anticipated need for drugs that are known P-glycoprotein (P-gp) or BCRP inhibitors, including their administration within 7 days of the P-gp or BCRP inhibitor prior to the first dose of investigational product. P-gp inhibitors may include amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir or verapamil. BCRP inhibitors may include curcumin, cyclosporine A, and eltrombopag.

22. Serum or urine pregnancy test (for females of childbearing potential) positive at screening.

23. Other 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 participant inappropriate for entry into this study.

24. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

The following guidelines are provided.

5.3.1. Photosensitivity

Participants will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the participants' exposure to light including sunlight, and high intensity ultraviolet B (UVB) light sources such as tanning beds, tanning booths and sunlamps. Participants should be encouraged to apply sunscreen/sunblock daily and to wear clothing that covers areas of exposed skin when outdoors during daylight hours.

5.3.2. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (Section 10.4 Appendix 4) and will confirm that the has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception

consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial, who do not meet 1 or more criteria required for participation in the trial during the screening procedures and are not subsequently assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). It should be stated if this information will be captured in the case report form (CRF) or elsewhere.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened participants should be assigned a different participant number as for the initial screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

For this study, the investigational product is PF-06939999.

Participants enrolled in Parts1A, 2A, 2B, and 2C will receive PF-06939999 orally daily on a continuous basis as monotherapy in 28 day cycles.

Participants enrolled in Parts 1B and 2D will receive PF-06939999 orally on a continuous basis in combination with docetaxel given on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, or participant refusal, whichever occurs first.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored- shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record. Participant will return all empty containers and unused product to the investigator.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. Site staff will instruct participants on the proper storage requirements for take home- study intervention.

8. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

6.2.1. Preparation and Dispensing

The investigational product (PF-06939999) should be dispensed at each visit per the schedule of treatment. A qualified staff member will dispense the investigational product in the bottles provided, in quantities appropriate for the study visit schedule. The participant/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site at the next study visit.

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

For Part 1B and 2D PF-06939999, docetaxel will be used in accordance with the US Package Insert (USPI).

6.2.2. Investigational Product Supplies

PF-06939999 will be supplied by Pfizer. The clinical sites will receive PF-06939999 prior to enrollment of the first participant.

The clinical site pharmacy will dispense the supply that is appropriate for the participant.

Docetaxel is commercially available and will be supplied by the clinical sites as standard of care and reimbursed by the participant's insurance. Pfizer will reimburse the cost of docetaxel for participants who do not have insurance.

6.2.3. Dosage Form(s) and Packaging

PF-06939999 will be provided as tablets for oral administration. The 0.5 mg, 1 mg and 5 mg, will be supplied in separate bottles and labeled according to local regulatory requirements.

Docetaxel is commercially available and will be used in accordance with the US Package Insert (USPI).

6.2.4. Administration

6.2.4.1. PF-06939999 Administration

Participants will swallow the investigational product whole, and will not manipulate (eg, crush) or chew the investigational product prior to swallowing. Participants who are unable to swallow whole tablets may dissolve their dose in oral syringe(s) as outlined in the IP manual to allow for suspension administration either orally or via an NG tube.

PF-06939999 will be administered orally initially QD, then BID or QD for subsequent cohorts on a continuous basis. If supported by emerging data, alternative intermittent dosing regimen may be considered. For monotherapy cohorts, a cycle is defined as continuous dosing of 28 days, regardless of missed doses or dose delays. For Cohorts 1B and 2D

(PF-06939999 in combination with docetaxel) a cycle is defined as 21 days to be consistent with docetaxel treatment cycles and dosing schedule.

For the BID dosing regimen, on days where the morning dose of PF-06939999 is held due to a specific study visit, the second dose on that day should be taken no sooner than 8 hours, and no later than 16 hours post the first dose on that day (allowable treatment window ±4 hours). For once daily dosing regimen, the allowable treatment window is ±4 hours.

PF-06939999 will be administered orally on an empty stomach without adjustment for body size at every cycle. Participants 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 participant misses a dose or day of treatment, they must be instructed not to "make it up" but to resume subsequent doses as prescribed. In addition, if a participant vomits any time after taking a dose; they must be instructed not to "make it up" but to resume subsequent doses as prescribed. Lastly, if a participant inadvertently takes 1 extra dose during a day, the participant should not take the next dose of PF-06939999.

Investigational product (PF-06939999) tablets can also be dissolved into a suspension which can be administrated orally or via nasogastric (NG) tube if needed. Detailed instructions for suspension preparation and administration are provided in the IP manual.

On Cycle 1 Day 15 and Day 16, Part 2 participants participating in the food effect assessment will receive PF-06939999 under fasted and fed conditions, respectively, at the site, and have blood samples collected for PK characterization.

A dosing diary will be given to the participant to support at-home dosing.

6.2.4.2. Food Requirements

6.2.4.2.1. Food Requirements (Except for the Food-Effect Cohort)

Oral PF-06939999 will be administered QD or BID with at least 8-oz (240 mL) of water or as a suspension for participants who are unable to swallow tablets. Investigational product is to be administered on an empty stomach, no food or liquids other than water will be consumed for 2 hours before and 1 hour following each dose throughout the study. These fasting requirements may be removed (via a letter to the investigators) if the data from the food-effect study (that will be performed in Part 2) indicate that there is not a substantial effect of food on the bioavailability of PF-06939999.

6.2.4.2.2. Food Requirements for the Food-Effect Sub-study

For all participants participating in the food-effect substudy (to be evaluated in at least 6 participants in Part 2B dose expansion), PF-06939999 will be administered under the fasted and fed conditions on Cycle 1 Day 15 and Day 16, respectively, and under empty stomach condition (see Section 6.2.4.2.1) for the remaining portion of the study.

Cycle 1 Day 15 (Fasted condition): PF-06939999 will be administered, following an overnight fast of at least 10 hours, with 8 ounces (240 mL) of water. No food will be allowed for an additional 4 hours post dose. Water will be allowed ad libitum except for 1 hour before and 1 hour after drug administration.

Cycle 1 Day 16 (Fed condition): Following overnight fasting of at least 10 hours, a test breakfast meal (described below) will be provided and must be consumed over 30 minutes. PF-06939999 will be administered with approximately 8 ounces (240 ml) of water 30 minutes after the start of the meal. No additional food will be allowed until at least 4 hours post-dose. Water will be allowed ad libitum except for 1 hour before and 1 hour after drug administration.

The test meal to be consumed will be a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) meal. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. An example test meal would be 2 eggs fried in butter, 2 strips of bacon (may be replaced with ham and cheese of similar caloric content), 2 slices of toast with butter, 4 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 participants may not be able to consume the entire meal. Study staff should record the percent of the test meal consumeed and the time it took to be consumed.

6.2.4.3. Docetaxel Administration

For participants in Parts 1B and 2D, docetaxel will be administered at 75 mg/m^2 intravenously over 1 hour on Day 1 of each 21 day cycle until disease progression, unacceptable toxicity, or participant refusal, whichever occurs first. All participants should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (eg, 8 mg BID) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Participants should be observed closely for hypersensitivity reactions, especially during the first and second infusion.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Eligible participants will be enrolled to receive PF-06939999 in an open-label, unblinded manner. In Part 1, participants will be successively assigned to the next available treatment slot. Dose level allocation will be performed by the sponsor after participants have given their written informed consent and have completed the necessary baseline assessments. The site staff will e-mail a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a participant identification number and supply

this number to the site. The participant identification number will be used on all study related- documentation at the site.

No participant shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the participant's enrollment;
- Specification of the dose level for that participant; and
- Permission to proceed with dosing the participant.
- In Part 2, allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to have an active or valid account and password with the IRT system, enter or select information including but not limited to the users ID and password, protocol number, specific protocol entrance criteria indicated in the system and the participant number. The site personnel will then be provided with, at a minimum, a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study interventions will be dispensed at the study visits as summarized in the SoA.

Returned PF-06939999 must not be redispensed to the participants.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Participant compliance with investigational product will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, and review of the participant diary. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

All investigational products will be distributed to the participant by the appropriately designated study staff at the investigational site. Participants will be required to return all unused study treatment at the beginning of each cycle. The number of tablets returned by the participant will be counted, documented, and recorded.

A participant diary will be provided to the participants to aid in compliance with the dosing instructions. The diary will be maintained by the participant to include missed or changed PF-06939999 doses. Participants will be required to return all bottles of PF-06939999 every cycle. The number of PF-06939999 tablets remaining will be documented and recorded at each clinic visit or Day 1 of each cycle. The participant diary may also be used to support this part of the PF-06939999 accountability process via a discussion between the study site staff and the participant. Discrepancies will be documented on the appropriate eCRF.

6.5. Concomitant Therapy

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions received by participants from screening until the end of study visit will be recorded on the CRF.

6.5.1. Potential Drug-Drug Interactions

All concomitant treatments that have a clinically significant potential drug interaction must be approved by the sponsor at study entry. Because inhibition of CYP3A4/5 isoenzymes may increase PF-06939999 exposure leading to potential increases in toxicities, the use of known strong and/or moderate inhibitors is not permitted within 10 days or 5 half-lives of the CYP3A4/5 inhibitors, whichever is longer, prior to the first dose of investigational product. Strong CYP3A4/5 inhibitors may include 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. Moderate CYP3A4 inhibitors may include erythromycin, verapamil, atazanavir, fluconazole, darunavir, diltiazem, delavirdine, aprepitant, imatinib, tofisopam, ciprofloxacin, and cimetidine.

Because induction of CYP3A4/5 isoenzymes may decrease PF-06939999 exposure leading to potential decrease in efficacy, the use strong/moderate CYP3A4/5 inducers is not permitted within 10 days or 5 half-lives of CYP3A4/5 inducers, whichever is longer, prior to the first dose of investigational product. Strong CYP3A4/5 inducers may include phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, and St. John's Wort. Moderate CYP3A4/5 inducers may include bosentan, efavirenz, etravirine, modafinil, and nafcillin. For Part 1B and Part 2D only, participants are allowed to receive dexamethasone (a moderate CYP3A4 inducer) for a limited duration as a premedication for docetaxel as indicated in Section 6.2.4.3.

Concomitant use of PF-06939999 and a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. CYP2D6 substrates of a narrow therapeutic index, may include thioridazine. Therefore, caution is warranted if coadministration of PF-06939999 with these and other CYP2D6 substrates occurs.

Because inhibition of P-glycoprotein (P-gp) or BCRP transporters may increase PF-06939999 exposure leading to potential increases in toxicities, the use of known inhibitors is not permitted within 7 days of P-gp or BCRP inhibitors prior to the first dose of investigational product. P-gp inhibitors may include amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir or verapamil. BCRP inhibitors may include curcumin, cyclosporine A, and eltrombopag.

Concomitant use of PF-06939999 and a substrate of the BCRP, or OCT1 transporters may increase the exposure of a substrate for the transporter. Therefore, caution is warranted if coadministration of PF-06939999 with BCRP, or OCT1 substrates occurs.

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

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted.

6.5.3. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current American Society of Clinical Oncology (ASCO) guidelines.

6.5.4. Hematopoietic Growth Factors

The use of granulocyte colony stimulating factors is permitted in this study. However, primary prophylactic use of granulocyte colony stimulating factors is not permitted during the first 28 days (DLT assessment period), but they may be used during this time to treat treatment emergent neutropenia. The use of these factors is as indicated by the current American Society of Clinical Oncology (ASCO) guidelines. Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

6.5.5. Acid Reducing Agents

The solubility PF-06939999 was greater than 2 mg/mL in the range from pH 7.0 to pH 1.1 (Section 2.2.3). Therefore, pH is not anticipated to impact oral absorption in the planned clinical dose range and acid reducing agents are permitted, including:

- H2-Receptor Antagonists (H2RAs) for symptomatic treatment of gastrointestinal disorder (including, but not limited to famotidine, ranitidine, nizatidine, cimetidine);
- Local antacids for symptomatic treatment of gastrointestinal disorder (eg, aluminum/calcium hydroxide, aluminum/calcium carbonate, bismuth subsalicylate);
- Acid reducing agents (including proton pump inhibitors) can be used for symptomatic treatment of gastrointestinal disorder.

6.5.6. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis beyond the first cycle is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drugdrug- interaction and assuming the drug is not included in Section 6.5.1 Potential Drug-Drug Interactions.

6.5.7. AntiInflammatory- Therapy

Antiinflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in Section 6.5.1 Potential Drug-Drug Interactions.

6.5.8. Corticosteroids

Chronic systemic corticosteroid use (prednisone >15 mg/day or equivalents) for palliative or supportive purposes is not permitted. However, corticosteroid use for a short duration (eg, ≥15 mg/day of prednisone, for 2 weeks) as symptomatic treatment on an individual basis may be considered after discussion with the sponsor's medical monitor or designee. For adrenal insufficiency replacement therapy, doses <15 mg/day will be allowed. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

6.5.9. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06939999 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06939999 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-06939999 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6.6. PF-06939999 Dose Modification

Every effort should be made to administer PF-06939999 on the planned dose and schedule. In the event of significant toxicity, dosing may be interrupted and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed (and attribution for the combination treatment – use if a combination is to be tested). Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom.

For Cohorts 1B and 2D, docetaxel dose modifications should be performed in accordance with the approved labeling (See Section 6.6.3).

6.6.1. PF-06939999 Dosing Interruptions

Participants experiencing Grade 3-4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have PF-06939999 interrupted. Appropriate followup- assessments should be done until adequate recovery occurs as assessed by the investigator. Doses may be held up to 4 weeks until toxicity resolution.

Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 6.6.2, unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the participant will need to return to the clinic to receive new drug supply.

Retreatment following treatment interruption for -treatment related- toxicity may not occur until all of the following parameters have been met:

- ANC ≥1,000/mm^3 for PF-06939999 monotherapy; ANC ≥1,500/$mm^3$for PF-06939999 in combination with docetaxel;
- Platelets count ≥50,000/mm^3;
- Nonhematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the participant).

If a treatment interruption 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 4 weeks of treatment interruption, PF-06939999 may be resumed. Refer to Section 6.6.2 for adverse events requiring dose reduction at the time of treatment resumption.

If participants require interruption of PF-06939999 due to treatment related toxicity for more than 4 weeks at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the Sponsor's medical monitor.

In the event of a treatment interruption for reasons other than treatment related- toxicity (eg, elective surgery) lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

6.6.2. PF-06939999 Dose Reductions

Following dosing interruption due to toxicity, the PF-06939999 dose may need to be reduced when treatment is resumed. Any dose reduction due to an adverse event (per protocol) during the first cycle will be qualified as participant experiencing DLT.

No specific dose adjustments are recommended for Grade 1/2 treatment related- toxicity. However, investigators should always manage their participants according to their medical judgment based on the particular clinical circumstances.

Participants experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Dose reduction of PF-06939999 by 1 and, if needed, 2 previously studied dose levels will be allowed depending on the type and severity of toxicity encountered. If previously studied dose levels are incomplete for QD schedule, the table below should be considered as a general recommendation. In addition, dose reduction to intermittent dose level can be considered for individual participants based on the type and severity of the toxicities after agreement between the investigator and the sponsor. Participants requiring more than 2 dose reductions 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 participant's source notes and CRF.

Table 12. PF-06939999 dose level (depending on RP2D decision)

Starting Dose	8 mg QD	6 mg QD	4 mg QD
- 1	6 mg QD	4 mg QD	2 mg QD
- 2	4 mg QD	2 mg QD	1 mg QD
- 3	Discontinue	Discontinue	Discontinue

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intrapatient dose re-escalation is not allowed.

For Part 1 dose escalation, participants experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved, and if in the opinion of the investigator and the sponsor, the participant is benefiting from therapy. In some cases, participants experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

For both Part 1 dose escalation and part 2 dose expansion, recommended dose reductions for PF-06939999 non-hematologic related toxicity are described in Table 13.

Table 13. Dose Modifications for PF-06939999 Related Toxicity: Nonhematologic

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nonhematologic	Continue at the same dose level.	Continue at the same dose level.	Hold PF-06939999 until toxicity is Grade ≤1, or has returned to baseline, within 4 weeks and then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.	Permanent discontinuation of study drug for related Grade 4 adverse events of any duration.**
Pancreatitis	Continue at the same dose level.	For Grade 2 pancreatitis, hold PF-06939999 until toxicity is resolved, then reduce the dose by 1 level.	For Grade 3 pancreatitis, consider discontinuation (continuation requires sponsor approval).*	Permanent discontinuation of study drug for related Grade 4 adverse events of any duration.**
Diarrhea	Continue at the same dose level.	For persistent Grade 2 diarrhea may consider to interrupt dosing, then restart at the same dose after toxicity is Grade ≤1. If a Grade 2 diarrhea caused weight loss, or other severe symptoms, discuss with sponsor and consider to reduce the dose by 1 level.	For Grade 3 diarrhea, hold PF-06939999 until toxicity is Grade ≤1, or has returned to baseline, then consider reducing the dose by 1 level.	Permanent discontinuation of study drug for related Grade 4 adverse events of any duration.**

* Participants may continue on trial if they are receiving clinical benefit after discussion between the investigator and sponsor.
** Exclusion: Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification. Grade 3 or 4 electrolyte abnormality lasting <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions. Grade 3 or 4 amylase and/or lipase must be accompanied by signs or symptoms or radiological evidence of pancreatitis.

For both Part 1 dose escalation and Part 2 dose expansion, recommended dose reductions for PF-06939999 hematologic related toxicity are described in Table 14.

Table 14. Dose Modifications for PF-06939999 Related Toxicity: Hematologic

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Continue at the same dose level.	Continue at the same dose level.	Hold PF-06939999 until toxicity is Grade ≤2, or has returned to baseline, and then reduce the dose by one level. • If toxicity reoccurs despite dose reduction, PF-06939999 may be held until recovery, then consider reducing the dose by one level.	Consider permanent discontinuation of study drug for related Grade 4 adverse events of any duration. (Continuation will require agreement between the investigator and sponsor).*
Neutropenia	Continue at the same dose level.	Continue at the same dose level.	Hold PF-06939999 until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level. • If toxicity reoccurs despite dose reduction, PF-06939999 may be held until recovery or ANC >1500 cells/mm^3, then consider reducing the dose by one level. • G-CSF for treatment are permitted based on Investigator judgment.	Consider permanent discontinuation of study drug for related Grade 4 adverse events of any duration. (Continuation will require agreement between the investigator and sponsor).* G-CSF for treatment are permitted based on Investigator judgement.

Table 14. Dose Modifications for PF-06939999 Related Toxicity: Hematologic

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	Continue at the same dose level.	Continue at the same dose level.	Hold PF-06939999 until platelets ≥75,000/mm^3. and then reduce the dose by one level. If toxicity reoccurs despite dose reduction, hold PF-06939999 up to 4 weeks until recovery and then reduce the dose by another dose level.	Consider permanent discontinuation of study drug for related Grade 4 adverse events of any duration. (Continuation will require agreement between the investigator and sponsor).* For platelet counts 10,000 – 25,000/mm^3, monitor every 3 days until recovery to >25,000/mm^3 For platelet counts ≤10,000/mm^3 monitor daily until recovery to >25,000/mm^3. Reduce PF-06939999 by 1 dose level. If toxicity reoccurs despite dose reduction, hold PF-06939999 until recovery and either continue at the same dose with increased monitoring, or further dose reduce by another dose level (for participants is in the first dose group, only 1 dose reduction is allowed).

* Participants may continue on trial if they are receiving clinical benefit after discussion between the investigator and sponsor. Withhold dose until toxicity is Grade ≤2, or has returned to baseline after agreement with sponsor resume treatment at a reduced dose level.

6.6.3. Docetaxel Dose Modifications

Hypersensitivity reactions (characterized by generalized rash/erythema, hypotension and/or bronchospasm, or anaphylaxis) require immediate discontinuation of the docetaxel administration infusion and administration of appropriate therapy.

Participants dosed at 75 mg/m^2 who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, nadir platelet count <25,000 cells/mm^3, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and then

resumed at 65 mg/m^2. For participants requiring further dose reduction, a dose of 65 mg/m^2.is recommended.

Participants who develop ≥ grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.(ref USPI).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

If investigational product is permanently discontinued, the participant will remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for survival. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Temporary Discontinuation

Participants who discontinue treatment due to disease progression that is subsequently determined to have been based on equivocal radiological findings, may resume treatment after discussion with the Sponsor's medical monitor.

See Appendix 13 for guidance for participants with active or presumed SARS-CoV2 infection.

7.1.2. Rechallenge

Participants who meet criteria for treatment discontinuation due to toxicity should not be rechallenged, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the Sponsor's medical monitor.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The Early Discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further 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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent:

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

Anti-tumor activity will be assessed through radiological tumor assessments conducted as specified in the schedule of activities. Assessment of response will be made using RECIST version 1.1 (see Section 10.11, Appendix 11: RECIST for details) by investigators or qualified designees (radiologist, etc.).

8.1.1. Safety Imaging Assessments

Unscheduled CT/MRI chest and abdomen with contrast should be obtained for all suspected cases of pancreatitis.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

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

During COVID-19 pandemic, please refer to Appendix 13 (Section 10.13) for safety and efficacy assessments.

8.2.1. Physical Examinations

Participants will have a physical examination to include weight, vital signs, assessment of ECOG performance status and height; height will be measured at screening only.

Findings should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an adverse event in the CRF.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Oral temperature, pulse rate, and blood pressure (BP) will be assessed.

Blood pressure and pulse rate measurements will be assessed in a sitting or semi-recumbent position (however the position should be maintainted throughout the study) with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.3. Electrocardiograms

Standard 12-Lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the Section 1.3 of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex.

All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. At each time point (see Table 5, Table 6, and Table 7), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. After Cycle 3, ECGs can be performed as clinically indicated. All ECG collection time points are with respect to PF-06939999 morning dosing. 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. To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 msec from the baseline and is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. In addition, if verified QTcF values continue to exceed the criteria above, 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.

If the QTcF interval reverts to less than the treshhold criteria listed above, and in the judgment of the investigator(s) and sponsor, it is determined that the cause(s) of QTcF prolongation is something other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above the threshold values, the investigational product will be held until the QTc interval decreases to below the threshold values. Participants will then restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to <480 msec after 2 weeks, or if at any time a participant has a QTcF interval >500 msec or becomes

symptomatic, the participant discontinuation will be discussed with the Sponsor. Additional triplicate ECGs may be performed as clinically indicated.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

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

ECG values of potential clinical concern are listed in Section 10.7 Appendix 7.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 Appendix 2: Clinical Laboratory Tests for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2 Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in women of childbearing potential (WOCBP) at the times listed in the SoA. Following a negative pregnancy test result at

screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the PF-06939999. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue PF-06939999 (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the investigational product.

During the long-term follow-up period in this study for survival, only SAEs will be actively elicited and collected after completion of the active collection period described above. The SAEs identified during long-term follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study intervention.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety 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 investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 Appendix 3: Adverse Events.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in in Section 10.3, Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 30 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. 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 AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant 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 study participant.

Such medication errors occurring to a study patie are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified -within 24 hours.

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

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form only when associated with an SAE.

8.4. Treatment of Overdose

For this study, any dose of PF-06939999 greater than the daily dose assigned will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06939999 (whichever is longer).
3. Obtain a blood sample for PK analysis within 30 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety only when associated with an SAE.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Plasma for analysis of PF-06939999 and docetaxel concentrations

Blood samples of approximately 3 mL, to provide a minimum of 1 mL of plasma, will be collected for measurement of plasma concentrations of PF-06939999 as specified in the Schedule of Activities (SoA). For Part 1B and Part 2D only, approximately 3 mL of blood samples (to provide a minimum of 1 mL of plasma) will be collected for measurement of

plasma concentrations of docetaxel as specified in the Schedule of Activities (SoA). Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

For Part 1B and Part 2D, the 1 hour samples for CCI should be collected from the contra-lateral arm of docetaxel infusion within 5 minutes of completing the infusion.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from participants experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Samples collected within the windows specified in the Schedule of Activities (SoA) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

Samples collected for analyses of plasma PF-06939999 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other CCI These data will not be included in the Clinical Study Report (CSR).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-06939999 will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs). Samples collected for measurement of plasma concentrations of docetaxel will be analyzed only if there is a need of docetaxel concentration data to evaluate safety or efficacy aspects related to concerns arising during or after the study. If analyzed, a validated analytical method in compliance with applicable SOPs will be used and the data will be included in the CSR.

8.5.2. Urine for Analysis of PF-06939999 Concentrations

In single agent dose expansion cohorts (Part 2A or Part 2C), urine samples will be collected for 1 dosing interval after PF-06939999 morning dosing on Cycle 1, Day 15 to measure PF-06939999 concentrations, and thereby determine the renal elimination of PF-06939999 from the body. Urine will be collected on Cycle 1, Day 15 from selected participants over 6-hour intervals (every 6 hours for 24 hours starting from the morning dose for QD; 0 to 6 hours and 6 to 12 hours post the morning dose for BID). Participants will empty their bladder just prior to morning dosing on Cycle 1, Day 15.

At the end of each urine collection period, the total volume will be measured and recorded. Voided urine should be collected in a container. The urine will then be mixed thoroughly and an aliquot will be withdrawn for the potential measurement of drug concentrations. The sample must be processed and shipped as indicated in the instructions provided by the sponsor.

The urine samples will be assayed using a validated analytical method in compliance with Pfizer SOPs.

Samples collected for analyses of urine PF-06939999 concentration may also be used for metabolite identification and/or evaluation of the bioanalytical method, or for other internal CCI purposes. These data will not be included in the CSR.

8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters will be evaluated in this study. See Section 8.8.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked biospecimens may be used for research related to drug response and the cancer under study. Genes and other analytes (eg, proteins, ribonucleic acid [RNA], nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for participants. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked

biospecimens. The optional additional research does not require the collection of any further samples.

See Section 10.5, Appendix 5 for information reagarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

8.8. Biomarkers

Biospecimens collected for pharmacodynamic and other biomaker assessments will include peripheral blood, and tumor tissues which will be used to analyze protein/amino acid derivatives as well as DNA and RNA for achieving planned biomarker objectives. Refer to the schedule of activities for sample collection time points and Study/Laboratory Manual for sample processing and shipping. The following biospecimen types are planned to be collected in support of study objectives. Additional biospecimens collected over the course of participant disease management may be submitted for biomarker analyses.

8.8.1. Archival/De Novo Tumor Biopsies

Tumor biospecimens from archival and/or de novo biopsies will be used to analyze candidate nucleic acid and protein biomarkers for their ability to identify those participants who are most likely to benefit from treatment with the study drugs and to assess PD activity of the tumor upon PF-06939999 treatment. Biomarkers may include, but are not limited to target expression, nucleic acid analyses, as well as cell types and constituents of the tumor microenvironment (TME). Additional information on tissue collection procedures can be found in the Laboratory/Study Manual.

