Protocol B7391007

A RANDOMIZED, DOUBLE-BLIND BRIDGING SAFETY AND EFFICACY STUDY OF PF-06439535 (CN) PLUS PACLITAXEL-CARBOPLATIN VERSUS BEVACIZUMAB-PLUS PACLITAXEL-CARBOPLATIN FOR THE FIRST-LINE TREATMENT OF CHINESE PARTICIPANTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

Statistical Analysis Plan
(SAP)

Version: 1

Date: 05 Jul 2019

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 05 July 2019	Original 27 Jun 2019	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B7391007. Two clinical study report (CSR) will be produced for this study. The primary CSR will be conducted on the primary completion date (PCD) using data as of Week 25, and the supplemental CSR will be conducted at the end of study using limited data from Week 25. This document mainly focus on the PCD analyses, and briefly describe the limited safety analyses for supplemental CSR. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Primary Objective:

- To explore similarity in efficacy of PF-06439535 (CN) and bevacizumab-EU, each in combination with paclitaxel and carboplatin, based on a descriptive estimation of objective response rate (ORR).

Secondary Objectives:

- To evaluate the safety of PF-06439535 (CN) plus paclitaxel and carboplatin and bevacizumab-EU plus paclitaxel and carboplatin;
- To evaluate the pharmacokinetics (PK) of PF-06439535 (CN) and bevacizumab-EU;
- To evaluate the immunogenicity of PF-06439535 (CN) and bevacizumab-EU.

Primary Endpoint:

- ORR, evaluating best overall responses achieved by Week 19 and subsequently confirmed by Week 25, in accordance with Response Evaluations Criteria in Solid Tumors (RECIST) version 1.1.

Secondary Endpoints:

- Safety characterized by type, incidence, severity, timing, seriousness, and relationship to investigational product of adverse events, including cardiotoxicity and infusion related reactions, and laboratory abnormalities;
- Trough and apparent peak PF-06439535 (CN) and bevacizumab-EU concentrations at selected cycles;
- Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing antibodies (NAb).

2.1.1. Primary Estimand

Primary estimand (Hypothetical and Treatment Policy) estimate the population average treatment effect of ORR for PF-06439535 (CN) relative to bevacizumab-EU by Week 19 for all randomized participants with advanced non-squamous NSCLC, reflecting the impact of new anti-cancer medications, but regardless of any other interventions. The estimand is defined according to the primary objective and is in alignment with the primary endpoint. It includes the following 4 attributes:

- Population: Patients who are diagnosed as advanced non-squamous NSCLC, as defined by the inclusion and exclusion criteria, and who are randomized;
- Variable: the best objective response achieved by Week 19 and subsequently confirmed by Week 25, in accordance with Response Evaluations Criteria in Solid Tumors (RECIST) version 1.1;
- Interventions: All responses data after start of new anti-cancer medications are excluded from the analysis. Other intercurrent events such as administration of concomitant therapy or adherence to randomized treatment assignment are not considered for analysis;
- Population-level summary: Difference and ratio of the objective response rate (ORR) between PF-06439535 (CN) and bevacizumab-EU.

2.1.2. Secondary Estimands

2.1.2.1. Estimand for Safety Evaluation

Secondary Estimand for Safety (Treatment Policy) estimate the population average treatment effect for the safety endpoints for PF-06439535 (CN) relative to bevacizumab-EU up to Week 25 for all randomized participants with advanced non-squamous NSCLC, regardless of any intervention. The estimand is defined according to the secondary safety objective and is in alignment with the safety endpoints. It includes the following 4 attributes:

- Population: Patients who are diagnosed as advanced non-squamous NSCLC, as defined by the inclusion and exclusion criteria, and who are randomized;

- Variable: Safety characteristics by type, incidence, severity, timing, seriousness, and relationship to investigational product of adverse events, including cardiotoxicity and infusion related reactions, and laboratory abnormalities;

- Interventions: Administration of concomitant therapy or adherence to randomized treatment assignment is not considered for analysis. All data collected (after concomitant therapy or after discontinuation of treatment) are included;

- Population-level summary: Summary of the AEs frequency and percentage for PF-06439535 (CN) and bevacizumab-EU treatment respectively and in total; Difference of the selected AEs (Pfizer Tier-1 and Tier-2 events) percentage between PF-06439535 (CN) and bevacizumab-EU.

2.1.2.2. Estimand for PK Evaluation

Secondary Estimand for PK (Hypothetical) estimate the population average treatment effect for the PK endpoints for PF-06439535 (CN) relative to bevacizumab-EU for all randomized participants with advanced non-squamous NSCLC, reflecting the impact of protocol deviations, if any, which may affect the PK assessment. The estimand is defined according to the secondary PK objective and is in alignment with the PK endpoint. It includes the following 4 attributes:

- Population: Patients who are diagnosed as advanced non-squamous NSCLC, as defined by the inclusion and exclusion criteria, and who are randomized;

- Variable: Trough and apparent peak PF-06439535 (CN) and bevacizumab-EU concentrations;

- Interventions: All data after an intervention (use of concomitant therapy prohibited by the protocol, use of a subsequent line of therapy, dosing error, discontinuation of treatment, discontinuation of study, etc), maybe excluded; The intervenations will be defined prior to unblinding the database;

- Population-level summary: Descriptive summary of PK concentrations for PF-06439535 (CN) and bevacizumab-EU treatment respectively.

2.1.2.3. Estimand for Immunogenicity Evaluation

Secondary Estimand for Immunogenicity (Treatment Policy) estimate the population average treatment effect for the immunogenicity endpoints for PF-06439535 (CN) relative to bevacizumab-EU for all randomized participants with advanced non-squamous NSCLC, regardless of any intervention. The estimand is defined according to the secondary immunogenicity objective and is in alignment with the immunogenicity endpoint. It includes the following 4 attributes:

- Population: Patients who are diagnosed as advanced non-squamous NSCLC, as defined by the inclusion and exclusion criteria, and who are randomized;

- Variable: Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing antibodies (NAb);

- Interventions: Administration of concomitant therapy or adherence to randomized treatment assignment is not considered for analysis. All data collected (after concomitant therapy or after discontinuation of treatment) are included;

- