Protocol *C3621001*

A PHASE 1/2 STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ESCALATING DOSES AND TREATMENT INTENSIFICATION OF A VACCINE-BASED IMMUNOTHERAPY REGIMEN-2 (VBIR-2) (PF-06936308) FOR ADVANCED NON-SMALL CELL LUNG CANCER AND METASTATIC TRIPLE-NEGATIVE BREAST CANCER

Statistical Analysis Plan (SAP)

Version: 1.0

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Date: 5-October-2018

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-06936308 is a vaccine-based immunotherapy regimen-2 (VBIR-2) that is currently being investigated in patients with advanced non-small cell lung cancer (NSCLC) and metastatic triple-negative breast cancer (mTNBC). The protocol C3621001 outlines the VBIR-2 study for Part 1 (dose escalation).

This document describes the planned statistical analyses for Protocol C3621001, dated 16 March 2018. 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).

Note: in this document any text taken directly from the protocol is *italicized*.

2.1. Study Design

This is a Phase 1, open label, multi-center, multiple dose, safety, PK, PD and immunogenicity study evaluating the components of VBIR-2 (PF-06936308) in patients with advanced NSCLC and metastatic TNBC. VBIR-2 consists of the following components: AdC68, pDNA, tremelimumab and anti-PD-1 (PF-06801591).

The study is divided into two parts, dose escalation (Part 1) followed by dose expansion (Part 2). The Part 2 dose expansion protocol specifics will be covered in a subsequent amendment once recommended phase 2 dose (RP2D)/MTD is reached in Part 1. The dose escalation (Part 1) is anticipated to have 7 cohorts and estimated to enroll approximately 36 patients in Part 1. The actual number of patients enrolled will depend on the tolerability of the components of the VBIR-2.

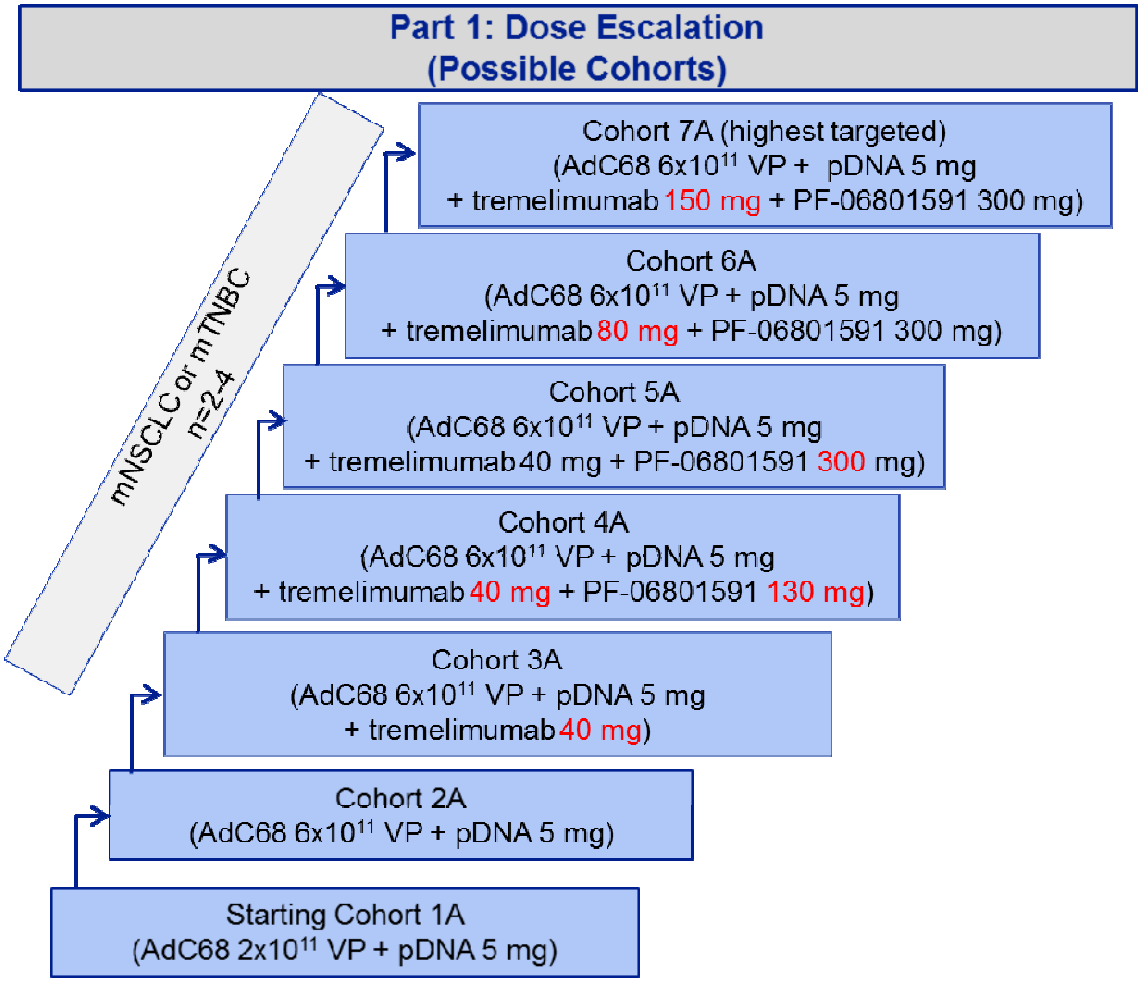
Part 1 (dose escalation) will include patients with advanced NSCLC and mTNBC for whom no standard therapy is available. Length of treatment is estimated to be 8-22 months, depending on each patient's disease status.

