Protocol B7661001

A FIRST-IN-HUMAN PHASE 1, DOSE ESCALATION, SAFETY AND PHARMACOKINETIC STUDY OF PF-06647020 IN ADULT PATIENTS WITH ADVANCED SOLID TUMORS

Statistical Analysis Plan Amendment (SAP)

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TABLE OF CONTENTS

[redacted]

LIST OF TABLES

Abbreviation	Term
ADA	Anti-drug Antibody
ADC	Antibody Drug Conjugate
ADCC	Antibody dependent cell mediated cytotoxicity
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
BP	Blood Pressure
C1D1	Cycle 1 Day 1
CBC	Complete Blood Count
CBR	Clinical Benefit Response
CDC	Complement Mediated Cytotoxicity
CL	Systemic Clearance
CNS	Central Nervous System
CR	Complete Response
CSC	Cancer Stem Cells
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DAI	Dosage Administration Instruction
DAR	Drug:mAb Ratio
DDI	Drug-Drug-Interaction
DLT	Dose Limiting Toxicities

Abbreviation	Term
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure During Pregnancy
EDTA	Ethylenediaminetetraacetic Acid
CCI [redacted]	[redacted]
EI	Equivalence Interval
ER	Estrogen Receptor
EudraCT	European Clinical Trials database
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FIP	First In Patient
FSH	Follicle Stimulating Hormone
GLP	Good Laboratory Practice
H&E	Hematoxylin and Eosin
HBV	Hepatitis B Virus
hCG	Human chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
ICH	International Conference on Harmonisation
ID	Identification
IEC	Institutional Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IOP	Intraocular Pressure
IP	Investigational Product
IP	Intraperitoneal
IRB	Institutional Review Board
IUD	Intrauterine Device
IV	Intravenous

Abbreviation	Term
LFT	Liver Function Tests
LSLV	Last Subject Last Visit
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg/kg	Milligram/kilogram
MMAE	Monomethyl Auristatin E
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
N/A	Not Applicable
NADPH	b-Nicotinamide Adenine Dinucleotide Phosphate
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OVCA	Ovarian Cancer
PCD	Primary Completion Date
PD	Progressive Disease
PD	Pharmacodynamic
PDX	Patient Derived Xenograft
PE	Physical Exam
PFS	Progression Free Survival
P-gp	P-glycoprotein
PgR	Progesterone Receptor
PK	Pharmacokinetic
PR	Partial Response
PR	Pulse Rate
PS	Performance Scale
PT	Prothrombin Time
PTK7	Protein Tyrosine Kinase 7
Q3W	Once every 21 days
QTcF	Fridericia QT Correction Formula

Abbreviation	Term
rCyp	Human Recombinant Cytochrome P450
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	Response Rate
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SRSD	Single Reference Safety Document
STD10	Severely Toxic Dose for 10% of the animals
t½	Terminal Half-Life
TNBC	Triple Negative Breast Cancer
ULN	Upper Limit of Normal
UPCR	Urine Protein to Creatinine Ratio
UPM	Unit Probability Mass
US	United States
Vss	Volume of Distribution at Steady State
WBC	White Blood Cell
WFI	Water for Injection

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This amendment amends the original statistical analysis plan (SAP) in order to provide additional analysis and programming specifications for endpoints collected in the clinical Protocol Amendment 7, dated 15 May 2017. Note, there is a protocol amendment 8 dated 09 November 2017 but it is for the United Kingdom only, it has no impact on this analysis plan.

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol B7661001 Amendment 7, dated 15 May 2017. This SAP is meant to supplement the study protocol. This SAP supersedes the statistical considerations identified in the protocol and, where considerations are substantially different they will be identified as such. Any deviations from this analysis plan will be described in the clinical study report (CSR). Any post-hoc, or unplanned analyses performed that are not specified in this SAP will be clearly identified in the CSR. This plan is developed and finalized prior to database lock of the clinical database. This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline (Guidance for Industry: Statistical Principles for Clinical Trials) and on the ICH E3 Guideline (Guidance for Industry: Structure and Content of Clinical Study Reports).

2.1. Study Design

This is a Phase 1, open label, multi-center, non-randomized, multiple dose, safety, pharmacokinetic and pharmacogenomic study, initially designed to evaluate single agent PF-06647020 in sequential cohorts of adult patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available. Successive cohorts of patients received doses of PF-06647020 intravenously Q3W starting at a dose of 0.2 mg/kg.

This clinical study will include two parts. Part 1 will estimate the MTD/RP2D in dose escalation cohorts in patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available. Part 2 will explore benefit from treatment and to better define the safety profile, as well as the RP2D.