8.8.2. Whole Blood and Plasma

Peripheral blood and derivatives (eg, plasma) will be used to analyze nucleic acids and amino acid derivatives to support study objectives. Examples may include free plasma CCI , cell free DNA (cfDNA) and gene expression analysis. Peripheral blood DNA sequencing will be used as normal control for identifying somatic mutations found in tumor samples and CCI will be used to identify potential PD and other CCI biomarkers. Additional analyses may be warranted based on emerging data. Note that plasma levels of CCI has been shown to be a predictor of renal and cardiovascular outcome in chronic kidney disease[26] in clinical settings which could facilitate the assay development.

See Section 10.5, Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

8.9. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. For participants with known computed tomography contrast allergy, a non contrast computed tomography of the chest with contrast enhanced abdominal and pelvic MRI can be used. 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). Assessment of response will be made using RECIST version 1.1 (see Section 10.11 Appendix 11) by investigators or qualified designees (Radiologist etc.).

All participant files and radiologic images must be available for source verification and for potential peer review.

8.10. Patient Reported Outcomes

Two PRO instruments will administered to participants with NSCLC in Part 2 of the study (Part 2A and 2D): (1) 7-item NSCLC-SAQ assessing key lung cancer symptoms of cough, pain, dyspnea, fatigue, and loss of appetite, and (2) 1-item PGIS to assess meaningful change in lung cancer symptoms. Both questionnaires will be administered at BL, 1-week, 1-month, 3-month, and EOT.

The purpose of the NSCLC-SAQ to assess the impact of PRMT5 on NSCLC symptoms and the PGIS will be used as an anchor to assess Meaningful Within-Patient Change (MW-PC) in NSCLC symptoms. The MW-PC is one of PRO statistical tests required by the FDA, as specified in the Patient-Focused Drug Development Guidance. Both the NSCLC-SAQ and PGIS from this trial will provide “early signals” on the impact of PRMT5 and guide endpoint development for upcoming pivotal trials. A separate Ad Hoc Analysis Plan will highlight the details of PRO analyses.

8.11. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and biomarker measurements.

9.1. Statistical Hypothesis

There will be no hypothesis testing in this study.

9.2. Sample Size Determination

The total number of participants for Part 1 is estimated to be approximately 40 (15 to 50). Subsequent participants will enter a Part 2, aimed at evaluating safety and anti-tumor activity of PF-06939999 at the RP2D. Approximately 80 participants are expected to be enrolled into Part 2.

9.2.1. Part 1 Dose Escalation

According to stopping criteria for dose escalation, approximately 15–50 participants will be enrolled in the Part 1 dose escalation portion of the study, however the total number of participants will depend on the number of dose levels needed to determine the MTD and number of participants evaluable for DLT at each dose level. It is envisioned that overall sample size for Part 1A will be approximately 40 participantsPart 1B is expected to have 6-9 participants enrolled.

9.2.2. Part 2 Dose Expansion

Part 2 (dose expansion) will enroll participants in 3 non-randomized monotherapy cohorts and 1 combination with Docetaxel cohort to further evaluate safety and preliminary antitumor activity of the compound at the RP2D corresponding to monotherapy and combination respectively. The Participants from Part 1 who were treated at the dose level selected for Part 2 and fulfilling Part 2 inclusion/exclusion criteria might be counted towards the sample size of Part 2 at the corresponding indication.

Each of the Parts 2A, 2B, 2C, and 2D will enroll approximately 20 participants. Sample size of 20 participants is chosen from practical considerations.

9.3. Populations for Analysis

1. Full analysis set.

   The full analysis set includes all enrolled participants.

2. Safety analysis set.

   The safety analysis set includes all enrolled participants who receive at least 1 dose of study treatment.

3. Per protocol analysis set (evaluable for MTD).

   The per protocol analysis set includes all enrolled participants who had at least 1 dose of study treatment and either experienced DLT or do not have major treatment deviations during the DLT observation period.

4. Modified Intent to Treat (mITT) set.

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

5. PK analysis sets.

   The PK parameter analysis population is defined as all enrolled participants treated who do not have protocol deviations influencing PK assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest.

   The PK concentration population is defined as all enrolled participants who are treated and have at least 1 analyte concentration.

6. Response Evaluable Set.

   The response evaluable population will include all participants who received at least 1 dose of study treatment and had baseline disease assessment or measurable disease at baseline, if applicable and at least 1 post baseline disease assessment.

7. PD/Biomarker analysis set(s).

   The PD/Biomarker analysis population is defined as all enrolled participants with at least 1 of the PD/Biomarkers evaluated at pre and/or post dose.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Maximum Tolerated Dose Determination

Determination of MTD will be performed using a Per-protocol analysis set (evaluable for MTD).

Bayesian adaptive approach:
The dose escalation in the Part 1A and Part 1B of the study will be guided by a Bayesian analysis of Cycle 1 dose limiting toxicity (DLT) data for PF-06939999. Toxicity is modelled using 2-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose in Part 1A and a 5-parameter model specifically developed for combinations in Part 1B.

Assessment of participant risk:
After each cohort of participants, the posterior distribution for the risk of DLT for new partcipants at different doses of interest for PF-06939999 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0, 0.16]
Targeted dosing:	[0.16, 0.33]
Overdosing:	[0.33, 1]

The escalation with overdose control (EWOC) principle:
Dosing decisions in Part 1A and Part 1B are guided by the escalation with overdose control principal.[1] A dose may only be used for newly enrolled participants if the risk of excessive toxicity at that dose is less than 25%.

Prior distributions in Part 1A for BID regimen:
Weekly informative prior distribution based on pre-clinical/expert opinion information will be chosen for the logistic parameters, see Section 10.9, Appendix 9.

Prior distributions in Part 1A QD regimen: The data from BID regimen have been used to set up a meta-analystic prior (MAP) and a mixture of the MAP and weakly informative prior has been used for Part 1A QD regimen.

Prior distributions in Part 1B: A meta-analytic-predictive (MAP) approach will be used to derive the prior distribution for model parameters used in Part 1B based on the data collected in Part 1A and original dose escalation studies of Docetaxel. A full description of the application of the MAP approach to derive the prior distributions of the model parameters is given in Technical Supplement to Appendix 10.9.

Starting doses in Part 1A and Part 1B:
The Part 1A starting dose is 0.5 mg/QD. For this dose the prior risk of overdosing is 6.4%, which satisfies the EWOC criterion. A full assessment of the prior risk to participants is given in Section 10.9, Appendix 9.

The starting dose in Part 1B will be a PF-06939999 RP2D-1 with fixed dose of docetaxel per standard of care. In addition, depending on the safety findings in Part 1A, and whether significant overlapping toxicities are expected in combination, the starting dose of PF-06939999 may be further modified but will not exceed the single agent RP2D.

Stopping criteria in Part 1A and Part 1B:
The maximum number of participants in dose escalation part of the trial was set to 50. The trial will be stopped when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD.
- The dose $\tilde{d}$ satisfies 1 of the following conditions:

- The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, Pr($0.16 \leq \pi_{\tilde{d}} < 0.33$)≥50%.

- A minimum of 15 participants have been treated in the trial.

9.4.2. Efficacy Analyses

Response Evaluable Set will be used for all response related analyses including ORR, DOR, PFS, and OS. Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, dose on Day 1, tumor response at each visit, and best overall response. In addition, progression date, death date, date of first response and last tumor assessment date and date of last contact will be listed.

Part 1and Part 2: Progression date, death date, date of first response and last tumor assessment date and date of last contact will be listed. The definition of each response category is provided in Section 10.11 Appendix 11 (RECIST v1.1). The proportion of participants with response will be presented for each dose level. Details of analysis will be included in Statistical Analysis plan.

Part 2: The Kaplan-Meier methods will be used to analyze all time to event endpoints. Median PFS and median OS (both if reached) will be reported. Proportion of participants alive at 6 mo, 1 year, and 2 years will be also presented. Efficacy data of participants from Part 1B who are dosed at the level selected for Part 2 and satisfy inclusion/exclusion criteria of the corresponding Part 2 cohort will be used in efficacy analysis conducted for that Part 2 cohort. Details of these endpoint analyses methods will be included in the Statistical Analysis Plan.

PFS is defined as the time from start date to date of first documentation of progression, or death due to any cause. Progression is defined as the appearance of local, regional or distant disease of the same type after complete response or progression of pre-existing lesions. Itdoes not include second primary malignancies of unrelated types.

OS is defined as the time from start date to date of first documentation of death due to any cause.

9.4.3. Safety Analyses

All safety analyses will be performed on the safety population.

Summaries and analyses of safety parameters will include all participants in the safety analysis set.

AEs, ECGs, BP, PR, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4.3.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

The mean of the replicate measurements (eg, triplicate ECGs obtained) will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTc value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the clinical study report (CSR) in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTc value and the average of the predose triplicate values on Day 1. In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as Cycle 1 Day 1 predose.