The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data. The dose level to be carried forward in subsequent cohorts may be different than those depicted in Table 2. *If the highest tested dose of one component is not tolerable, then a lower or intermediate dose could be*

carried forward in subsequent cohorts. If a component is not tolerable, it could be excluded from the dose escalation.

The overall design is presented in Figure 1.

Figure 1. Overall Study Design Part 1



Maintenance Treatment Schedule for anti-PD-1 (PF-06801591) starting at Month 9, will continue to be administered every 4 weeks.
Maintenance Treatment Schedule for pDNA and tremelimumab after Month 8 will be administered every 8 weeks starting with Month 10.
Treatment will be continued until disease progression, unacceptable toxicity, death, or patient's or investigator's decision.

Part 2 (dose expansion) will require a protocol amendment; only a high level study design is described below. Details of the patient population, inclusion-exclusion criteria, and detailed

study design with statistical calculations will be covered in a subsequent amendment once RP2D/MTD is reached in Part 1.

Part 2 will enroll patients in a design with 3 simultaneous non-randomized cohorts to further evaluate the safety and antitumor activity of the VBIR-2 regimen in patients with advanced NSCLC and mTNBC.

- *mNSCLC expansion cohorts ≥ second line (2L) patients with no more than 2 prior chemotherapy containing regimens:*
  - *Cohort 1 mNSCLC (n ~ 15);*
    - *≥Second line (2L) PD-L1 negative patients (PD-L1 positive < 1%).*
  - *Cohort 2: mNSCLC (n ~ 20);*
    - *≥2L patients who are PD-L1 positive ≥ 1% with approximately equal number of patients who have low and high PD-L1 expression (1%-49% and ≥50% respectively).* [2, 3]
- *mTNBC expansion cohort ≥2L mTNBC patients (all subtypes) with no more than 2 prior chemotherapy containing regimens:*
  - *Cohort 3: mTNBC (n ~26);*
    - *≥2L mTNBC (all subtypes).*

Patients will participate in the treatment period of the study for approximately 9-12 months depending on type of advanced disease. This includes a 28 day screening period followed by two cycles of treatment (each 4 months in duration for a total of 8 months). After completion of two cycles, patients will then enter the maintenance phase of the study.

Treatment will continue until: disease progression, unacceptable toxicity, death or patient's or investigator's decision occurs. Patients who demonstrate clinical benefit with manageable toxicity and who are willing to continue receiving study treatment will be given the opportunity to continue treatment upon agreement between the investigator and sponsor. When the patient discontinues treatment, they will then enter a 6 month post-dose follow-up period to assess safety and pharmacodynamics. The end of the study is the last patient last visit.

The treatment effect of cancer immunotherapy can often be delayed. Therefore, patients should be encouraged to continue on study treatment for at least 24 weeks before an investigator considers removing the patient due to disease progression, as long as:

- *Patient and investigator agree.*
- *Patient continues to meet all other study protocol eligibility criteria.*
- *Acceptable toxicity.*
- *No deterioration of patient performance status.*

2.1.1. Starting Dose Part 1

The dose escalation could include an increase in the dose of one component of the regimen or could include the addition of the lowest dose of an additional component. Seven planned dose escalation cohorts may be investigated:

- *(AdC68 2 x 10^{11} VP + 5 mg pDNA).*
- *(AdC68 6 x 10^{11} VP + 5 mg pDNA).*
  - *If needed – dose reduction of the AdC68 dose to 2 x 10^{11} VP is allowed.*
- *(AdC68 6 x 10^{11} VP + 5 mg pDNA + 40 mg tremelimumab).*
- *(AdC68 6 x 10^{11} VP + 5 mg pDNA + 40 mg tremelimumab + 130 mg PF-06801591).*
  - *If needed – dose reduction of the tremelimumab dose is allowed.*
- *(AdC68 6 x 10^{11} VP + 5 mg pDNA + 40 mg tremelimumab + 300 mg PF-06801591*).*
- *(AdC68 6 x 10^{11} VP + 5 mg pDNA + 80 mg tremelimumab + 300 mg PF-06801591*).*
- *(AdC68 6 x 10^{11} VP + 5 mg pDNA + 150 mg tremelimumab + 300 mg PF-06801591*).*

*Note: *If needed, dose reduction of the tremelimumab dose is allowed in cohorts with 300 mg anti-PD-1 (PF-06801591) (see Section 5.4.3.2* in the protocol*).*

2.1.2. Criteria for Dose Escalation

The principles of modified toxicity probability interval (mTPI) design (Ji et al., 2010)4, will be utilized for the dose escalation portion of the study.