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This study also includes a DDI sub-study for evaluating the effect of multiple-dose fluconazole on the PK of unconjugated payload (PF-06380101).

[redacted]

The DDI sub-study is an open-label, 2-period, fixed sequence design in up to 10 patients to determine the effect of multiple-dose fluconazole, a model moderate CYP3A4 inhibitor, on the PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101), when fluconazole is co-administered with PF-06647020. The sub-study will be in a separate cohort from the studies for TNBC, NSCLC and OVCA, and study design and procedure details can be found in Appendix 7 of Protocol Amendment 7.

In Amendment 7, safety, PK and effectiveness of every 2 week (Q2W) dosing schedule for PF-06647020 as a single agent treatment or in combination with avelumab regimen will be evaluated in patients with platinum resistant or refractory OVCA and recurrent advanced NSCLC regimenwill be evaluated.

Approximately, 190 patients are to be enrolled in this study (including Q2W Regimen Expansion). The actual number of patients enrolled will depend upon tolerability of PF-06647020 and the number of dose levels required to identify the MTD/RP2D.

Patients will participate in the study for approximately 6 months or until disease progression, (PD) as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) or irRECIST in Cohort 3 of the Q2W regimen expansion, patient withdrawal of consent or unacceptable toxicity occurs, patient loss to follow up, or the study is terminated by the Sponsor, whichever comes first. The projected 6 months study duration includes a 4 week screening period, a 4 month treatment period and a 4 week post dose follow-up period. A follow-up visit within 4 weeks after the last dose of study drug for adverse event (AE) and serious adverse event (SAE) collection will be conducted. The time on study can vary depending on the observed toxicity and potential benefit an individual patient derives. The study is expected to be completed in approximately 36 months.

2.2. Study Objectives

2.2.1. Dose Escalation (Part 1) Objectives

2.2.1.1. Primary Objectives

- To assess safety and tolerability at increasing dose levels of PF-06647020 administrated intravenously on every 21-day dosing schedule to patients with advanced solid tumors unresponsive to currently available therapies, or for whom no standard therapy is available.

- To determine the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

2.2.1.2. Secondary Objectives

- To evaluate the overall safety profile.

- To characterize the single and multiple dose pharmacokinetics of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101).

- To evaluate the immunogenicity as measured by presence of anti-drug antibodies (ADA) in patients treated with PF-06647020.

- To document any preliminary evidence of anti-tumor activity.

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2.2.2. Dose Expansion (Part 2) Objectives

2.2.2.1. Primary Objectives

- To further evaluate safety and tolerability of PF-06647020 at the MTD and to establish RP2D in patients with NSCLC, TNBC and OVCA.

2.2.2.2. Secondary Objectives

- To evaluate the overall safety profile at the RP2D.

- To evaluate preliminary anti-tumor activity of PF-06647020 at the RP2D in patients with NSCLC, TNBC, and OVCA.

- To evaluate the single and multiple dose PK of ADC (PF-06647020), total antibody (hu6M024 mAb), and unconjugated payload (PF-0638010).

- To evaluate the immunogenicity as measured by presence of ADA in patients treated with PF-06647020.

- To evaluate the effect of the co-administration of fluconazole on the PK of unconjugated payload (PF-06380101), ADC (PF-00647020) and total antibody (hu6M024 mAb) following administration of ADC (PF-06647020).

- To assess the effects of fluconazole on the safety and tolerability of a single dose of PF-06647020. biomarkers in archival tumor biopsies, pre- and post-treatment tumor biopsies (if available).

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2.2.3. Objectives for Q2W Regimen

2.2.3.1. Primary Objectives

- Part 1: To assess safety and tolerability at increasing dose levels of PF-06647020 administered intravenously as a single agent on a Q2W dosing schedule.

- Part 1: To determine the MTD and select the RP2D of PF-06647020 as a single agent treatment on a Q2W dosing schedule.

- Part 2: To evaluate the overall safety profile of PF-06647020 as a single agent and in combination with avelumab at Q2W dosing schedule in OVCA and NSCLC patients at the RP2D.

  [Ref: Appendix 8, Section A3 in Protocol Amendment 7].

2.2.3.2. Secondary Objectives

- To characterize the single and multiple dose PK of ADC (PF-06647020), total antibody (hu6M024 mAb) and unconjugated payload (PF-06380101) when PF-06647020 administered alone or on combination with avelumab, and PK of avelumab.

- To evaluate the immunogenicity as measured by presence of ADA in patients treated with PF-06647020 or PF-06647020 in combination of avelumab.