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 (HR) (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 interval, PR interval (PR), QRS, QTcF (and other correction factors, eg, QTcB as appropriate), and dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor depending on HR (default QTcF) 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 interval and changes from baseline in corrected QT after treatment by dose and time point. Details of additional analysis (if any) will be specified in SAP.

9.4.3.2. Adverse Events

AEs will graded by the investigator according to the CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event data will be reported in tables and listings. Summaries of adverse event by mapped terms, appropriate thesaurus level, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of adverse events leading to death and premature withdrawal from study treatment. The number and percentage of participants who experienced any 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). Listings of DLTs and deaths will be provided.

9.4.3.3. Laboratory Test Abnormalities

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

9.4.4. Other Analyses

9.4.4.1. Pharmacokinetic Analyses

9.4.4.1.1. Single dose and Steady-State PF-06939999 pharmacokinetic Analysis

Plasma concentrations of PF-06939999 will be summarized descriptively (n, mean, standard deviation, coefficient of variation [CV], median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time.

Individual participant plasma PF-06939999 concentration-time data within a dose interval after Cycle 1 Day 1 and Cycle 1 Day 15 will be analyzed using noncompartmental methods to determine single- and multiple- dose PK parameters. Single-dose PK parameters to be estimated will include the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC) from time 0 to the last sampling time point within the dose inveral (AUC_{last}), and if data permit, AUC from time 0 extrapolated to infinity (AUC_{inf}), terminal elimination half life ($t_{1/2}$), apparent oral plasma clearance (CL/F), and apparent volume of distribution (Vss/F or Vz/F). Multiple-dose PK parameters to be estimated will include steady state Cmax ($C_{max,ss}$), T_{max}, AUC within 1 dose interval ($AUC_{tau,ss}$), minimum plasma concentration ($C_{min,ss}$), steady-state CL/F (CLss/F), and if data permit, apparent volume of distribution (Vss/F), $t_{1/2}$, and accumulation ratio (Rac). The single dose and steady state PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose level, cycle and day.

Dose normalized AUC_{inf} ($AUC\tau$ at steady state), AUC_{last} and C_{max} for PF-06939999 in plasma will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual participant values and the geometric means for each dose.

For Part 1B and Part 2D, if the samples collected for measurement of plasma concentrations of docetaxel are analyzed (see Section 8.5.1), these plasma docetaxel concentrations will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by cycle, day and nominal time.

Urine PF-06939999 concentrations will be summarized by descriptive statistics (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV). Renal clearance will be estimated if data permit.

Metabolite Profiling

Plasma metabolite profiling will be summarized in a separate report and not included in the CSR.

9.4.4.1.2. Effect of Food on PF-06939999 Pharmacokinetics

The effect of food will be assessed based on AUC_{last} and C_{max} by determining the ratios (fed/fast) of geometric means of these PK parameters and the 90% confidence intervals for the ratios.

9.4.4.2. Pharmacodynamic/Biomarker Analyses

For PD samples including tumor CCI IHC and plasma CCI summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels) will be determined at baseline and post-treatment. Further analysis will be specified in SAP.

Clinically relevant and interpretable biomarker assessments generated for Primary and Secondary objectives will be summarized in the CSR. Other biomarker data might be summarized in a separate technical document.

9.4.4.3. Analysis of PRO data

Patient reported outcome data in the form of NSCLC-SAQ and PGIS will be presented as participant data listings that include, but are not limited to participant demographics, dose on Day 1, outcomes metrics, and change from baseline in corresponding parameter. Additional analytic details will be highlighted in the SAP as well as a separate PRO Analysis Plan. All PRO results will be summarized as a separate document.

9.4.4.4. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

Population PK assessment may be conducted with plasma PF-06939999 concentrations from all participants using the nonlinear mixed effect modeling approach in accordance with regulatory guidance. Subjects who provide at least 1 post dose drug concentration measurement and have no major protocol deviations influencing the PK assessment will be included in the population PK analysis. The population PK analysis will estimate typical value and variability for parameters including absorption rate constant (Ka), CL/F, and volume of distribution (Vd/F). Also, the influence of selected potential covariates on the PK parameters will be explored; the potential covariates to be explored will include selected demographics and participant characteristics (eg, body weight, sex, age).

The population PK model may be further combined with data on biomarkers and relevant efficacy and safety endpints for population PK/PD analysis. The population PK and PK/PD analysis, if performed, will be reported in a Population Modeling and Analysis Report (PMAR), separate from the clinical study report of this study.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

Discussions between the investigators and the sponsor regarding safety will occur in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and determine if further participant enrollment is appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. 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 regulatory 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional CCI research. The investigator or authorized designee will explain to each participant the objectives of the CCI research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for CCI research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study 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 addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

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 participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant 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 European Union (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 PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have 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.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Site Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The

investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source data includes medical records, clinical laboratory reports, radiology reports or other sources per site practices.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;

- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. 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.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the

participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 15. Safety Laboratory Tests

Hematology	Chemistry	Serology	Coagulation	Urinalysis	Pregnancy Test
Hemoglobin*	ALT	HBV*	PT	Urine dipstick for urine blood or leukocyte esterase: If positive perform microscopy (Reflex Testing).	For female participants of childbearing potential, serum or urine.
Platelets*	AST	HCV Ab*	PTT		
WBC	Bicarbonate	HIV			
Absolute Neutrophils	CRP	Reticulocyte count**			
Absolute Lymphocytes	Alk Phos	Peripheral blood smear**			
Absolute Monocytes	Sodium				
Absolute Eosinophils	Potassium				
Absolute Basophils	Magnesium			Urine dipstick for urine protein: If positive perform microscopy (Reflex Testing).	**Tumor Markers** CA-125 for participants with cervical or endometrial cancer only.
RBC	Chloride				
MCV	Total calcium				
	Total bilirubin***				
	Total Protein				
	BUN or Urea				
	Creatinine				
	Uric Acid				
	Glucose (nonfasted)				
	LDH				
	Albumin				
	Phosphorus or Phosphate				
	Amylase				
	Lipase				
	Triglycerides				

Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; HBV = hepatitis B; HCV = hepatitis C; IFNγ = interferon-gamma; IL = interleukin; INR = International Normalized; LDH = lactate dehydrogenase; MCV = mean corpuscular volume PTT = partial thromboplastin time; RBC = red blood cells; TNFα = Tumor necrosis factor- alpha; WBC = white blood cells.

* Hepatitis B testing includes: Hepatitis B Surface Ag (HBsAg), Total Hepatitis B Core Ab (anti-HBc), Hepatitis B Surface Ab (anti-HBs) as clinically indicated IgM antibody to hepatitis B core antigen (IgM anti-HBc), HCV Ab (also known As Hepatitis C Antibody).

** Grade ≥3 thrombocytopenia should trigger a blood smear for differential. Reticulocyte count should be performed per schedule of acitivity. In addition, Grade≥ 3 anemia should trigger a recticulcyte count if not done within 7 days.

*** For potential Hy's Law 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, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Signs, symptoms, and/or clinical sequelae resulting from lack of anti-tumor activity will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of anti-tumor activity will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of anti-tumor activity” constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded 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.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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.
- 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 active collection 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 active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Assessment of Intensity section).
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are

considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding	All (and exposure during pregnancy [EDP] supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- The investigator will then record all relevant AE/SAE information in the CRF.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Grade	Clinical Description of Severity
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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- 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. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 90 days after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s) plus an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- Use of an additional highly effective contraceptive method with a failure rate of <1% per year as described below in Section 10.4.4 for a female partner of childbearing potential.
- Male participants should be advis ed of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak when having sexual intercourse with a WOCBP who is not currently pregnant.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  OR

- Is a WOCBP and is abstinent from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and be the preferred and usual lifestyle of the participant.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

   - Documented bilateral salpingectomy;

   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female.

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

   - Oral;

   - Intravaginal;

- Transdermal;
- Injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation.
   - Oral;
   - Injectable.
   - Effective Methods
3. Male or female condom with or without spermicide.
4. Cervical cap, diaphragm, or sponge with spermicide.
5. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.4.4. Collection of Pregnancy Information

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

- 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).
- A male 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 participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an 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 participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety 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 Safety 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 termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure 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 to Pfizer Safety 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 sponsor. 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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA:

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-06939999 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Samples for banking (see Section 8.7.2) will be stored indefinitely or other period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Banked biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.
- Additional whole blood samples will be collected (see Table 5, Table 6, Table 7, Table 8, and Table 9) for DNA sequencing to detect germline mutations to serve as a control for somatic mutation analysis. This analysis is independent of the genetic analyses as stated above.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator 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, physical assessment, and CT/MRI scans if hepatic neoplasia is suspected.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as SAEs
• QTcF prolongation >500 msec. • New ST-T changes suggestive of myocardial ischemia. • New-onset left bundle branch block (QRS >120 msec). • New-onset right bundle branch block (QRS >120 msec). • Symptomatic bradycardia. • Asystole: • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node. • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer. • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm. • Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.7.1. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided.

See Section 7.1.1 for temporary discontinuation of the study intervention.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.8. Appendix 8: Country-Specific Requirements

10.8.1. France Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

   No participants or third-party payers will be charged for investigational product.