An mTPI design, targeting a DLT rate of 27.5% and an acceptable DLT equivalence interval (22.5% to 32.5%), will be utilized in the dose escalation phase.

The dose levels to be evaluated are given in Section 2.1.1 in the protocol. If a high DLT rate is observed at the starting dose, the study may explore a lower dose or may be stopped.

Each cohort would enroll 2 to 4 DLT evaluable patients and at least 6 and up to 12 patients would be enrolled at a dose level that is predicted to be the MTD as per the mTPI method. Dose cohorts with an acceptable safety profile may be expanded up to N=12 to further assess safety, CCI [redacted] *pharmacokinetics,* CCI [redacted]*. Decisions to enroll additional patients at dose levels already cleared for safety will be based on clinical judgment.*

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in the current dose level to determine one of the following dose-finding decisions: the subsequent dose should be escalated, maintained at the current dose, or de-escalated in the next cohort of 2 to 4 patients, or the trial should be terminated. It is currently envisaged that AdC68 6 x 10^{11} VP + 5 mg pDNA + 150 mg tremelimumab + 300 mg ANTI-PD-1 (PF-06801591) will be RP2D.

Decision rules are based on calculating posterior probabilities of 3 dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as (0; pT-e1), the over-dosing interval (pT+e2, 1), and the proper-dosing interval (pT- e1, pT+ e2), where e1 and e2 are small fractions. In study, e1 is

selected as 0.05 and e2 is selected as 0.05, therefore, the target interval for the DLT rate is (0.225, 0.325). The 27.5% target, the symmetry of the Equivalence Interval and its upper limit were chosen based on safety considerations. The prior distribution of DLT is set as a beta (0.5, 0.5), and the threshold probability for early termination and dose exclusion is set to0.95. Even though the upper limit of the mTPI is higher than 27.5%, doses with an incidence of DLT >27.5% (eg, 3 out of 9) cannot be declared as the MTD.

The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose-escalation I, overdosing corresponds to a dose de-escalation (D/U), and proper dosing corresponds to remaining at the current dose (S).

Table 1. Decision Rules

#DLTs	1	2	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	E	E	E	E	E	E	E	E
2		U	D	S	S	S	S	S	S	S	E	E
3			U	U	D	D	S	S	S	S	S	S
4				U	U	U	U	D	S	S	S	S
5					U	U	U	U	U	D	S	S
6						U	U	U	U	U	U	U

- *Columns indicate number of patients in the cohort and rows indicate number of patients with DLTs*
  *E= Escalate to the next higher dose; **S**: Stay at the same dose; **D**: De-escalate to the previous lower dose; **U**: De-escalate to the previous lower dose and the current dose will never be used again in the trial*

If a patient discontinues close to Day 28 for reasons other than toxicity and due to an evident non drug-related event, the patient may be deemed evaluable for safety if safety assessments have been unremarkable and the investigator and sponsor's medical monitor both agree that the patient is evaluable for DLT safety observation.

The dose escalation Part 1 of the study will stop if any of the following criteria is met:

1. *The maximum sample size has been achieved (approximately 36 patients in total as per the current dosing schedule);*
2. *6 to 12 patients have been enrolled at a dose level that is predicted to be the MTD according to* Table 1*;*
3. *All dose levels explored appear to be overly toxic, and the MTD cannot be determined;*
4. *All candidate dose levels have been tested and deemed safe.*

As an example, if the total number of patients (cumulative in the study) treated at the current dose is 4, the following dosing rules are applied:

- 0 DLT -> escalate
- 1 DLT -> remain at the same dose
- 2 DLTs -> De-escalate to the previous or intermediate lower dose
- 3-4 DLTs -> De-escalate and consider current dose as intolerable

Activation of each cohort will occur no sooner than 28 days after the first 2-4 patients receive the first AdC68 vaccination, but may occur later if the sponsor and investigators determine additional safety data is needed. The Pfizer clinical team and investigators will review all available safety data from the previous and current cohorts prior to making a decision to dose escalate. If no safety issues that would prohibit dose escalating are observed, the next cohort of patients would be open for accrual.

If dose escalation continues up to a predefined Maximum Feasible Dose (MFD), the escalation is halted without a maximum tolerated dose (MTD) estimate. In those circumstances, the MFD may be the recommended Phase 2 dose (RP2D).

2.1.3. DLT Definition

Severity of adverse events (AEs) will be graded according to the details specified in the protocol.

2.1.4. MTD Definition

The MTD is defined as the highest dose with true toxicity probabilities in the equivalence interval (EI) where the EI is defined as (22.5%, 32.5%).

