PROTOCOL B0601002

A PHASE 1, OPEN-LABEL, DOSE ESCALATION STUDY OF PF-04518600 AS A SINGLE AGENT AND IN COMBINATION WITH PF-05082566 IN PATIENTS WITH SELECTED LOCALLY ADVANCED OR METASTATIC CANCERS

STATISTICAL ANALYSIS PLAN AMENDMENT (SAP)

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Author: PPD

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Abbreviation	Term
Ab	antibody
ADA	anti-drug antibody
AE	adverse event
AEs	adverse events
AIDS	acquired immunodeficiency syndrome
Alk Phos	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
ANOVA	analysis of variance
APCs	antigen presenting cells
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
AUC	area under the (concentration-time) curve
BCL	B-cell lymphoma
BP	blood pressure
BUN	blood urea nitrogen
C	cycle
C_{av}	average concentration
C_{max}	maximum concentration
C_{min}	minimum concentration
CxDx	cycle x day x
CBA	cytometric bead array
CBC	Complete blood count
CDS	core data sheet
CHF	congestive heart failure
CI	confidence interval
CL	clearance
CNS	central nervous system
CRF	case report form
CR	complete response
CSA	clinical study agreement
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTC	common terminology criteria
CTCs	circulating tumor cells
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
D	day
DAI	dosage and administration instructions
DLI	donor lymphocyte infusion
DLT	dose limiting toxicities
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	eastern cooperative oncology group
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EFS	event free survival

Abbreviation	Term
EudraCT	European clinical trials database
FDA	food and drug administration (United States)
FDAAA	food and drug administration amendments act (United States)
FFPE	formalin-fixed paraffin-embedded
FIP	first in patient
FSH	follicle-stimulating hormone
GCP	good clinical practice
GITR	glucocorticoid-induced tumor necrosis factor receptor
Gp100	glycoprotein 100
HBV	hepatitis b virus
hCG	human chorionic gonadotropin
HCV	hepatitis c virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
IB	investigator's brochure
ICD	informed consent document
ICH	international conference on harmonization
ICOS	inducible t-cell co-stimulator
IEC	institutional ethics committee
ID	identification
IFNγ	interferon gamma
IgG	immunoglobulin g
IHC	immunohistochemistry
IL-	interleukin
IM	immunomodulatory
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
KLH	keyhole limpet hemocyanin
LAG3	lymphocyte-activation gene 3
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
mTPI	modified toxicity probability interval
mAb	monoclonal antibody
MD	multiple dose
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
OBD	optimal biological dose
ORR	objective response rate
OS	overall survival
pT	target probability
PBMCs	peripheral blood mononuclear cells
PCD	primary completion date

Abbreviation	Term
PDs	pharmacodynamics
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PE	physical exam
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetics
PLTS	platelets
PR	partial response
PS	performance status
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease
SDo	Single Dose
SPC	summary of product characteristics
SRSD	single reference safety document
T	time
T1/2	terminal elimination half-life
TBNK assay	TBNK lymphocyte assay
TCR	T-cell receptor
Th	T-helper
TILs	tumor infiltrating lymphocytes
TNF	tumor-necrosis factor
TNF-α	tumor-necrosis factor alpha
TNFR	tumor-necrosis factor receptor
TNFSF4	tumor necrosis factor (ligand) superfamily,member 4
Tregs	T regulatory cells
TTP	time to progression
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USPI	United States package insert
VEGF	Vascular Endothelial Growth Factor
Vss	Volume of distribution at steady state
WBC	White blood cell count

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is an amendment to the original SAP.