3. Urgent Safety Measures

   In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

4. Termination Rights

   Pfizer retains the right to discontinue development of PF-06939999 at any time.

The investigator agrees to abide by the ethical principles set forth in the World Health Organization's Guiding Principles for Human Cell, Tissue and Organ Transplantation (WHA63.22) (http://www.who.int/transplantation/en/) with regard to the study.

10.9. Appendix 9: Detailed Dose Escalation/De-escalation Scheme for BLRM Design

This appendix provides the details of the statistical model, the description of prior distribution. The results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model could be found in the separate Technical supplement to this appendix.

10.9.1. Statistical Model

Let $\pi\ (d\ )$ be the risk of DLT for PF-06939999 given as a single agent at dose d. The dose-DLT model is logistic:

$$\text{logit}\left(\pi\ (d\ )\right)\ = \log(\alpha\ ) + \beta \log(d/d^*)$$

d^*=50 mg/BID or 100 mg total daily dose and used to scale the doses of PF-06939999. Hence, α (>0) are the PF-06939999 odds of a DLT at d^*; and β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

10.9.2. Prior Specifications for BID Regimen

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the parameters $\log(\alpha\ )$ and $\log(\beta\ )$. A weakly informative prior was used as there were no relevant human historical DLT data available. It was assumed that model parameters will follow a bivariate normal (BVN) distribution

$$(\log(\alpha), \log(\beta)) \sim N_2(\mu, \Sigma)$$

with prior means $\mu = (\mu_1, \mu_2)$, and prior covariance matrix S composed of standard deviations σ_1, σ_2 and correlation ρ. It was assumed that

$$(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho) = (\text{logit}(p^*), 0, 2, 1, 0)$$

Here, p^* is the anticipated DLT rate at the scaling dose d^*. It was assumed based on pre-clinical data that DLT rate at 50 mg/BID dose was 0.33.

This prior is considered to be weakly informative (Neuenschwander et al. 2014).

The prior distributions of the model parameters are provided in Table 16 illustrates the resulting prior distribution of DLT rate derived from the prior given in Table 17 and rounded to 3 decimal points. Based on the available information the starting dose of PF-06939999 = 0.5 mg/QD satisfies the EWOC criteria.

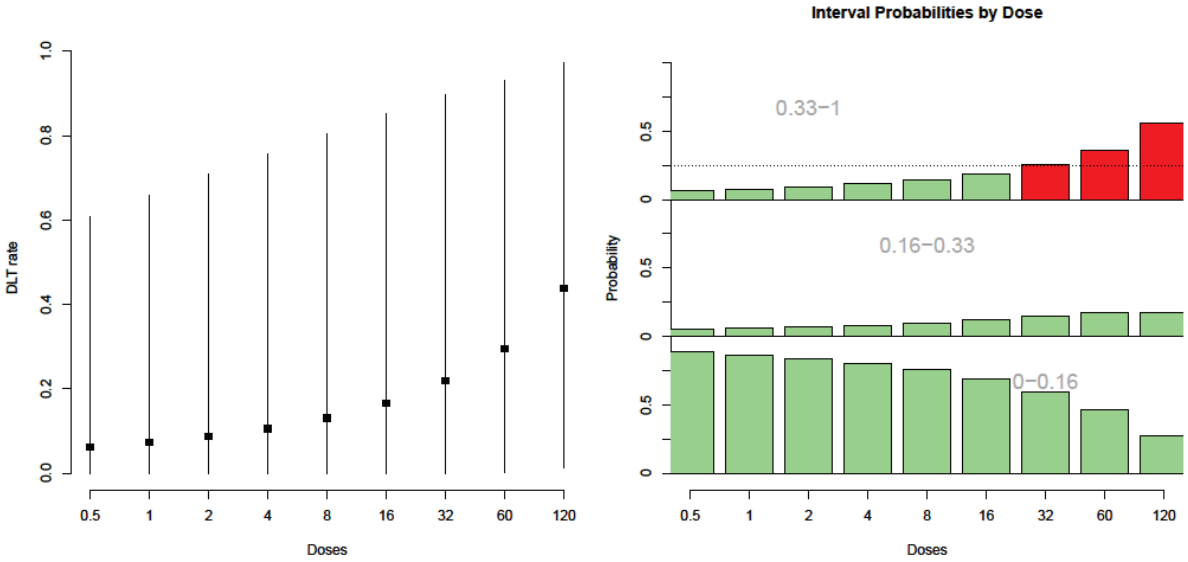
Table 16. Prior Distribution for the Model Parameters (BID regimen)			
PF-06939999 single agent parameters: BVN weakly informative prior			
Parameters	Means	Standard deviations	Correlation
$(\log(\alpha), \log(\beta))$	-0.708,0	2, 1	0

Table 17. Summary of Prior Distribution of Dose Limiting Toxicity Rates for PF-06939999 (BID regimen)

PF-06939999 dose		Prior probabilities that DLT rate is in the interval:			Mean	SD	Quantiles		
Total (mg/day)	BID (mg) am/pm	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
0.5	0.5/0	0.885	0.051	0.064	0.062	0.151	0.000	0.002	0.607
1	0.5/0.5	0.864	0.060	0.076	0.073	0.164	0.000	0.003	0.658
2	1/1	0.838	0.069	0.093	0.087	0.179	0.000	0.006	0.710
4	2/2	0.803	0.082	0.115	0.106	0.196	0.000	0.012	0.756
8	4/4	0.757	0.096	0.147	0.131	0.216	0.000	0.024	0.804
16	8/8	0.691	0.119	0.190	0.167	0.239	0.000	0.048	0.853
32	16/16	0.593	0.149	0.258	0.220	0.264	0.000	0.097	0.896
60	30/30	0.466	0.172	0.362	0.295	0.288	0.002	0.188	0.931
120	60/60	0.270	0.174	0.556	0.438	0.313	0.013	0.398	0.973

Abbreviations: BID = twice daily; SD = standard deviation

Figure 2. Summary of Prior Distribution of Dose Limiting Toxicity Rates for PF-06939999 with BID regimen (total daily dose)



10.9.3. Prior Specifications for QD Regimen

The data from BID regimen and original weakly informative prior were used to set up a prior for QD regimen. The MAP prior was used to borrow the information form the BID regimen. However, to safeguard against unwarranted use of historical information a mixture prior is recommended which is adopted in this study. Then a mixture of weakly informative prior and MAP prior was used with mixing probabilities 0.2 and 0.8 respectively.

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ for the part of the study with the QD regimen using DLT data from the BID regimen. It was assumed that model parameters will follow a bivariate normal (BVN) distribution

$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi \sim \text{BVN}(\mu, \psi)$$

The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic parameters, and ψ is the between-regimen covariance matrix. Covariance matrix ψ is defined by the standard deviations $(\tau_1,\ \tau_2)$, and correlation ρ. More details of the MAP prior derivation are described in Technical supplement to this appendix.

The MAP prior takes the following form

$$(\mu_1, \mu_2, \tau_1, \tau_2, \rho) = (1.13, -0.12, 1.55, 0.65, 0.72).$$

Then a robust prior is achieved via the following mixture $0.8\ N_2(\mu,\ \psi)_{MAP} + 0.2\ N_2(\mu, \Sigma)_{Weak}$

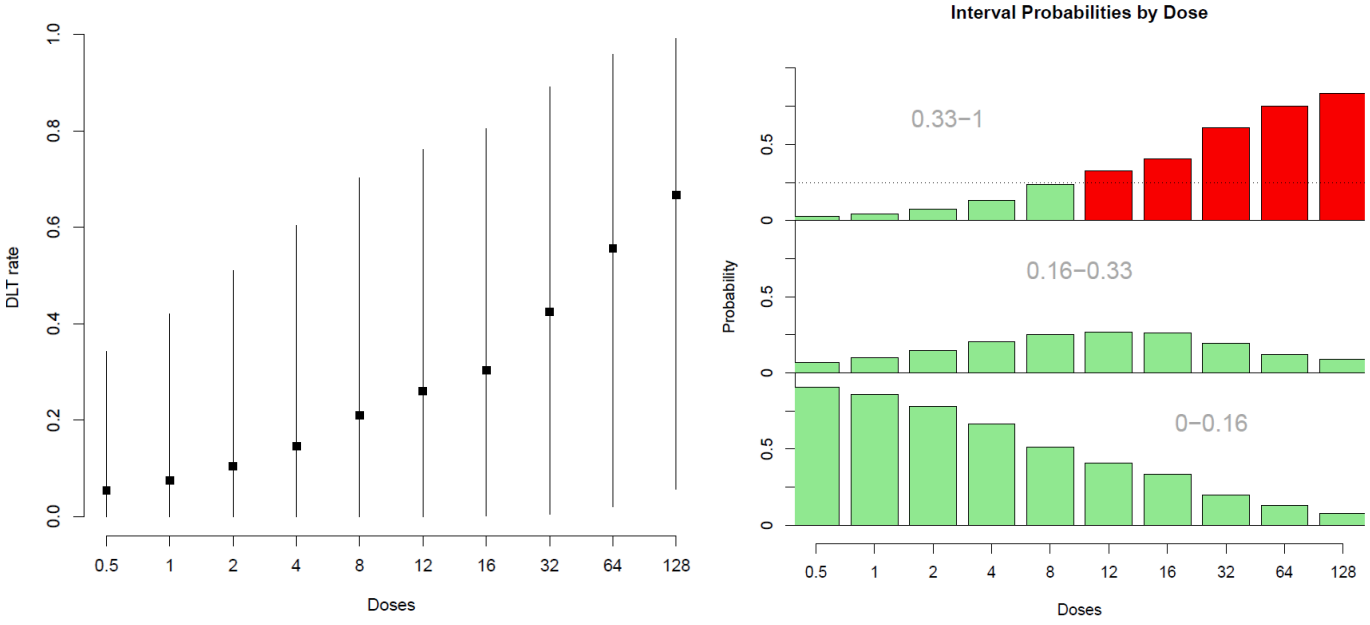
The entire prior distributions of the model parameters are provided in which illustrates the resulting prior distribution of DLT rate derived.