- To evaluate anti-tumor activity of PF-06647020 as a single agent and when given in combination with avelumab in patients with OVCA and NSCLC.

  [Ref: Appendix 8, Section A3 in Protocol Amendment 7].

2.2.3.3. CCI [redacted]

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

[redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

This is an open-label, unblinded clinical trial. Treatment safety and effectiveness are to be monitored continuously. Upon all Part 1, Part 2 and DDI patients being treated for 72 weeks, if deemed necessary, an interim clinical study report may be generated to summarize safety, toxicity, PK/PD and clinical response of Q3W regimen..

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No formal hypothesis testing will be done. .

4.2. Statistical Decision Rules

The initial Statistical Decision rulefor dose escalation based on a Bayesian mTPI procedure are described in the following table:

Table 1. Decision Rules

Number of patients treated at a Dose Level											
DLT	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12
0	E	E	E	E	E	E	E	E	E	E	E
1	na	S	S	S	E	E	E	E	E	E	E
2	U	D	D	S	S	S	S	S	S	S	S
3		U	U	D	D	S	S	S	S	S	S
4			U	U	U	D	D	D	D	D	S
5				U	U	U	U	U	D	D	D
6					U	U	U	U	U	U	D
7						U	U	U	U	U	U

D: De-escalate the dose; E: Escalate the dose; S: Stay at the dose; U:Unacceptable toxicity; na: Not applicable

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis Set (FAS) is defined as all enrolled patients.

5.2. 'PER PROTOCOL' Analysis Set Evaluable for MTD

The per protocol analysis set includes all enrolled patients who receive at least one dose of study medication and who do not have major treatment deviations during first cycle with a baseline disease assessment and at least one post-baseline disease assessment. Patients with major treatment deviations in the DLT observation period are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include:

- Administration of less than 33% of the planned dose of PF-06647020 (provided that the reduction is not due to toxicity attributable to PF-06647020;

- Administration of more than 33% of the planned dose of PF-06647020 failure to satisfy major entry criteria (eg, confirmation of the target disease, signed informed consent);

- Use of other anticancer treatments during the active treatment and disease follow up phases other than as defined/allowed in this protocol;

- A baseline disease assessment and at least one post-baseline disease assessment.

5.3. Safety Analysis Set

The Safety Analysis Set is defined as all patients who receive at least 1 full or partial dose of study medication.

5.4. OTHER ANALYSIS SETS

5.4.1. PK Concentration Analysis Set

The PK concentration analysis population is defined as patients who receive at least 1 dose of study treatment and who have at least 1 measurable concentration.

5.4.2. PK Parameter Analysis Set

The PK parameter analysis population is defined as patients who receive at least 1 dose of study treatment and have sufficient information to estimate at least 1 of the PK parameters of interest.

CCI [redacted]

5.4.4. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as patients who receive at least 1 dose of study treatment and have at least 1 ADA sample collected.

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5.4.6. Drug-Drug Interaction (DDI) Study Analysis Set

The DDI Study analysis set is defined as patients who participate in the drug-drug interaction substudy, and have at least one of the study required PK samples.

5.5. Treatment Misallocations

This is an unblinded MTD dose finding study. Patients will be included in the cohort defined by their initial dose.

5.6. Protocol Deviations

Protocol deviations will be defined and this analysis plan to be updated before database lock.

5.6.1. Deviations Assessed Orior to Randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

5.6.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

Baseline is defined as the last planned visit measurement prior to the first dose of study medication administration; otherwise, the last available measurement prior to the first dose of study medication administration is to be adopted as Baseline.

6.1. Efficacy Endpoints

In this First in Patient study anti-tumor activity is a secondary objective.

Following assessments based on RECIST 1.1 are to be summarized:

- Overall Response Rate (ORR).

The ORR is defined as the percentage of patients with best overall response (BOR) of CR or PR relative to the appropriate analysis set.

- Disease Control (DC).

A patient with a BOR of CR, PR, non-CR/non-PD or SD is defined as having **DC**.

The **DC rate** is defined as the percentage of patients with DC according to the appropriate analysis set. In addition, a **DC rate at week X** would be to calculate a PFS Kaplan-Meier rate at week X.

- Duration of Response (DoR).

For patients with an objective response, **DoR** is the time from first documentation of PR or CR to date of first documentation of PD or death due to any cause.

Censoring: Same as censoring for primary definition of progression free survival (PFS) used in the study. Duration of response is only calculated on the subset of patients having CR or PR.

- Time to progression (TTP).

TTP is the time from start date to the date of the first documentation of PD.

- Progression free survival (PFS).