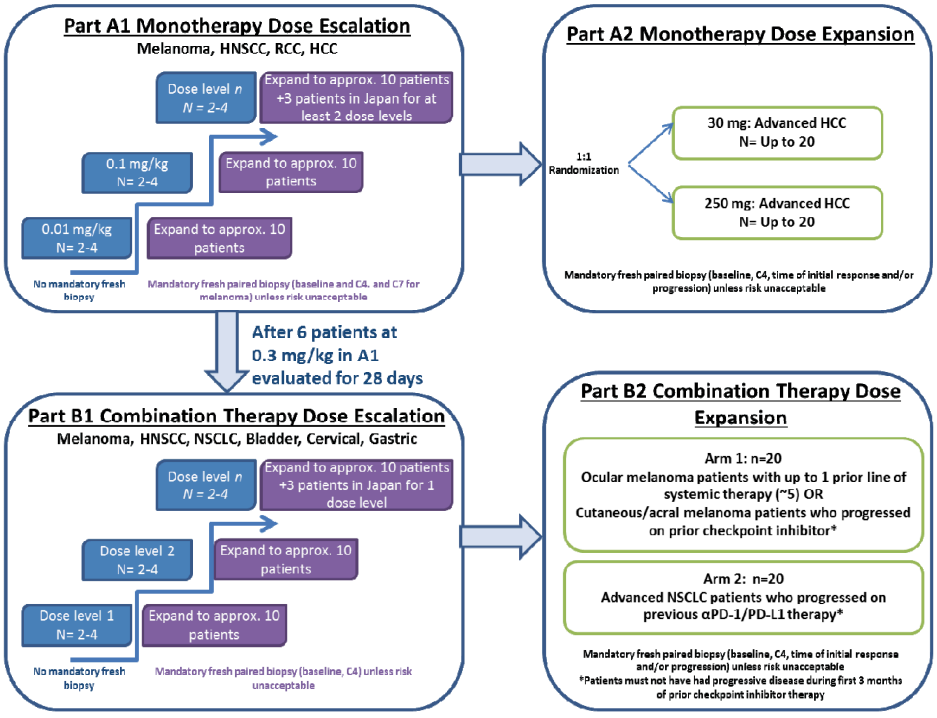
2. INTRODUCTION

This document describes the planned statistical analyses for Protocol B0601002 Amendment 5, dated 16 August 2017. This statistical analysis plan (SAP) amendment 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, multiple dose, dose escalation, safety, pharmacokinetic, and pharmacodynamic study of PF 04518600 monotherapy in Part A, and PF 04518600 in combination with utomilumab in Part B. Each part includes a dose escalation phase, and a dose expansion phase. A maximum of approximately 210 patients are expected to be enrolled into the study.

Figure 1. Study Schematic



All patients will complete up to 4 weeks of screening. Following the initial dose(s), treatment with investigational product will continue until either disease progression by immune related response evaluation criteria in solid tumors (irRECIST), patient refusal, or unacceptable toxicity occurs, or end of study, whichever occurs first. Patients will be allowed to stay on study, if the treating physician feels that it is in the patient's best interest in the case of radiological progression, and the absence of clear clinical progression. A follow up visit approximately 4 weeks after the last dose for adverse event (AE) and serious AE (SAE) collection will be conducted. Late immune related adverse events will be evaluated up to 98 days after the first dose(s) of Cycle 1. Because atypical tumor responses after growth of preexisting lesions or appearance of new lesions have been observed with immune checkpoint inhibitors, study B0601002 will assess tumor response based on both response evaluation criteria in solid tumor (RECIST) and Immune related Response Criteria Derived From RECIST v1.1 (irRECIST). Survival data will also be collected.

Part A Monotherapy

Part A1 Monotherapy Dose Escalation

Part A1 monotherapy dose escalation phase will enroll approximately 58 adult patients with locally advanced or metastatic cancers hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC) or head and neck squamous cell carcinoma (HNSCC). The actual number of patients enrolled will depend on the observed safety and tolerability profile of PF-04518600, the number of dose levels that will be tested and expanded to characterize the pharmacodynamic or immunomodulatory (IM) effects, and the number of dose levels required to identify the maximum tolerated dose (MTD) or optimal biological dose (OBD). Six dose levels are proposed: 0.01, 0.1, 0.3, 1.5, 3.0 and 10.0 mg/kg. Each cohort will include an initial cohort of 2-4 patients that may be expanded to approximately 10 patients. Approximately 3 patients enrolled in Japan will be included for at least 2 dose levels. A modified toxicity probability interval (mTPI) method,[1] targeting a dose limiting toxicities (DLT) rate of 25% and an acceptable DLT interval (20% 30%), will be utilized for dose escalation.

Part A2 Monotherapy Dose Expansion

Part A2 monotherapy dose expansion phase will randomize HCC patients 1:1 to flat dose levels of either 30 mg (Arm 1) or 250 mg (Arm 2) of PF 04518600 given every 2 weeks. Both doses were chosen based on data from Part A1. Each arm in Part A2 will include approximately 20 HCC patients.