Table 18. Summary of Prior Distribution of Dose Limiting Toxicity Rates for PF-06939999 (QD regimen)

PF-06939999 dose	Prior probabilities that DLT rate is in the interval			Mean	SD	Quantiles		
Total (mg/day)	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
0.5	0.907	0.066	0.027	0.055	0.100	0.000	0.016	0.343
1	0.858	0.097	0.044	0.075	0.117	0.000	0.029	0.421
2	0.781	0.145	0.074	0.103	0.138	0.000	0.051	0.510
4	0.665	0.205	0.130	0.146	0.165	0.000	0.089	0.604
8	0.510	0.254	0.235	0.210	0.195	0.000	0.155	0.703
12	0.407	0.266	0.327	0.260	0.215	0.000	0.211	0.761
16	0.335	0.260	0.405	0.303	0.228	0.000	0.262	0.804
32	0.196	0.195	0.609	0.425	0.259	0.004	0.421	0.891
64	0.128	0.122	0.750	0.556	0.283	0.020	0.603	0.958
128	0.075	0.090	0.834	0.666	0.282	0.059	0.749	0.991

Abbreviations: QD = once daily; SD = standard deviation

Figure 3. Summary of Prior Distribution of Dose Limiting Toxicity Rates for PF-06939999 (total daily dose, QD regimen)



10.9.4. Model description and prior specification for Part 1B

Details of model specification for combination with Docetaxel are presented in Technical supplement to this Appendix. Details of selected priors will be finalized when DLT data for Part 1A becomes available.

References

1. Neuenschwander B, Matano A, Tang Z, Roychoudhury S, Wandel S and Bailey S. A Bayesian Industry Approach to Phase I Combination Trials in Oncology. In *Statistical Methods in Drug Combination Studies*. Zhao W and Yang H (eds), Chapman & Hall/CRC, 2014.

2. Schimidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D., & Neuenschwander, B. (2014). Robust Meta-Analytic-Predictive Priors in CLinical Trials with Historical Control Information. *Biometrics, 70*, 1023--1032.

10.10. Appendix 10: ECOG Performance Status

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.

*As published in Am J Clin Oncol 5:649-655, 1982.

10.11. Appendix 11: RECIST (Response Evaluation Criteria In Solid Tumors) Version 1.1 Guidelines

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

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 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 [based on Prostate Cancer Working Group 3 (PCWG3) criteria]: Bone disease is defined as present or absent and will be followed as non-target lesions.
- Previous local treatment: A previously irradiated lesion (or lesion patiented 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 2 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

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

Table 19. 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

Table 20. Objective Response Status at each Evaluation for Participants 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

10.12. Appendix 12: Bone Marrow Reserve in Adults

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 : Cranium Mandible	 165.8 16.4	 0.75 0.75	136.6 124.3 12.3	 13.1	 13.1
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle : 2 Humerus, head & neck 2 Scapulae 2 Clavicles	 26.5 67.4 21.6	 0.75 0.75 0.75	86.7 20.0 50.5 16.2	 8.3	 8.3
STERNUM AND RIBS	Sternum Ribs: 1 pair 2 3 4 5 6 7 8 9 10 11 12	39.0 10.2 12.6 16.0 18.6 23.8 23.6 25.0 24.0 21.2 16.0 11.2 4.6	0.6 All 0.4	23.4 82.6 4.1 5.0 6.4 7.4 9.5 9.4 10.0 9.6 8.5 6.4 4.5 1.8	2.3 7.9	 10.2
PELVIC BONES	Sacrum 2 os coxae	194.0 310.6	0.75 0.75	145.6 233.0	13.9 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

10.13. Appendix 13: Alternative Measures During Public Emergencies

The alternative study procedures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix is currently in effect applies for the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories). Notify Pfizer when conditions have returned to business as usual.

10.13.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per exclusion criterion #8. When the infection resolves, the patient may be considered for re-screening.

10.13.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record PF-06939999 administration, including compliance and missed doses as detailed in the SOA.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Contraception check as detailed in the SOA. Confirm that the participant is adhering to the contraception method(s) required in the protocol.
- Review and record contraceptive method and results of pregnancy testing. Refer to Appendix 4 and Section 10.13.3 of this appendix regarding pregnancy tests
- Provide instructions for laboratory testing and radiological assessments as described in Section 10.13.3 and 10.13.7.

- Review and record safety and efficacy result if applicable

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.13.3. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology;
- Blood chemistry;
- Coagulation;
- Urinalysis;
- Pregnancy test.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.13.4. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.13.5. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

PF-06939999 may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the PF-06939999. Pfizer does not permit the shipment of PF-06939999 by mail. The tracking record of shipments and the chain of custody of PF-06939999 must be kept in the participant's source documents/medical records. Study participants must provide their verbal consent to allow the site to provide their contact details to a courier for the purpose of shipping PF-06939999 to them. The verbal consent should be documented in the source documents/medical records. Administration of docetaxel must be performed in person at the Study site.

Ongoing participants who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection, should follow the treatment guidelines:

- For symptomatic participants with active SARS-CoV2 infection, investigational treatment should be delayed for at least 14 days from start of symptoms. This delay is intended to allow resolution of symptoms of SARS-CoV2 infection

- Prior to restarting treatment, the participant should be afebrile for 72 hours and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Please inform the study team when treatment is restarted.

See Section 7.1.1.

Continue to consider potential drug-drug interactions as described in Section 6.5.1 for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.13.6. Home Health Visits

A home health care service may be considered to facilitate scheduled visits per the Schedule of Activities only after Sponsor's approval. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Physical Exams;

- Vital Signs (including height and weight);

- Safety laboratory blood draws (including hematology, blood chemistry, coagulation);

- Urinalysis;

- Blood draw for PK and PD;

- ECGs, if available;

- Also all assessments included in Telehealth Visits (Section 10.13.2).

10.13.7. Efficacy Assessments

If the participant is unable to visit the study site for radiological tumor assessments, the participant may visit an alternative facility to have these assessments performed as described in the SOA. Qualified study site personnel must order, receive, and review results.

10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti-HBc	hepatitis B core antibody(ies)
Anti-HBs	Hepatitis B Surface antibody(ies)
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{last}	AUC from time 0 to the last sampling time point within the dose inveral
AUC_{inf}	AUC from time 0 extrapolated to infinity
AUCsd,τ	is the single-dose AUC within one dose interval
$AUC_{tau,ss}$	AUC within one 1 dose interval
AV	Atrioventricular
BBS	Biospecimen Banking System
BID	twice daily
BLRM	Bayesian Logistic Regression Model
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
BVN	bivariate normal
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
C4D1	Cycle 4 Day 1
CCC	clear cell carcinoma
CFR	Code of Federal Regulations
ChTx	platinum-based doublet chemotherapy
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	Oral plasma clearance
CL_{ss}/F	steady state CL/F
C_{max}	maximum observed concentration
C_{max},ss	steady state C_{max}
C_{min}	minimum plasma concentration
C_{min},ss	steady state C_{min}
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials

Abbreviation	Term
COV	cornonavirus
CPI	checkpoint inhibitors
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough conentration
CV	coefficient of variation
DDI	drug-drug interations
DILI	drug-induced liver injury
DLBCL	diffuse large b-cell lymphoma
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DU	dispensable unit
EC	ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of treatment
ETOH	Ethanol
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	escalation with overdose control
FDA	Food and Drug Adminsitration
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimuating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
H2RA	H2 – receptor antagonist
HBcAb	hepatitis B core antibody

Abbreviation	Term
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committee
IFN	interferon-gamma
IgM	Immunoglobulin M
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRT	Interactive Response Technology
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWR	Interactive Web Response
Ka	absorption rate constant
K2 EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
MAD	maximum administered dose
Map	meta-analytic-predictive
MCV	mean corpuscular volume
MD	multiple dose
MEC	molar extinction coefficient
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodyplastic syndrome
mITT	modified intent to treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