PFS is the time from randomization date to date of first documentation of PD or death due to any cause.

Similar assessments based on irRECIST will be summarized. The definitions for irBOR (including irCR, irPR, irSD, irPD etc.), irPFS, and irTTP are similar with those defined above based on RECIST 1.1 except that irRECIST criteria are used in defining each of the tumor response.

6.2. Safety Endpoints

- Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study of both Q2W and Q3W regimen.
- Adverse Events (AEs): Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication.
- AEs will be graded by the investigator according to CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients 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.
- Laboratory abnormalities.
- Vital signs.
- ECGs.

6.3. CCI [redacted]

- CCI [redacted]
- CCI [redacted]

[redacted]

- CCI [redacted].

6.4. Pharmacokinetics Endpoints

Drug concentrations of ADC (PF-06647020), total antibody (hu6M024 mAb), unconjugated payload (PF-06380101), and avelumab (combination of PTK7 ADC and avelumab cohort only) will be measured using validated methods. PK parameters will be determined from the respective concentration-time data using standard noncompartmental methods. Actual sample collection times will be used for the parameter calculations. For ADC (PF-06647020), total antibody (hu6M024 mAb), and avelumab (PTK7 ADC in combination of avelumab cohort) , PK parameters including maximum concentration (Cmax), time to maximum concentration (Tmax), area under the concentration-time curve over 1 dosing interval (AUCτ), area under the concentration-time curve from time 0 to the last measurable concentration (AUClast), and if data permit or if considered appropriate, area under the concentration-time curve from time 0 extrapolated to infinity time (AUCinf), terminal elimination half-life (t½), clearance (CL), volume of distribution at steady state (Vss), and accumulation ratio (Rac) will be calculated. For unconjugated payload (PF-06380101), PK parameters including Cmax, Tmax, AUClast, AUCinf, AUCτ, t½, and Rac will be calculated as appropriate. For avelumab, PK parameters including Cmax, Tmax, AUClast, AUCinf, AUCτ, t½, CL, Vss and Rac will be calculated as appropriate.

PK parameters will be derived from the concentration-time data as follows:

Parameter	Definition	Method of Determination
AUC_{last}	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration	Linear/Log trapezoidal method
AUC_{τ}	Area under the concentration-time profile from time zero to the time τ, the dosing interval	Linear/Log trapezoidal method
AUC_{inf}	Area under the concentration-time profile from time zero extrapolated to infinite time	$AUC_{(0\text{-}t[last])}$ + (Clast*/kel), where Clast* is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$T_{½}$	Terminal elimination half-life	Loge(2)/kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL	Clearance	Dose/ AUC_{inf} for cycle 1; Dose/ AUC_{τ} for cycle 4
V_{ss}	Volume of distribution at steady state	CL×MRT
R_{ac}	Observed accumulation ratio	$AUC_{cycle\ 4,\ \tau}$/ $AUC_{cycle\ 1,\ \tau}$

Blood samples collected for fluconazole concentrations (DDI study only) will only be analyzed if fluconazole concentration data are required for interpreting the PF-06380101 PK results.

6.5. PD Endpoint

CCI [redacted] Samples will be assayed using a validated analytical method in compliance with Pfizer standard operating procedures.

CCI [redacted]

6.6. Immunogenicity Endpoints

For the immunogenicity data, the percentage of patients with positive ADA of PF-06647020 or avelumab, and Nab each will be summarized by dose level (Part 1) or by treatment arms (Part 2). For patients with positive ADA or Nab, the magnitude (titer), time of onset, and duration of ADA or Nab response will also be described, if data permit. Potential impact of immunogenicity on PK and CCI [redacted], safety/tolerability and efficacy of PF-06647020 will be explored, if data is warranted.

6.6.1. Outcomes Research Endpoints

Not applicable

6.7. Covariates

The analyses of the MTD do not use covariates, and none will be defined. There are no planned comparisons between dose groups.

7. HANDLING OF MISSING VALUES

Missing data will be excluded from the tabular summaries.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

The statistical summaries are non-inferential. The data are summarized by cohort defined by the initial dose of the study drug. Where applicable the summaries of the MTD may include a Bayesian credible interval based on the posterior density from the full probability model.

8.1.1. Analyses for Continuous Data

Continuous data will be summarized with the mean, median, minimum, maximum and standard deviation. Missing values will be excluded from the analysis.

8.1.2. Analyses for Categorical Data

Categorical data will be summarized by number of unique patient incidence. Missing data will be excluded from the analysis.

8.1.3. Analyses for Binary endpoints

Binary data will be summarized using number of unique patient incidence, and Wilson's confidence interval for binomial proportions may be presented.