Even though the mTPI model may select an MTD with an incidence of DLTs that is higher than 32.5% since mTPI decision rules are based on unit probability mass (UPM) and not on point estimates of the DLT rate (see Section 9.2.1), doses with an incidence of DLT >32.5% (eg, 3 out of 9) cannot be declared as the MTD. In practice, model recommendations may be overridden by clinical judgment, and MTD with an incidence of DLTs that is higher than 32.5% will not be considered acceptable to be selected as MTD.

2.1.5. Late Onset Toxicity and Toxicities Observed in the Expansion Phase

Adverse events that meet the same grading criteria as the DLT criteria listed above occurring after the DLT observation period in Part 1, but before completion of the first cycle of treatment will lead Pfizer to immediately schedule a meeting with the investigators to review the details of the potential late onset toxicity and determine if the enrollment has to be held for this dose level, continued, or if a dose reduction should be implemented for all ongoing patients. Late onset toxicities meeting the definition of a DLT will be used in the evaluation of the MTD.

In addition, adverse events that meet the same grading criteria as the DLT criteria listed above will prompt Pfizer to immediately schedule a meeting with the investigators to review

the details of the toxicity and determine the necessary action to be implemented for all patients.

2.1.6. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further investigation based on Phase 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

2.2. Study Objectives

Primary Objectives:

- *To assess safety and tolerability of increasing dose levels of VBIR-2.*
- *To characterize the dose limiting toxicities (DLTs) and overall safety profile of escalated doses of VBIR-2.*
- *To assess safety and tolerability at increasing dose levels of VBIR-2 components in successive cohorts of patients in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D)/schedule.*

Secondary Objectives:

- *To evaluate the immune response elicited by VBIR-2 to the 3 selected tumor antigens.*
- *To evaluate the PK of tremelimumab and of anti-PD-1 (PF-06801591) after SC administration.*
- *To evaluate the anti-drug antibody (ADA) response of tremelimumab and anti-PD-1 (PF-06801591) after SC administration with the other components.*
- C [redacted]
- *To document any preliminary evidence of anti-tumor activity.*

CCI [redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

There are no formal interim statistical analyses in this open-label, unblinded clinical trial. Treatment safety and effectiveness are to be monitored continuously.

A check for futility will be carried out after at least 10 patients are enrolled in each cohort in Part 2 as detailed in Section 4.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The expansion phase of the study (Part 2) will consists of three single arm cohorts: Cohort 1B, 2B and 3B respectively; the recommended dose from Part 1 will be used in this phase. Approximately n=15 patients would be enrolled in Cohort 1B of mNSCLC ≥2L PD-L1 negative patients and n=20 in Cohort 2B, approximately n=10 mNSCLC ≥2L patients who are PD-L1 positive >1% and <50% and n=10 mNSCLC ≥2L patients who are PD-L1 positive ≥50%. For the mTNBC cohort, the study will enroll n=26 patients and have approximately 80% power with 1-sided alpha=0.1 to detect an ORR of 50% with a null hypothesis of 30% ORR.

4.2. Statistical Decision Rules

See Section 2.1.2 for the details of the decision rule of dose escalation part.

5. ANALYSIS SETS

5.1. Full Analysis Set

The full analysis set includes all enrolled patients.

5.2. Pharmacokinetic Analysis Set

5.2.1. Concentration Analysis Set

There are two moieties measured from PK perspective; PF-06801591 and tremelimumab. Hence there are two PK concentration analysis sets. For each moiety, the PK concentration population is defined as all enrolled subjects treated who have at least 1 concentration in at least 1 treatment period and who do not have major protocol deviations.

5.2.2. Parameter Analysis Set

There are two moieties measured from PK perspective; PF-06801591 and tremelimumab. Hence there are two PK parameters analysis sets. For each moiety, the PK parameter analysis population is defined as all enrolled subjects treated who have at least 1 of the PK parameters of interest in at least 1 treatment period and who do not have major protocol deviations.

CCI

[redacted]

5.4. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

[redacted]

5.5. Other Analysis Sets

- *Per protocol analysis set.*

  The per protocol (PP) analysis set includes all enrolled patients who receive at least one dose of all assigned regimen components administered Cycle 1 Day 1 of study medication and who do not have major protocol deviations during the 28 days after the first vaccination.

- *Modified Intention-to-Treat analysis set.*

  CCI *modified Intention-to-Treat (mITT), which is defined as all enrolled patients who received at least one dose of all assigned regimen components administered.* CCI *a patient must have at least 1 valid and determinate assay result related to the proposed analysis. Patients who have no valid and determinate assay result related to any proposed analysis will be excluded from the mITT analysis set.*

CCI

- *Immunogenicity analysis set.*

  The immunogenicity analysis set includes all enrolled patients who receive at least one dose of the VBIR-2 component that is the subject of the immunogenicity assessment (tremelimumab or anti-PD-1 (PF-06801591)).