Part B Combination Therapy

Part B1 Combination Therapy Dose Escalation

Part B1, the combination therapy dose escalation phase, will enroll approximately 53 patients. At least 6 patients must have been evaluated for the 28 day DLT observation period at the 0.3 mg/kg dose level in Part A1 PF-04518600 (OX40 agonist) monotherapy before Part B1 can be initiated. Part B1 will study sequential dose levels of PF-04518600 (0.1, 0.3, 1.0 and 3 mg/kg) combined with either 20 mg or 100 mg of

utomilumab (4-1BB agonist) in adult patients with non-small cell lung cancer (NSCLC), HNSCC, melanoma, bladder, gastric or cervical cancer who are unresponsive to currently available therapies or for whom no standard therapy is available. The starting dose level will be 0.1 mg/kg of PF-04518600 and 20 mg of utomilumab, given no sooner than 30 minutes apart.

A mTPI method, targeting a DLT rate of 25% and an acceptable DLT interval (20%-30%) will be utilized for dose escalation.

Part B2 Dose Expansion

Part B2 combination therapy dose expansion phase will further evaluate safety and anti-tumor activity of the combination of 30 mg PF-04518600 and 20 mg of utomilumab. Part B2 will be divided into 2 arms:

Arm 1 *will enroll melanoma patients who have either:*

a. *Ocular melanoma; and have received no more than one line of systemic therapy for metastatic disease. Patients must not have received immune modifying agents (eg, anti-PD-L1, anti-PD1, anti-CTLA4, TNF agonist, etc.) for metastatic disease; or*

b. *Cutaneous/acral melanoma; and have 1) only previously received systemic therapy for advanced/metastatic disease with the following therapies: BRAF and MEK inhibitors, anti-PD-L1, anti-PD-1, or anti-CTLA4 and 2) have received checkpoint inhibitor (anti-PD-L1, anti-PD-1, or anti-CTLA4) based treatment as most recent line of therapy on which disease progressed, as long as progression did not occur in the first 3 months of receiving checkpoint inhibitor treatment.*

Arm 2 will *enroll NSCLC patients who have:*

a. *Previously received prior anti-PD-L1 or anti-PD-1 mAb as most recent therapy; and,*

b. *did not have progressive disease as best overall response on recent PD-L1/PD-1 therapy (ie, stable disease ≥3 months, PR, or CR), and 3) who subsequently progressed on PD-L1/PD-1 therapy.*

2.2. Study Objectives

2.2.1. Objectives for Part A Monotherapy

2.2.1.1. Objectives for Part A1 Monotherapy Dose Escalation

Primary Objective:

- To assess safety, and tolerability at increasing dose levels of PF-04518600 in patients with selected advanced or metastatic solid tumors in order to establish the MTD.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in patients with selected advanced or metastatic solid tumors solid tumors.
- To characterize the single dose and multiple dose PK of PF-04518600 following IV administration.
- To evaluate the immunogenicity of PF-04518600 following IV administration.
- To characterize the degree of target engagement (TE) by PF-04518600 at multiple doses by measuring unbound (free) cell surface OX40 in peripheral blood.

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2.2.1.2. Objectives for Part A2 Monotherapy Dose Expansion

Primary Objectives:

- To establish the RP2D of PF-04518600 in patients with selected advanced or metastatic HCC.
- To further characterize the safety and tolerability of PF-04518600 in patients with selected advanced or metastatic HCC.

Secondary Objectives:

1. To assess preliminary anti-tumor clinical activity of PF-04518600 in patients with selected advanced or metastatic HCC.

2. To characterize the single dose and multiple dose PK of PF-04518600 following IV administration.

3. To evaluate the immunogenicity of PF-04518600 following IV administration.

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[redacted]

2.2.2. Objectives for Part B Combination Therapy

2.2.2.1. Objectives for Part B1 Combination Therapy Dose Escalation

Primary Objective:

- To assess safety and tolerability at increasing dose levels of PF-04518600 in combination with utomilumab in patients with selected advanced or metastatic solid tumors and to estimate MTD of the combination.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in combination with utomilumab.

- To characterize single and multiple dose pharmacokinetics of PF-04518600 and utomilumab when given in combination.

- To evaluate immunogenicity of PF-04518600 and utomilumab when given in combination.

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[redacted]

2.2.2.2. Objectives for Part B2 Combination Therapy Dose Expansion

Primary Objective:

- To further assess safety and tolerability of PF-04518600 in combination with utomilumab in patients with melanoma or NSCLC in order to establish RP2D for the combination.

Secondary Objectives:

- To assess preliminary anti-tumor clinical activity of PF-04518600 in combination with utomilumab.
- To characterize single and multiple dose pharmacokinetics of PF-04518600 and utomilumab when given in combination.
- To evaluate immunogenicity of PF-04518600 and utomilumab when given in combination.

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[redacted]

2.3. Endpoints

2.3.1. Endpoints for Part A Monotherapy

2.3.1.1. Endpoints for Part A1 Monotherapy Dose Escalation

Primary Endpoints:

- Dose limiting toxicities (DLTs) observed in each patient during the first 98 days in order to determine the MTD.
- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to study therapy PF-04518600.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.

- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.

- Overall survival rates at 6 months, 1 year and 2 years.

- Pharmacokinetic parameters of PF-04518600:

  Single Dose (SDo) - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit.
  Multiple Dose (MD) (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, , and R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sdo,\tau}$) as data permit

- Incidence of ADA and NAb against PF-04518600.

- Levels of free OX40 receptor expressed on T cells in peripheral blood.

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[redacted]

2.3.1.2. Endpoints for Part A2 Monotherapy Dose Expansion

Primary Endpoints:

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to study therapy PF-04518600.

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.

- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.

- Overall survival rates at 6 months, 1 year and 2 years.

- Pharmacokinetic parameters of PF-04518600:

  Single Dose (SDo) - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit.

  Multiple Dose (MD) (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, , and R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sdo,\tau}$) as data permit

- Incidence of ADA and NAb against PF-04518600.

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

2.3.2. Endpoints for Part B Combination Therapy

2.3.2.1. Endpoints for Part B1 Combination Therapy Dose Escalation

Primary Endpoints:

- DLTs observed in each patient during the first 98 days in order to determine the MTD.

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to PF-04518600/utomilumab combination.

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 years.
- Pharmacokinetic parameters of PF-04518600 and utomilumab:

  Single Dose (SDo) - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit.

  Multiple Dose (MD) (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, , and R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sdo,\tau}$) as data permit

- Incidence of ADA and NAb against PF-04518600 and utomilumab.

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2.3.2.2. Endpoints for Part B2 Combination Therapy Dose Expansion

Primary Endpoints:

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to PF-04518600/utomilumab combination.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary Endpoints:

- Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.
- Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.
- Overall survival rates at 6 months, 1 year and 2 year.
- Pharmacokinetic parameters of PF-04518600 and utomilumab:

  Single Dose (SDo) - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit.

  Multiple Dose (MD) (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, , and R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sdo,\tau}$) as data permit.
- Incidence of ADA and NAb against PF-04518600 and utomilumab.

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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

There are no formal interim statistical analyses in this open label, unblinded clinical trial. During the conduction of the study, the Pfizer study team will review safety, immunogenicity, pharmacokinetics, pharmacodynamics, CCI and other data throughout the study.

Of the Bayesian mTPI procedure for assessing dose limiting toxicity, as the data arrive, it may become necessary to consider updating the Bayesian model and update the Bayesian Posterior Distribution.

Based on emerging data from Parts B1 and B2, if no response has been seen by the time the 10th patient enrolls in either arm in B2, enrollment may pause until a patient experiences a response or after the 16 week tumor assessment for the 10th patient, whichever is first. If at least 1 response does not occur in the first 10 patients in an arm, then enrollment may stop in that arm. Enrollment will continue in any arm that has at least 1 responder in the first 10 patients. If there are responders in both arms before the 10th patient enrolls, then enrollment will continue to the full 20 patients for each arm.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

This clinical trial implements a Bayesian procedure to determine the MTD. No classical hypothesis testing will be done. Decisions will be based on Bayesian posterior probabilities arising from a full hierarchical probability model.

4.2. Statistical decision rules

The initial Statistical Decision rules are described in the following table:

Table 1. Decision Rules

	Number of Patients Treated at a Dose level										
Number of Patients Having 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	n/a	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;
n/a: Not applicable

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis Set (FAS) is defined as all enrolled patients who receive at least one full or partial IV infusion of study drug PF-04518600.

5.2. 'PER PROTOCOL' Analysis Set evaluable for MTD

The per protocol analysis set includes all enrolled patients who receive at least two cycles of study medication and who do not have major treatment deviations during first two cycles.

5.3. Safety Analysis Set

The Safety Analysis Set is the same as the Full Analysis Set.

5.4. OTHER ANALYSIS SETS

5.4.1. PK Concentration Analysis Set

The PK Concentration Analysis Set is defined as all patients randomized and treated who have at least 1 measurable concentration.

5.4.2. PK Parameter Analysis Set

The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest.

5.4.3. PD/Biomarker analysis set

The PD/Biomarker analysis population is defined as all enrolled patients with at least 1 of the PD/Biomarker evaluated at pre- and/or post-dose, and measurable PK concentrations.

5.5. Treatment Misallocations

This is an unblinded MTD dose finding study. Patients will be included in the cohort based on their actual treated 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 prior 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.

5.7. Baseline and Covariates

Baseline measurement is defined as the planned Baseline 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.

5.8. Efficacy Endpoints

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

RECIST 1.1 objective tumor response criteria are stated below:

Evaluation of target lesions:

> Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
>
> Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
>
> Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum

must also dem- onstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions:

Complete Response (CR): Disappearance of all non-target le-sions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target le- sion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see com- ments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Following assessments are to be summarized:

- Overall Response Rate (ORR) - ORR is defined as the percentage of patients with best overall response (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. Due to the tumor response is not a primary endpoint, CR or PR assessment based on RECIST 1.1 does not require confirmation.

CR: Complete response is defined (per RECIST 1.1) as disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

PR: Partial response is difined (per RECIST 1.1) as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

SD: At least one objective status of stable or better documented at least 6 (-5 Days) 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 or SD.

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 (-5 days) weeks after start date)

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

irRECIST

In addition to the RECIST 1.1, this study is also assessing patients' response using irRECIST criteria.

For irRECIST, with the exception of a complete response assessment, only target and new measurable lesions are taken into account. In contrast to RECIST v1.1, the irRECIST:

Requires confirmation of both progression and response by imaging at least 4 weeks from the date first documented, and

Does not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the study.

irRECIST responses are defined as follows:

- **Overall immune-related complete response (irCR):** Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.
- **Overall immune-related partial response (irPR):** Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases ≥30%.
- **Overall immune-related stable disease (irSD):** Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions does not meet criteria for irCR or irPR, (compared to baseline) or immune-related progressive disease (irPD, compared to nadir).

- **Overall immune-related progressive disease (**irPD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions increases ≥20% (compared to nadir) with a minimum absolute increase of 5 mm, confirmed by a repeat, consecutive observation at least 4 weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (ie, added to the target lesion measurements). In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

New non-measurable lesions: Do not define progression but preclude irCR.

Table 2. Overall Responses Derived from Changes in Target, Non-target, and New Lesions

Measurable disease	**Non-measurable disease**		
Target and New Measurable Lesions (Tumor Burden)[a]	**Non-Target Lesions**	**New, non-measurable Lesions**	**Overall response using irRECIST [b]**
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

[a] Decreases assessed relative to baseline
[b] Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

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.

The best overall response is the best response recorded from the start of the study treatment until the end of treatment without requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Table 3. Scenarios of Assignments of Best Overall Response (irBOR) using irRECIST where Confirmation of Response or Progression is Required

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
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.

- Duration of Stable Disease - Duration of stable disease is defined from the start of the treatment until the criteria for progression are met, taking as reference the smallest tumor measurements recorded since the treatment started, including the baseline measurements. This endpoint is applicable to the subset of patients who achieved a best overall response of stable disease (SD), those patients whose best overall response is not SD will be excluded from this endpoint analysis. A minimum of 6 weeks (with a - 5 days window, which is essentially a minimum of 37 days) interval of two assessments is required for this endpoint.

- Progression free survival (PFS) – PFS is the time from randomization date to date of first documentation of PD based on RECIST, irRECIST or death due to any cause.

Table 4. PFS Outcome and Event Dates

Situation	**Date of Progression/Censoring**	**Outcome**
No adequate baseline assessment	Start date	Censored
PD or death ≤12 weeks after last adequate tumor assessment	Date of PD or death	Event
No PD but withdraw due to clinical progression	Date of last adequate tumor assessment	Event
PD or death >12 weeks after the last adequate tumor assessment [a]	Date of last adequate tumor assessment [a] documenting no PD prior to new anti-cancer therapy or missed assessments	Censored
No PD		
New anti-cancer therapy given		
[a] 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 5.

Table 5. 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 12 *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 *12 weeks* after last adequate tumor assessment.

- Disease Control (DC) a patient with a BOR of CR, PR, 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.

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 6 similarly to PFS but not including death as an event.

Table 6. TTP Outcome and Event Dates

Situation	**Date of Progression/Censoring**	**Outcome**
No adequate baseline assessment	Start date	Censored
PD ≤*12 weeks* after last adequate tumor assessment or ≤ *12 weeks* after start date	Date of PD	Event
No PD/ withdraw due to clinical progression	Date of last adequate tumor assessment	Event
PD >*12 weeks* after the last adequate tumor assessment [a]	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		
[a] 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 7.

Table 7. 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 *12 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 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 *12 weeks* after last adequate tumor assessment.