8.1.4. Analyses for Time-to-Event Data

The median, percentiles and probabilities at particular points in time are estimated using the method of Kaplan and Meier.

8.2. Statistical Analyses

8.2.1. Primary Analysis

The primary analysis will be based on the Safety Analysis Set. The analysis is to summarize the adverse event incidence and will implement Pfizer standard summaries for adverse events. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the Study Design section. Adverse Events constituting DLTs will be listed per dose level. Because the intent is to find a desirable dose that meets the tolerability criteria based on DLT rate while demonstrating clinical activity based on response rate, descriptive statistics (n, frequency, and percentage) will be resorted. Corresponding listings of data will be generated.

8.2.2. Efficacy Analyses

No formal hypothesis testing will be performed on analysis of efficacy endpoints. Efficacy analysis will be summarized by dosing regimen, tumor type and dose.

Descriptive statistics (frequency and percentage) for tumor response (CR, PR, PD, SD, etc.), ORR, DCR will be presented, based on RECIST 1.1 and irRECIST, separately.

The time to event endpoints such as PFS, TTP, and DOR will be summarized using the Kaplan Meier method. DOR is only for the subset patients who achieved the best overall response (BOR, or irBOR) of CR (irCR) or PR (irPR), and may also be summarized as a general continuous variable for which mean, standard deviation, minimum, maximum and median of duration in unit of weeks.

8.2.2.1. Progression-Free Survival (PFS)

PFS is the time from randomization date to date of first documentation of PD or death due to any cause.

PD or death within 16 weeks of the last adequate tumor assessment or start date will be counted as an event according to the tumor assessment date or date of death, as appropriate.

Censoring: Patients without an event or with an event more than 16 weeks after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment that documented no progression. In addition, if a new anti-cancer therapy is started prior to an event; the patient will be censored on the date of the last adequate tumor assessment that documented no progression prior to the start of the new anti-cancer therapy.

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined based on RECIST 1.1 and/or irRECIST (for combination cohort only) criteria. Time points where the response is NE or no assessment was performed will not be used for determining the censoring date.

Patients with no baseline tumor assessment (including patients with an inadequate baseline assessment) or with no adequate post-baseline tumor assessments within 16 weeks after the start date will be censored on the start date, unless the patient dies within 16 weeks of the start date, in which case, death will be an event on date of death.

Events and censoring rules are summarized in Table 2.

Table 2. PFS Outcome and Event Dates

Situation	**Date of Progression/Censoring**	**Outcome**
No adequate baseline assessment	Start datea	Censoreda
PD or death ≤16 weeks after last adequate tumor assessment or ≤16 weeks after start date	Date of PD or death	Event
No PD/withdraw due to clinical progression	Date of last adequate tumor assessment	Event
PD or death >16 weeks after the last adequate tumor assessmentb	Date of last adequate tumor assessmentb documenting no PD prior to new anti-cancer therapy or missed assessments	Censored
No PD		
New anti-cancer therapy given		

[a] If the patient dies ≤*16 weeks* after start date, the death is an event with date on death date.
[b] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the start date; if the criteria were met the censoring will be on the start date.

Reasons for censoring should be summarized according to the categories in Table 3.

Table 3. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment.	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event more than 16 weeks from last adequate post-baseline tumor assessment/start date.	Event after missing assessments[a]
4	No event and [withdrawal of consent date ≥start date OR End of study (EOS) = Subject refused further FU].	Withdrawal of consent
5	No event and lost to follow-up in any disposition page.	Lost to follow-up
6	No event and [EOS present OR disposition page for any EPOCH after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment.	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met.	Ongoing without an event

[a] More than *16 weeks* after last adequate tumor assessment.

8.2.2.2. Time to progression (TTP)

TTP is the time from start date to the date of the first documentation of PD.

In TTP analysis, deaths are censored, either at the time of death or at an earlier visit representing informative censoring (non-random pattern of loss from the study).

Censoring: Same as censoring for the definition of PFS. In addition patients who die without PD will be censored on the date of the last adequate tumor assessment that documented no progression.

Events and censoring rules are summarized in Table 4 similarly to PFS but not including death as an event.

Table 4. TTP Outcome and Event Dates

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment	Start date	Censored
PD ≤*16 weeks* after last adequate tumor assessment or ≤*16 weeks* after start date	Date of PD	Event
No PD/ withdraw due to clinical progression	Date of last adequate tumor assessment	Event
	Date of last adequate tumor assessment[a] documenting no PD prior to new anti-cancer therapy or missed visits.	Censored
No PD		
New anti-cancer therapy given		
Death due to any cause		

Reasons for censoring should be summarized according to the categories in Table 5.