5.6. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg vomiting) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

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

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

6.1. Efficacy Endpoint(s)

CCI *The main analysis populations will be based on mITT and EP (see Section Analysis Sets).*

Disease response will be presented in the form of patient data listings that include, but are not limited to starting dose, disease response at each visit, and best overall response. In addition, progression date, death date, date of first response and last disease assessment date, and date of last contact will be listed.

Summary of objective response rates will be provided by descriptive statistics. Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 by calculating the Objective Response Rate (ORR) and Progression-Free Survival (PFS).

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

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

Duration of Response (DOR) is defined as the duration of overall response measured from the time measurement criteria are met for complete response (CR) or partial response (PR) (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Duration of Stable Disease (DOSD) is defined as stable disease measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

For tumor response data, the following analyses may be performed:

1. Tumor response (CR, PR, SD, PD, etc.) by cohort and visit, separately for RECIST 1.1 and irRECIST. Investigator provided tumor response will be presented by descriptive statistics (frequency and percentage).

2. Best overall response, by cohort, across all available tumor assessments from both treatment period and maintenance period, separately for RECIST 1.1 and irRECIST. Best overall response will be derived programmatically. In the tabular data presentation, a row of CR+PR will be added to show the results of ORR. With RECIST 1.1, tumor response (CR or PR) confirmation is optional as response rate is not the primary endpoint of the study, hence unconfirmed best overall response will be derived and presented. With irRECIST, tumor response (irCR or irPR) and disease progression (irPD) are required to be confirmed, however in this study tumor response confirmation is not required, therefore unconfirmed best overall response will be derived and presented. Descriptive statistics (frequency and percentage) will be provided.

In the "unconfirmed" analyses (ie, tumor response or progression without confirmation required), all tumor assessments data will be included for analyses. Specifically, regardless if a patient's tumor response or progression is subsequently confirmed or not, the patient data will all be included in the "unconfirmed" analyses. This is a more comprehensive analysis where tumor confirmation is not required and not taken into account. For example in the ORR analysis, if a patient achieved CR or PR, regardless it is subsequently confirmed or not, the patient will be included in the numerator.

Additional summary combining data across different cohorts may be generated if deemed necessary. Swimmer plots will be used to display duration of treatment and tumor response at each applicable time point. Waterfall plot for individual tumor size percent change from baseline, and spider plot for individual tumor size percent change from baseline over time will be presented. These plots will be presented for RECIST 1.1 and irRECIST separately.

For all time-to-event endpoints, the Kaplan-Meier analysis may be performed if deemed necessary at the time of data analysis. If the Kaplan-Meier analysis is performed for progression-free survival, an event is defined as the first occurrence of "PD" status by investigator or death, whichever comes first, under RECIST; and is defined as the first occurrence of "irPD" status that has been subsequently confirmed or death, whichever comes first, under irRECIST. Time zero for all time-to-event analyses will be defined as the first vaccination on Cycle 1 Day 1. CCI [redacted]

Antitumor response and tumor control duration based on total measurable tumor burden as assessed by the Immune-Related Response Criteria Derived from RECIST 1.1 (irRECIST) (Appendix 4).

6.2. Safety Endpoints

The main analyses of DLTs will be based on the Per Protocol analysis set. Patients not meeting the criteria for inclusion in the Per Protocol Analysis set (ie, not evaluable for assessment of DLTs) will be replaced.

6.2.1. Analysis of Primary Endpoint

Dose Limiting Toxicity (DLT) is the primary endpoint of the study. The occurrence of DLTs observed in the dosing cohorts will govern the dose escalation as described in Section 2.1. If

a patient is withdrawn from study for any reason other than a DLT prior to completion of the 28-day safety observation period, a replacement patient will be assigned for the same dose as the replaced patient. The properties of the statistical methods for the analyses of DLTs are described in section Statistical Methods and Properties. Adverse Events constituting DLTs will be listed per dose level. Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (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 treatment. 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 by dose and by cycle.

6.2.2. Adverse Events

Any events occurring following start of treatment for the first time or increasing in severity will be counted as treatment emergent. *The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 6 months; except as indicated below after the last administration of the investigational product.*

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

Events that occur in a non-treatment period (for example, washout or follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

6.2.3. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be the last predose measurement of before the first dose of any component of the study treatment.

6.2.4. Vital Signs

Vital signs will include measurements of blood pressure, pulse, and temperature (oral, temporal, ear). On dosing days, vital signs should be measured prior to administration of any of the study treatments. Sitting blood pressure (BP) and pulse after approximately 5 minutes rest, will be measured with the patient's arm supported at the level of the heart and recorded to the nearest mmHg sufficient. The same arm (preferably the dominant arm) should

preferably be used throughout the trial. A blood pressure cuff, which has been properly sized and calibrated, should be used to measure blood pressure. The use of automated devices for measuring BP is acceptable. Vitals signs, including temperature, pulse, and BP to be recorded 1-hour post-study drug administration during each Cycle on Days 1, 29, 57, and 85. Baseline vital sign will be the last predose measurement of before the first dose of any component of the study treatment.