DC, DoR, DoSD, PFS and TTP will be assessed based on RECIST and irRECIST criteria, respectively.

- Overall Survival (OS);
- Overall Survival Rate at 6 months, 1 year and 2 years.

Overall survival is the time from start date to date of death due to any cause.

Censoring: Patients last known to be alive are censored at date of last contact.

Date of Last Contact

The date of last contact will be derived for patients not known to have died at the analysis data cutoff date using the latest complete date (non-imputed) among the following:

- All patient assessment dates (eg, blood draws [laboratory, PK], vital signs, performance status, ECG, tumor assessments, concomitant radiation, surgery);
- Start and end dates of follow-up anti-cancer therapies;
- AE start and end dates;

- Last date of contact where "Subject Remains in Follow-up" collected on the "Survival Follow-up" eCRF (do not use date of survival follow-up assessment unless status is alive);

- Study drug start and end dates;

- Randomization date;

- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Note:

- Only dates associated with patient visits or actual examinations of the patient should be used. Dates associated with a technical operation unrelated to patient status (eg, the date a blood sample was processed) should not be used.

- Assessment dates after the cutoff date will not be applied to derive the last contact date.

Follow-up time for Overall Survival

A variety of methods are used to summarize the extent of follow-up in a study with censoring, as described by Schemper et al (1996), including:

- Reversing the censoring and event indicators and estimating follow-up time with the method of Kaplan and Meier (referred to as the "Kaplan-Meier potential follow-up or reversed Kaplan-Meier method").

- Calculating the "observation time" (start date to date of death or last contact date) and presenting descriptively.

- Calculating "censoring time" (start date to date of last contact for those without event) to evaluate if one treatment arm has much larger values than the other.

- Other methods as presented in Schemper et al (1996).

Preliminary evidence of anti-tumor activity based on response rate (RR), as assessed using the RECIST version 1.1, and /or irRECIST

5.9. Safety Endpoints

- Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study of both Part A1 and Part B1.

- 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 as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

- Vital signs.

- ECGs.

- Cytokine release syndrome.

5.10. Pharmacokinetics Endpoints

Pharmacokinetic parameters of PF-04518600 for both Parts A1 and A2, and PF-04518600 and utomilumab for Parts B1 and B2:

Single Dose (SDo) - C_{max}, $AUC_{sdo,\tau}$, AUC_{inf}, $t_{1/2}$, as data permit.
Multiple Dose (MD) (assuming steady-state is achieved) - $C_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, , and R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sdo,\tau}$) as data permit

Blood samples for the analysis of PF-04518600, and utomilumab concentrations will be collected according to the Schedule of Activities in the protocol. PK parameters will be determined from the concentration-time data using standard noncompartmental methods:

Parameter	Definition	Method of Determination
AUC_{τ}	Area under the concentration-time profile from time zero to the time τ, the dosing interval	Linear/Log trapezoidal method
C_{max}	Maximum observed concentration	Observed directly from data
C_{min}	Lowest concentration observed during the dosing interval	Observed directly from data
C_{av}	Average concentration at steady state	$AUC_{ss,\tau}$ / τ
$t_{½}$	Terminal elimination half-life	Loge(2)/k_{el}, where k_{el} 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.
AUC_{inf}	Area under the concentration versus time curve from zero time to infinity	AUC_{last} + ($C_{last}^{\dagger}$/ k_{el}), where AUC_{last} is the area under the concentration-time curve from time zero until the last measurable concentration; $C_{last}^{\dagger}$ is the estimated concentration at the time of the last quantifiable concentration.
CL	Clearance	Dose/ $AUC_{ss,\tau}$
V_{ss}	Volume of distribution at steady state	CL×MRT
R_{ac}	Accumulation ratio	$AUC_{ss,\tau}$ / $AUC_{sdo,\tau}$

CCI

[redacted]

5.12. Immunogenicity Endpoint

Incidence of anti-drug antibodies (ADA) and neutralizing antibody (NAb) against PF-04518600 (Parts Ax and Bx); and incidence of ADA and NAb against utomilumab (Parts Bx) will be summarized.

PK and PD responses may be evaluated on patients with positive ADA.

Tumor response may be tabulated by with or without ADA if data permits.

5.13. Outcomes Research Endpoints

N/A

6. HANDLING OF MISSING VALUES

Missing data will be excluded from the tabular summaries.

6.1. Pharmacokinetics

6.1.1. 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.)

6.1.2. Deviations, Missing Concentrations and Anomalous Values

Subjects who experience events that may affect their PK profile (eg, incomplete dosing due to injection reactions) may be excluded from the PK analysis.