Table 5. TTP Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before PD.	Start of new anti-cancer therapy
3	Event more than *16 weeks* from last adequate post-baseline tumor assessment/start date	Event after missing assessments[a]
4	Death prior to PD	Death due to any cause
4	No PD and [withdrawal of consent date ≥ start date OR End of study (EOS) = Subject refused further FU]	Withdrawal of consent
5	No PD and lost to follow-up in any disposition page	Lost to follow-up
6	No PD and EOS present OR disposition page for any EPOCH after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No post-baseline tumor assessment
7	No PD and none of the conditions in the prior hierarchy are met	Ongoing without an event

[A] more than *16 weeks* after last adequate tumor assessment.

8.2.2.3. Duration of Response (DoR)

For patients with an objective response, **DoR** is the time from first documentation of PR or CR to date of first documentation of PD or death due to any cause.

Censoring: Same as censoring for primary definition of PFS used in the study.

8.2.2.4. Overall Response Rate (ORR)

The ORR is defined as the percentage of patients with a BOR of CR or PR relative to the appropriate analysis set.

Category of Best Overall Response:

Best overall response: The **BOR** is the best response recorded from start date until the end of study, disease progression or start of new anti-cancer therapy whichever is earlier.

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

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

SD: At least one objective status of stable or better documented at least 6 (-.5) weeks (in consideration of study monitoring schedule) after start date and before progression and the start of new anti-cancer therapy but not qualifying as CR or PR.

PD: Progression documented after start date and not qualifying as CR, PR , SD or NE.

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

- Early death : death prior to 6 weeks after start date;
- No post-baseline assessments;
- All post-baseline assessments have overall response NE;
- New anti-cancer therapy started before first post-baseline assessment;
- SD too early (<6 (-0.5) weeks after start date).

Special and rare cases where BOR is NE due to early SD will be classified as ‘SD too early’.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Derivation of BOR and irBOR

Examples of objective status sequences and overall response for a tumor assessment interval of at least 4 weeks and at least as long as the minimum assessment time to qualify as SD are shown in Table 3. This will vary for other assessment schedules.

Table 6. Derivation of Best Overall Response When Confirmation Of Response Is Required

Objective status at:				
Assessment 1	Assessment 2	Assessment 3	Assessment 4	Overall Response
Death				NE
CR	CR	PD		CR
CR	NE	CR	PD	CR
PR	CR	CR	PD	CR
PR	CR	PD		PR
PR	PR	PD		PR
PR	SD or NE	PR	PD	PR
PR	PR	CR	PD	PR
CR	PR			Not allowed. Reappearance is progression
CR	PD			SD
PR	PD			SD
SD or NE	CR	PD		SD
SD or NE	PR	PD		SD
SD	PD			SD
PD				PD
No or NE assessment				NE
NE	PD			PD
NE	No or NE assessment			NE
NE	NE	PD		NE

Table 7. Scenarios of Assignments of Best Overall Response using irRECIST

Objective status at:				
Assessment 1	Assessment 2	Assessment 3	Assessment 4	ir Best Overall Response
Death				NE
irCR	irCR	irPD		irCR
irCR	NE	irCR	irPD	irCR
irPR	irCR	irCR	irPD	irCR
irPR	irCR	irPD		irPR
irPR	irPR	irPD		irPR
irPR	irSD or NE	irPR	irPD	irPR[a]
irPR	irPD	irPR		irSD
irPR	irPR	ircR	irPD	irPR
ircR	irPR			irPR
ircR	irPD			irSD
irPR	irPD			irSD
irPR				irSD
irSD or NE	ircR	irPD		irSD
irSD or NE	irPR	irPD		irSD
irSD	irPD			irSD
irPD	irPD			irPD
irPD	Death			irPD[b]
irPD				NE
No or NE assessment				NE
NE	irPD			NE
NE	No or NE assessment			NE
NE	NE	irPD		NE

a. if irPRs are at least 4 weeks apart; b. Death due to disease progression
"ir" indicates immune responses assigned using irRECIST. irBOR=best overall response. irCR=complete response. irPR=partial response. NE=not evaluable. irPD=confirmed progression. irSD=stable disease. RECIST=Response Evaluation Criteria in Solid Tumors.

8.2.2.5. Disease Control Rate (DCR)

A patient with a BOR of CR, PR, non-CR/non-PD or SD is defined as having **Disease Control.**

The **DCR** is defined as the percentage of patients with DC according to the appropriate analysis set.