6.2.5. ECG

Electrocardiogram machines to be utilized in this study will be supplied by a third party vendor.

At screening, a single 12-lead ECG tracing (with a 10-second rhythm strip) will be obtained. For Cycle 1 Day 1 and all subsequent specified time points (see Schedule of Activities in the protocol), triplicate 12-lead ECG tracings (with a 10-second rhythm strip) will be obtained.

Generally, baseline and all corresponding time point ECGs should not be collected within 3 hours after food or beverage consumption and should be performed after the patient has rested quietly for at least 10 minutes in a supine position. All 12 lead ECGs should be confirmed by a qualified person at the institution and will be reviewed by a central laboratory.

At each time point, (see the Schedule of Activities), three consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor it is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to 500 msec. Patients will then re-start the investigational product at the next lowest dose level.

If the QTcF interval has still not decreased to 500 msec after 2-weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

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

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

Baseline is defined as the pre-dose ECG collected before the first dose of any component of the study treatment.

6.2.6. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed if collected in the sponsor's database.

6.3. Pharmacokinetic Parameters

Tremelimumab single-dose PK parameters, including the maximum concentration (C_{max}), time to maximum concentration (T_{max}), and area under the concentration versus time curve (AUC) from time zero to the last quantifiable time point prior to the second tremelimumab dose (AUC_{last}) and if data permit, AUC from time zero extrapolated to infinity (AUC_{inf}); and trough concentrations after multiple dosing (C_{trough}).

PF-06801591 single-dose PK parameters, including C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}; and C_{trough} after multiple dosing.

6.4. PD Endpoints

None.

6.5. Other Endpoints

None.

6.6. Covariates

None.

7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

7.1. 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).

7.2. Deviations, Missing Concentrations and Anomalous Values

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 at a particular time point if more than 50% of the data are missing.

7.3. Pharmacokinetic Parameters

For both tremelimumab and PF-06801591, 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. In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie analysis of variance), PK parameters coded as NC will also be set to missing.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

CCI [redacted] Part 2 (dose expansion) will require a protocol amendment; only a high level study design is described in the protocol. For the mTNBC cohort, the study will enroll n=26 patients and have approximately 80% power with 1-sided alpha=0.1 to detect an ORR of 50% with a null hypothesis of 30% ORR.

8.2. Statistical Analyses

8.2.1. Pharmacokinetic Analysis

Patients who receive the designated investigational product of interest and have at least one post-dose drug concentration measurement will be included in the PK data analysis. The actual time of sample collection will be used in PK parameter calculation. In the event that the actual sampling time is not available, the nominal time may be used if there is no evidence that the actual sampling time deviates substantially from the nominal time.

8.2.1.1. Tremelimumab and PF-06801591 Pharmacokinetics

Presentation of Tremelimumab and PF-06801591 concentration-time data:

The concentration-time data of tremelimumab and PF-06801591 will be presented as below:

- A listing of all concentrations by cohort, subject ID and nominal time for each compound. The concentration listings will also include the actual times. Deviations from the nominal time will be given in a separate listing for each compound;

- A summary of concentrations for each compound by cohort and nominal time, where the set of statistics will include n, mean, standard deviation, median, coefficient of variation (cv), percentage cv, minimum, maximum, geometric mean, and the number of concentrations above the lower limit of quantification;

- For the concentration-time data after the first dose, median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time postdose) for tremelimumab (for Cohorts 3A through 7A) and PF-06801591 (for Cohorts 4A through 7A);

- For the concentration-time data after the first dose mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time postdose) for tremelimumab (for Cohorts 3A through 7A) and PF-06801591 (for Cohorts 4A through 7A).

For drug concentration summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used.

Calculation of PK parameters:

For patients of Cohorts 3A through 7A, the concentration-time data of tremelimumab after the first dose will be analyzed individually by non-compartmental methods to determine the PK parameters. For patients of Cohorts 4A through 7A, the concentration time data of PF-06801591 after the first dose will be analyzed individually by non compartmental methods to determine the PK parameters.

For each compound, the PK parameters to be estimated will include the maximum drug concentration (C_{max}), time to maximum drug concentration (T_{max}), and area under the concentration versus time curve (AUC) from time zero to the last quantifiable time point prior to the second tremelimumab or PF-06801591 dose (AUC_{last}), and if data permit, AUC from time zero extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), and apparent clearance (CL/F).

In addition, the accumulation ratio (R_{ac}) as calculated by the ratio of the trough concentration prior to the fifth tremelimumab or PF-06801591 dose (on Cycle 2 Day 1) to the concentration prior to the second tremelimumab or PF-06801591 dose (on Cycle 1, Day 29) will be determined individually if data permit.