Abbreviation	Term
MVAC	methotrexate/vinblastine sulfate/doxorubicin hydrochloride/cisplatin)
MW-PC	Meaningful Within-Patient Change
N/A	not applicable
NCI	National Cancer Institute
NG	nasogastric
NHL	non-Hodgkins lymphoma
NOAEL	no-observed-adverse-effect level
NPC	neural stem/progenitor cells
NSCLC	non-small cell lung cancer
CCI	[redacted]
ORR	overall response rate
OS	overall survival
PAD	pharmacologically active dose
PCWG3	Prostate Cancer Working Group 3
PCD	primary completion date
PD	pharmacodynamics(s)
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PFS	progression-free Survival
PGIS	patient global impression of severity
PK	pharmacokinetic(s)
PMAR	Population Modeling and Analysis Report
PMT	protein methyltransferase
PR	partial response
PRMT5	protein arginine methyltransferase 5
PRO	patient reported outcome
PS	performance status
PT	prothrombin time
PVC	premature ventricular complex
QD	once daily
QTc	corrected QT
QTcB	corrected QT (Bazett method)
QTcF	corrected QT (Fridericia method)
Rac	accumulation ratio
RARS	refractory anemia with ring sideroblasts
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
CCI	[redacted]
RP2D	Recommended Part 2 Dose
RR	the interval between successive heartbeats
SAE	serious adverse event

Abbreviation	Term
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SD	single dose
SD	standard deviation
CCI	[redacted]
SFRF2	splicing factor, arginine/serine-rich 2 protein
snRMP	small nuclear ribonucleoprotein
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TBili	total bilirubin
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
T_{max}	time to maximum concentration
TTP	time to progression
TME	tumor microenvironment
Tmax,ss	maximum steady state concentration
U2AF1	U2 small nuclear RNA auxiliary factor 1
ULN	upper limit of normal
US	United States
USPI	United States product insert
UVB	ultraviolet B
Vd/F	volume of distribution
Vss/F	apparent volume of distribution steady state
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

1. Tighiouart M and Rogatko A. Dose finding with escalation with overdose control (EWOC) in cancer clinical trials. Statistical Science 2010; 25(2): 217–226.

2. Stopa N, Krebs JE, Shechter D. The PRMT5 arginine methyltransferase: many roles in development, cancer and beyond. Cell Mol Life Sci 2015; 72(11):2041-59.

3. Climente-Gonzalez H, Porta-Pardo E, Godzik A, et al. The functional impact of alternative splicing in cancer. Cell Rep 2017; 20(9):2215-26.

4. Gonsalvez GB, Tian L, Ospina JK, et al. Two distinct arginine methyltransferases are required for biogenesis of Sm-class ribonucleoproteins. J Cell Biol 2007; 178(5):733-40.

5. Bezzi M, Teo SX, Muller J, et al. Regulation of constitutive and alternative splicing by PRMT5 reveals a role for Mdm4 pre-mRNA in sensing defects in the spliceosomal machinery. Gene Dev 2013; 27(17):1903-16.

6. Koh CM, Bezzi M, Low DH, et al. MYC regulates the core pre-mRNA splicing machinery as an essential step in lymphomagenesis. Nature 2015; 523(7558):96-100.

7. Braun CJ, Stanciu M, Boutz PL, et al. Coordinated splicing of regulatory detained introns within oncogenic transcripts creates an exploitable vulnerability in malignant glioma. Cancer Cell 2017; 32(4):411-426.e11.

8. Neuenkirchen N, Chari A, Fischer U. Deciphering the assembly pathway of Sm-class U snRNPs. FEBS Lett 2008; 582(14):1997-2003.

9. Chan-Penebre E, Kuplast KG, Majer CR, et al. A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models. Nat Chem Biol 2015; 11(6):432-7.

10. Gerhart SV, Kellner WA, Thompson C, et al. Activation of the p53-MDM4 regulatory axis defines the anti-tumour response to PRMT5 inhibition through its role in regulating cellular splicing. Sci Rep 2018; 8(1):9711.

11. Gu Z, Gao S, Zhang F, et al. Protein arginine methyltransferase 5 is essential for growth of lung cancer cells. Biochem J 2012; 446(2):235-41.

12. Kahles A, Lehmann KV, Toussaint NC, et al. Comprehensive analysis of alternative splicing across tumors from 8,705 patients. Cancer Cell 2018; 34(2):211-224.e6.

13. Darman RB, Seiler M, Agrawal AA, et al. Cancer-associated SF3B1 hotspot mutations induce cryptic 3' splice site selection through use of a different branch point. Cell Rep 2015; 13(5):1033-45.

14. Obeng EA, Chappell RJ, Seiler M, et al. Physiologic expression of Sf3b1(K700E) impaired erythropoiesis, aberrant splicing, and sensitivity to therapeutic spliceosome modulation. Cancer Cell 2016; 30(3):404-17.

15. Fong JY, Pignata L, Goy PA, et al. Therapeutic targeting of RNA splicing catalysis through inhibition of protein arginine methylation. Cancer Cell. 2019;36(2):194-209.

16. Yoda S, Dagogo-Jack I, Hata AN. Targeting oncogenic drivers in lung cancer: recent progress, current challenges and future opportunities. Pharmacol Ther 2019;193:20-30.

17. Taxotere® (docetaxel) Prescribing information. Sanofi-aventis U.S. LLC. June 2019.

18. Seiler M, Peng S, Agrawal AA, et al. Somatic mutational landscape of splicing factor genes and their functional consequences across 33 cancer types. Cell Rep 2018; 23(1):282-296.e4.

19. Zhao J, Sun Y, Huang Y, et al. Functional analysis reveals that RBM10 mutations contribute to lung adenocarcinoma pathogenesis by deregulating splicing. Sci Rep 2017; 7:40488.

20. Economopoulou P, Perisanidis C, Giotakis EI, et al. The emerging role of immunotherapy in head and neck squamous cell carcinoma (HNSCC): anti-tumor immunity and clinical applications. Ann Transl Med 2016; 4(9):173.

21. Suresh T, Burtness B. The emerging role of immunotherapy in head and neck squamous cell cancer. Am J Hematol Oncol 2017; 13(6):20-7.

22. About Non-Small Cell Lung Cancer. American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017.

23. Dammeijer F, Lievense LA, Veerman GD, et al. Efficacy of tumor vaccines and cellular immunotherapies in non-small-cell lung cancer: a systematic review and meta-analysis. J Clin Oncol 2016; 34(26):3204-12.

24. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. New Engl J Med 2006; 355:2542-50.

25. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010; 21(9):1804-9.

26. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016; 17(11):1497-508.

27. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 2005; 352(8):786-92.

28. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. Sci Transl Med 2012; 4(120):120ra17.

29. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350(21):2129-39.

30. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015; 373(2):123-35.

31. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372(21):2018-28.

32. Zatloukal PHD, Park K, Kang J, et al. Randomized phase II clinical trial comparing tremelimumab (CP-675,206) with best supportive care following first line platinum-based therapy in patients with advanced non-small cell lung cancer. J Clin Oncol 2009; 27(Suppl):Abstr 8071.

33. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol 2014; 6(5):112-20.

34. Herszenyi L, Tulassay Z. Epidemiology of gastrointestinal and liver tumors. Eur Rev Med Pharmacol Sci 2010; 14(4):249-58.

35. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. Lancet 2013; 381(9864):400-12.

36. Raufi AG, Klempner SJ. Immunotherapy for advanced gastric and esophageal cancer: preclinical rationale and ongoing clinical investigations. J Gastrointest Oncol 2015; 6(5):561-9.

37. Piulats JM, Matias-Guiu X. Immunotherapy in endometrial cancer: in the nick of time. Clin Cancer Res 2016; 22(23):5623-5.

38. Longoria TC, Eskander RN. Immunotherapy in endometrial cancer - an evolving therapeutic paradigm. Gynecol Oncol Res Pract 2015; 2:11.

39. Marth C, Landoni F, Mahner S, et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28(Suppl 4):iv72-iv83.

40. Borcoman E, Le Tourneau C. Pembrolizumab in cervical cancer: latest evidence and clinical usefulness. Ther Adv Med Oncol 2017; 9(6):431-9.

41. Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. Lancet 2009; 374(9685):239-49.

42. Rouanne M, Roumiguie M, Houede N, et al. Development of immunotherapy in bladder cancer: present and future on targeting PD(L)1 and CTLA-4 pathways. World J Urol 2018; 36(11):1727-40.

43. Roupret M. Immunotherapy for bladder cancer: the fight is on. World J Urol 2018; 36:1699-701.

44. Emrich IE, Zawada AM, Martens-Lobenhoffer J, et al. CCl [redacted] outperforms asymmetric dimethylarginine (ADMA) and other methylarginines as predictor of renal and cardiovascular outcome in non-dialysis chronic kidney disease. Clin Res Cardiol 2018; 107(3):201-13.

45. Xu Q, Xu F, Liu L, et al. Compositional analysis of asymmetric and symmetric dimethylated H3R2 using liquid chromatography-tandem mass spectrometry-based targeted proteomics. Anal Chem 2016; 88(17):8441-9.