In summary tables and plots of median profiles, 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 for any time point at which more than 50% of the data are missing.

6.1.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. Statistical Methods

The statistical summaries are non-inferential. The data are summarized by cohort defined by the initial dose of the study drug.

7.1.1. Analyses for Continuous Data

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

7.1.2. Analyses for Categorical Data

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

7.1.3. Analyses for Binary endpoints

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

7.1.4. Analyses for Time-to-Event endpoints

Time- to- event endpoint will be analyzed using Kaplan- Meier estimates.

7.2. Statistical Analyses

7.2.1. Primary Endpoints Analysis

The primary analysis will be based on the Full 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 reported. Corresponding listings of data will be generated.

7.2.2. Secondary Endpoints Analyses

Analysis of Progression Free Survival, a “time to event endpoint," will define time from the baseline date. Summaries of n and % of patients with PFS, and data listing will be generated. If sufficient numbers of patients are available, the PFS will also be summarized using the Kaplan Meier method. PFS rates at 6 months, 1 year and 2 years will be estimated using Kaplan Meier Method. Summary statistics (N, mean, SD, min, max) and data listings will be prepared for duration of Stable Disease (SD), and duration of Response (DR). Similar approach will be applied to Overall Survival (OS).

Percentage of tumor burden change from baseline will be summarized according to scheduled events.

Summary statistics and data listings of raw values and changes in immunohistochemistry (IHC) assessment of tumor-infiltrating lymphocytes (including but not limited to CD4 and CD8) in paired tumor biopsy collected at pre and post-treatment time points will be prepared.

7.2.3. Safety Analyses

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

Data will be summarized by cohort, defined by the initial dose. When the initial dose is determined to be the MTD, then the tables will also label the dose as the MTD.

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

Adverse Events

Adverse Events (AEs) 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 CTC 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 medication, medical history, ECOG performance status, and primary diagnosis will be tabulated and listed. 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 14 days. Day 1 of a cycle is the first date of 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 14 days from Day 1 of the previous cycle (only applies to cycle 2 and above);
- Dose reduction—A decrease in the administered total daily dose (non-zero) 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. Listings of prior, concomitant, and further therapies will be provided separately.

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 CCI [redacted] and its purpose is to generate hypotheses for further investigation.

Cytokine Release Syndrome

Patient incidence and percentage of cytokine release syndrome will be tabulated by dose received. Further assessments on the impact on the tumor response may be performed when data warranted.

Electrocardiograms (ECG)

Triplicate 12-lead ECGs will be performed per Schedule of Activities. The Day 1 triplicate ECG prior to treatment administration will be used as baseline; if it is missing, values from the single ECG taken at screening will be used for baseline.

The following will be presented:

1. Summaries of quantitative results (QT, QTc, RR, PR, QRS, heart rate) and changes from baseline will be summarized by visit for all scheduled visits. For triplicate ECGs, the mean of the three ECGs will be used as the value for each parameter. Results of ECGS done as additional follow-up for prolonged PK t1/2 and unscheduled ECG results will be listed but not summarized.
2. Summaries of qualitative results (normal; abnormal, not clinically significant [NCS]; abnormal, clinically significant [CS]; and unevaluable) will be summarized by visit for all scheduled visits. For triplicate ECGs, the most serious evaluation (abnormal CS, abnormal NCS, unevaluable, normal) of the triplicate tests will be used.
3. Shift tables based on interpretation (normal; abnormal, NCS; abnormal, CS; and unevaluable) will be prepared for baseline versus the final scheduled ECG.
4. The number (%) of subjects with maximum post-dose QTc values and maximum increases from baseline in the following categories will be tabulated:

Safety QTc

Borderline	**(msec)**	**Prolonged**	**(msec)**
Absolute	value	≥450 - <480	≥480
Absolute	change	≥30 - <60	≥60

In addition, the number of subjects with absolute QT and QTc values ≥500 msec will be listed. This table and the corresponding listing will include all ECG results, whether scheduled or not.

All ECG results, including those taken as additional follow-up for prolonged PK and unscheduled measurements, will be listed.

Echocardiogram or Multigated Acquisition (MUGA) Scan

Echocardiogram or multigated acquisition (MUGA) will be evaluated in patients with previous history of anthracycline treatment. For these patients, an echocardiogram or MUGA will be performed at screening and every 3 months whilst on treatment and when clinically indicated. An echocardiogram or MUGA will be performed at the end of treatment (EOT) visit if not performed within 3 months of discontinuation. The following parameters will be evaluated: ventricular function (including left ventricular ejection fraction [LVEF], end systolic volume [ESV] and end diastolic volume [EDV]), qualitative evaluation of chamber size, and wall motion. Summary statistics of the raw and change from baseline will be presented by dose and visit while data warranted. Data listings will be generated.

Evaluation of Drug-Induced Serious Hepatotoxicity

Hepatocellular injury (usually detected by serum ALT or AST elevations) can be caused by drugs that cause severe DILI (eg, aspirin, tacrine, statins, and heparin) as well as by drugs that do cause such injury. In order to properly monitor any sign of drug induced liver injury due to study medication, summary tables of subject incidences according to the following criteria will be generated by time points.

- ALT, AST: >3x-, 5x-, 10x- and 20x ULN;
- Total Bilirubin: > 2x ULN;
- Alkaline phosphatase > 2 x- ULN.

Summary of subject incidence table of subjects having altered liver function that meets Hy's law definition defined below will also be produced.

For patients with AST or ALT, and total bilirubin within the normal ranges:

- ALT or AST ≥3x ULRR;
- Alkaline phosphatase (ALP) ≤ 2x ULRR; and
- Total Bilirubin ≥ 2x ULRR.

For patients with preexisting AST or ALT baseline values above the normal range:

- AST or ALT value ≥2 times the baseline values and ≥3 x ULN, or ≥8 x ULN (whichever is smaller).

For patients with pre-existing values of total bilirubin above the normal range:

- Total bilirubin level increased from baseline by an amount of at least 1 x ULN **or** if the value reaches ≥3 x ULN (whichever is smaller).

Graphs will be produced to examine the peak total bilirubin versus the peak ALT values, and the peak AST values (normalized to the ULRR of the respective lab parameter), respectively, in order to assess the potential DILI. In addition, individual subject line plots, mean (± SE) plots, mean change from baseline (± SE) plots by treatment over time may also be generated.

7.2.4. 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.

Urine Pregnancy test results will be presented in the listings.

Cardiac enzymes, troponin T and NT-pro BNP, and Hepatitis B, C and HIV tests results: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody (HCV Ab) and human immunodeficiency virus (HIV) serology will be listed. Summary tables of raw and chnge from baseline of HBV and HCV over time, and line plots of individual patients and group mean (± SE) will be generated by treatment group for monotherapy and combination therapy, respectively.

7.2.5. Pharmacokinetic Analyses

7.2.5.1. Pharmacokinetic Parameters

The PK parameters detailed in Section 6.1 will be listed and summarized for subjects in the PK analysis set (as defined in Section 5.4). Missing values will be handled as detailed in Section 7.1. Each PK parameter will be summarized by dose and cycle and will include the set of summary statistics as specified in the table below:

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

There will be 1 summary table presenting all PK parameters. This will include data from all cohorts and will be summarized by dose group and cycle.

To assess the relationship between the PK parameters (for each analyte) and dose, dose normalized AUC_{τ} and C_{max} will be plotted against 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.

7.2.5.2. Pharmacokinetic Concentrations

To assess the single dose PK profile of PF-04518600 PK concentrations 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 7.1 above.

Presentations for PF-04518600 will include:

- A listing of all concentrations sorted by dose, subject ID, cycle, 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, cycle, 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, cycle, 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, cycle, 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.

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.

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CCI [redacted] CCI

7.2.7. Immunogenicity Analysis

Anti- PF-04518600 and Utomilumab antibody

A listing, sorted by subject and study day, of the result of anti- PF-04518600 and utomilumab antibody 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.

Summary statistics and data listings of raw values and changes in immunophenotyping of circulating T cell subsets (naïve, effector, central memory and regulatory) and activation markers including, but not limiting to Ki67, and human leukocyte antigen (HLA)-DR at pre and post-treatment time points will be prepared.

8. REFERENCES

1. Y. Ji, Y. Li And G. Yin Bayesian Dose Finding In Phase I Clinical Trials Based On A New Statistical Framework, Statistica Sinica 17(2007), 531-547.

9. APPENDICES

[This section is optional]

Appendix 1. DATA DERIVATION DETAILS

TBD

Appendix 1.1. Definition and use of visit windows in reporting

TBD

Appendix 1.2. Definition of Protocol Deviations that Relate to Statistical Analyses/Populations

TBD

Appendix 1.3. Further Definition of Endpoints

TBD

Appendix 1.4. List of Non-standard Listings, Figures and Tables Required

TBD