PK parameters will be calculated using standard non-comparmental methods:

Parameter	***Method of Determination***
AUC_{last}	Linear/log trapezoidal method
AUC_{inf}[a]	$AUC_{last} + C_{last}/k_{el}$, where C_{last} is the predicted concentration at the last quantifiable timepoint (T) estimated from the log-linear regression analysis, and kel is the terminal phaser rate constant by a linear regression of the log-linear concentration time curve. The terminal log-linear phase will be determined from a minimum of 3 concentration time data points and will be verified with r^2 value.
C_{max}, T_{max}	Observed directly from data
CL/F	$Dose/AUC_{inf}$
$t_{1/2}$	$ln2/k_{el}$

[a]if data permit.

Each PK parameter will be summarized by dose and will include the set of summary statistics as specified in the table below:

Table 2. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, CL/F and V_Z/F	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

8.2.1.2. Tremelimumab and PF-06801591 Immunogenicity

For patients receiving tremelimumab, the percentage of subjects with positive ADA and neutralizing antibodies will be summarized by dosing cohort. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response (in weeks and months) will also be described, if data permit.

For patients receiving PF-06801591, the percentage of subjects with positive ADA and neutralizing antibodies will be summarized by dosing cohort. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response (in weeks and months) will also be described, if data permit.

Time of onset will be calculated as (date of first positive ADA result - date of first dose of tremelimumab / PF-06801591 + 1). The duration of ADA response will be calculated as (Date of last positive ADA result - date of first positive ADA result + 1). Relevant descriptive statistics (namely mean, median, SD, min, max) maybe summarized for the magnitude (titer), time of onset, and duration of ADA response in weeks and months.

CCI

[redacted]

8.3. Safety Analysis

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06936308.

No formal analyses are planned for safety data. The safety and other endpoints detailed in Section 6.1 will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the safety analysis set.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

Data will be reported in accordance with the sponsor reporting standards.

8.3.2. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, ethnicity, weight, body mass index and height. Each will be summarized by sex at birth and 'All Subjects' for each cohort separately and overall in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment.

[redacted]

Data will be reported in accordance with the sponsor reporting standards.

8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

8.3.5. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 6.1.3.

8.3.6. Vital Signs Data

Absolute values and changes from baseline for systolic and diastolic blood pressure and pulse rate will be summarized by cohort, treatment and time postdose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.4.

Mean changes from baseline for systolic and diastolic blood pressure and pulse rate will be plotted against time postdose. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figure using separate lines. Corresponding individual plots of changes from baseline will also be produced for each cohort and treatment. Maximum absolute values and changes from baseline for vital signs will also be summarized.

8.3.7. ECG Data

Centrally read ECG will be collected. Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by cohort, treatment and time postdose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 6.2.5.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time postdose. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figure. Corresponding individual plots of changes from baseline will also be produced for each cohort and treatment.

Changes from baseline in QTcF will also be plotted separately against drug concentrations. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Different symbols will be used for each treatment. There will be 1 plot for each cohort.

Maximum increase from baseline for QTcF, heart rate, QT, PR and QRS will be summarized by cohort and treatment, according to sponsor reporting standards.

In addition for QTcF, heart rate and QT, the differences between each dose for each subject will be summarized and plotted (N, mean, 90% confidence interval) for each cohort, dose and timepoint (including baseline).

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized. All values meeting the criteria of potential clinical concern will be listed.

Listings of subjects with any single postdose value ≥500 msec will also be produced for QTcF.

QTcB will be listed only and not summarized.

8.3.8. Other Safety Data

None.

8.3.9. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

8.3.10. Screening and Other Special Purpose Data

Prior concomitant medications for cancer therapy, response to regimen, prior radiation treatment and prior anti-cancer surgery collected at screening will be provided in the listings.

9. REFERENCES

1. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.

2. Kumar R, Collins D, Dolly S, et al. Targeting the PD-1/PD-L1 axis in non-small cell lung cancer. Curr Probl Cancer, 41, 2017:111-124.

3. Garon EB, Rizvi NA. Pembrolizumab for the Treatment of Non–Small-Cell Lung CancerN Engl J Med 2015; 372(21):2018-2018.

4. Ji Y, Liu P, Li Y, et al. A modified toxicity probability interval method for dose-finding trials. Clinical Trials 2010; 7:653-63.

10. APPENDIX

Appendix 1. Time to Event Data Analysis Censoring Rules

Table 3. Progression Free Survival and Duration of Response

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	First dosing date in Cycle 1	Censored
No on-study assessments	First dosing date in Cycle 1	Censored
Alive, on treatment[2] and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation[2]	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation[2]	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation[2]	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation[2]	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1: For date of censorship, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.
2: or within 28 days of discontinuation of treatment.

Table 4. Time to Progression

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	First dosing date in Cycle 1	Censored
No on-study assessments	First dosing date in Cycle 1	Censored
Alive, on treatment[2] and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation[2]	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation[2]	Censored

Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation[2]	Censored
New anticancer treatment <28 days after discontinuation of treatment without progression	Date of last objective tumor assessment prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Start date (C1D1)	Censored
Death without objective progression prior to treatment discontinuation[2]	Date of last objective tumor assessment prior to death	Censored
Progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1: For censoring date, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.
2: or within 28 days of discontinuation of treatment.