8.2.2.6. Clinical Benefit Response (CBR)

The clinical benefit response is defined as a CR, PR or SD lasting for 6 cycles or greater. CBR rate with 95% confidence interval will be tabulated by dosing regimen and tumor type.

8.2.3. Safety Analyses

Safety data will be summarized using Pfizer standard data summary procedures.

Data will be summarized by dosing regimen and dose.

A breakdown of demographic data will be provided for age, race, weight, body mass index, and height by cohort defined by initial dose.

Adverse Events,

AEs including irAE (combination cohort only) will be graded by the investigator according to the CTCAE version 4.03 and coded using the MedDRA. The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). The Safety Analysis Set will be used.

Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test. The analyses will summarize laboratory tests both in the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory abnormalities. The Safety Analysis Set will be used.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal high/low or not done.

Study Conduct and Patient Disposition

An accounting of the study patients will be tabulated. The subject evaluation groups will be listed. The Full Analysis Set will be used.

Subject discontinuation from treatment and study will be tabulated and listed separately with their reason for discontinuation. The Safety Analysis Set will be used.

Baseline Characteristics

Baseline characteristics such as demographics, prior line of therapy, medical history, Eastern Cooperative Oncology Group (ECOG) performance status, baseline CA-125 and primary diagnosis will be tabulated and listed by dose and dosing regimen, and by tumor type and dosing regimen. For ECOG performance status a shift table (worst post-baseline vs baseline may be produced). The Safety Analysis Set will be used.

Treatment Administration/Compliance

Listings and tables by dose level will be provided. Cycle length is 21 days for the Q3W Regimen and 28 days for the Q2W Regimen. Day 1 of a cycle is the date of first dose within that cycle. The safety analysis set will be used.

Dose modifications may occur in the following ways:

- Cycle delay—Day 1 of current cycle starts later than 28 days from Day 1 of the previous cycle (only applies to cycle 2 and above) for the Q3W Regimen. Day 1 of current cycle starts later than 35 days from Day 1 of the previous cycle for the Q2W Regimen;

- Dose reduction—A decrease greater than 0.5 mg/kg equivalent in the administered total daily dose compared to the planned total daily dose upon enrollment. If in the CRF the prescribed dose unit is mg/kg, but the actual dose is in mg the actual dose mg/kg should be calculated considering the body weight of the patient at that visit.

Intra-patient dose escalation is not allowed in this study. The following will be summarized by subject for each dose level:

- Number of subjects per dose level;

- Median and range of number of cycles started per subject;

- Number (%) of subjects starting a cycle (1, 2, 3…);

- Number (%) of subjects with cycle delays;

- Number (%) of dose interruptions (include both known and unknown dates);

- Number (%) of subjects with dose reductions;

- Number (%) of each reason (AE vs. Other) for cycle delays, dose interruptions and dose reductions;

- Time on treatment (median, range).

  The following will be summarized by cycle received for each dose level:

- Total number of cycles started;

- Number of cycles started per subject (median, range);

- Number of cycles before 1st delay (median, range);

- Number of cycles before 1st reduction (median, range);

- Number of cycles before 1st interruption (median, range).

The following will be summarized for cumulative dose by dose level and cycle:

- Summary statistics (mean, median, standard deviation and range) of cumulative dose and percent of starting dose (compared to Day 1 dose of each cycle)

Listings by subject (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0 mg), administered total daily dose for each period, any missed doses with unknown dates (Y/N), number of missed doses with unknown dates, reason for any dosing changes.

Listings by subject and each cycle (ordered by dose level): cycle length, total planned dose, administered total dose, percentage of planned dose, dose delay (yes/no), dose reduction (yes/no), and dose interruption (yes/no).

Prior, Concomitant, and Further Therapies

Prior, concomitant, and further therapies (drug and non-drug treatments) will be coded by the World Health Organization (WHO) medical dictionary. Summary tables, listings of prior, concomitant, and further therapies will be provided separately.

Anti-PF-06647020 and anti-avelumab antibody

For anti- PF-06647020 and anti-avelumab antibody, a listing, sorted by subject and study day, of the result of specific ADAantibody at screening (positive/negative [<1:negative]), the specificity, and titer will be listed. Summary counts of the patients, who are positive for the antibody, will be derived by study treatment and visit for the safety population. No summary statistics other than those cited above, will be generated.

The following data will also be summarized by treatment and in accordance with the current sponsor reporting standards:

> Discontinuations, Adverse Events, laboratory data, vital signs, ECG and concomitant medication data will be summarized by cohort defined by initial dose in accordance with current Pfizer data standards.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation.