DOSD and DOR

Censoring rules for DOSD and DOR will be the same as for PFS.

Appendix 2. ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

*AS PUBLISHED IN AM J CLIN ONCOL 5:649 655, 1982

Appendix 3. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

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

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease**:** Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a

single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

- one or more target measurable lesions have not been assessed;

- or assessment methods used were inconsistent with those used at baseline;

- or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

- or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of stable disease (SD) or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

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

Table 5. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 6. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Appendix 4. Immune-Related Response Criteria Derived from RECIST 1.1 (irRECIST)

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics.

This is particularly true for immunotherapeutic agents such as anti-CTLA4 and anti-PD-1/anti-PD-L1 antibodies which exert the antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects.[1,2] Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organization (WHO) criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.[3,4]

Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced CR or PR but were flagged as PD by WHO criteria.[3,4]

On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into the RECIST v1.1 (irRECIST).

For irRECIST, only target and measurable lesions are taken into account. In contrast to RECIST v1.1, irRECIST:

- Requires confirmation of progression 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 (minimum of 10 mm longest diameter per non-nodal lesion and 15 mm shortest diameter per nodal lesion, 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 trial.

irRECIST is 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 is neither irCR, 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). A lymph node has to be ≥15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

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

Overall responses derived from changes in index, non-index, and new lesions are outlines in Table 7.

Table 7. Overall Response Derived from Changes in Index, Non-index and New Lesions

Measurable response	**Non-measurable Response**		**Overall response using irRECIST[b]**
Index and New Measurable Lesions (Tumor Burden)[a]	**Non-Index Lesions**	**New Non-Measurable Lesions**	
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. Decrease 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.

Appendix 5. Statistical Methods for Immunogenicity (serology)

Definitions:

Let x_i, i=1, 2, n, be the titer for subject i where n is the number of subjects. Then the geometric mean titer (GMT) is defined as follows

$$GMT=\exp[(1/n)\Sigma\log(x_i)],$$

where log is the natural logarithm.

Within each vaccine group and for each antibody, geometric mean titers (GMTs) will be calculated. Each titer will be logarithmically transformed for analysis. Two (2)-sided, 80% confidence intervals will be constructed by back transformation of the confidence intervals for the mean of the logarithmically transformed assay results.

Let x_i, i=1, 2, n, be the titer for test group and let y_i, i=1, 2, m, be the titer for reference group. Then the geometric mean ratio (GMR) is defined as follows:

$$GMR=\exp[(1/n)\Sigma\log(x_i) - (1/m)\Sigma\log(y_i)].$$

Also for the GMRs, the confidence intervals will be constructed by back transformation of the confidence intervals for the mean difference of the logarithmically transformed assay results (*test* relative to *reference*).

Let x_i, i=1, 2, n, be the titer prior vaccination and let y_i, i=1, 2, n, be the titer post vaccination. Then the geometric mean fold rise (GMFR) is defined as follows:

$$GMFR=\exp[(1/n)\Sigma\log(y_i/x_i)].$$

For the geometric mean fold rise, the confidence intervals will be constructed by back transformation of the confidence intervals for the mean difference of the logarithmically transformed assay results (*post* to *prior*).

GMTs, GMRs and GMFR will be estimated by an ANCOVA model with natural log transformed anti-body titer as outcome variable, and treatment group as factor and baseline (in log scale) as covariates at each of the post-dose measurement. These analyses based on log-transformed data, the LSMEAN estimates and confidence interval will be back-transformed (exponentiated) and presented. The estimated treatment difference and corresponding confidence intervals from the model will also be back-transformed.

-For GMTs the variable of interest, that will be back transformed, is log (x_i)

x_i, i=1, 2, n, be the titer for subject i

-For GMFRs the variable of interest, that will be back transformed, is log (y_i) – log (x_i)

x_i, i=1, 2, n, be the titer prior vaccination and let y_i, i=1, 2, n, be the titer post vaccination

Back-transformation of estimated difference in GMTs (with contrasts) is interpreted as GMR between treatment and placebo group.

In addition to the adjusted analysis for GMTs, GMRs and GMFRs between groups through analysis of covariance, unadjusted (crude) GMTs, GMRs and GMFRs will be calculated as a sensitivity analysis.

For GMTs, two (2)-sided, 80% confidence intervals will be constructed by back transformation of the confidence intervals for the mean of the logarithmically transformed assay results computed using the Student t distribution.

For the GMRs, the confidence intervals will be constructed by back transformation of the confidence intervals for the mean difference of the logarithmically transformed assay results (*test* relative to *reference*) computed using the Student t distribution.

For reporting purposes, 1 decimal place will be used for geometric mean titers (GMTs), and 2 decimal will be used for geometric mean ratios (GMFRs, GMRs).