8.2.4. Other Safety Data – Screening and Other Special Purpose Data

Prior medication(s), non-drug treatment(s), medical history and physical examination will be listed in accordance with the sponsor reporting standards. Medical history will be mapped using the MedDRA thesaurus.

Serum/urine Pregnancy test results will be presented in the listings.

8.2.5. PK Analyses

8.2.5.1. Concentrations below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

8.2.5.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of the median values at each time point, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

8.2.5.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters. Each PK parameter will be summarized by regimen, dose and cycle and will include the set of summary statistics as specified in the table below:

Parameter	Summary statistics
AUC_{last}, AUC_{∞}, AUC_{τ}, C_{max}, CL, V_{ss}, and R_{ac}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum
T_{max}	N, median, minimum, maximum

To assess the relationship between the PK parameters and dose, dose normalized AUC∞, AUClast, AUCτ, and Cmax will be plotted against regimen, dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg/kg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented are presented on the plot.

8.2.5.4. PK Concentrations

To assess the PK profiles of PF-06647020 (ADC), total antibody, unconjugated payload, and avelumab (PTK7 ADC in combination of avelumab cohort), PK concentrations of each analyte will be listed, summarized and plotted for subjects in the PK analysis set (as defined in Section 5.4), where missing and BLQ values will be handled as detailed in Section 8.2.5.1 above.

Presentations for each PK analyte will include:

- A listing of all concentrations sorted by dose, subject ID, period and nominal time post-dose. The listing of concentrations will include the actual sample collection times, and the time of dosing. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by dose and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations against nominal time post-dose by dose (based on the summary of concentrations by dose and time post-dose), with all doses presented on the same plot. Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Mean concentrations against nominal time post-dose by dose (based on the summary of concentrations by dose and time post-dose), with all doses presented on the same plot. Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Plots of individual concentrations against actual time post-dose (separate plots for each dose). Two plots per dose will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Plots of concentration against actual time post-dose by subject (separate line for each dose). Two plots per subject will be generated, so that the concentrations can be presented on linear and logarithmic scales.

In addition to the above, a median plot (linear and log scale) of the predose concentrations at each cycle against day will be provided for each dose, on the same plot, in order to assess the attainment of steady-state. Individual subject profiles will also be plotted.

For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

8.2.6. Drug-Drug Interaction Analysis (DDI sub-study only)

For DDI sub-study, the primary PK parameters for puopose of evaluating drug interactions will be dose normalized AUC∞, AUClast, AUCτ, and Cmax for unconjugated payload (PF-06380101) in the absence (Reference) and presence (Test) of fluconazole. AUC parameters and Cmax will be natural log transformed and subjected to ANOVA test; the adjusted mean differences (Reference – Test) and corresponding 90% confidence intervals (CIs) will be derived. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the geometric mean ratios (GMRs) and the associated 90% CIs. No formal confirmatory hypothesis testing will be conducted.

A similar analysis will be conducted for ADC (PF-06647020), total antibody (hu6M024 mAb), and unconjugated payload/ADC exposure ratios (AUC, Cmax), as supportive data.

Summary statistics and figures of Cmax and AUC values of unconjugated payload (PF-06380101), ADC (PF-06647020), total antibody (hu6M024 mAb), as well as unconjugated payload/ADC exposure ratios will be presented by Cycles (Cycle 1 - ADC alone vs. Cycle 2 - ADC in the presence of fluconazole). Data from patients prematurely ending participation in the study or failing to meet evaluation criteria may be excluded from pharmacokinetic data evaluation.

Presentations for each PK analyte will include:

- Median concentrations against nominal time postdose following administration of PF-06640707 without and with fluconazole (cycle 1 vs. cycle 2). Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Dose normalized median concentrations against nominal time postdose following administration of PF-06640707 without and with fluconazole (cycle 1 vs. cycle 2). Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Mean concentrations against nominal time postdose following administration of PF-06640707 without and with fluconazole (cycle 1 vs. cycle 2). Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Dose normalized mean concentrations against nominal time postdose following administration of PF-06640707 without and with fluconazole (cycle 1 vs. cycle 2). Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Plots of individual concentrations against actual time postdose following administration of PF-06640707 without and with fluconazole (cycle 1 vs. cycle 2).

Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

CCI [redacted]

[redacted]

9. REFERENCES

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2. L. Seymour, J. Bogaerts, A. Perrone, et al, iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncology, 2017; 18: e143-52.

3. Food and Drug Administration Guidance For Industry Clinical Trial Endpoints For The Approval Of Cancer Drugs And Biologics http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf.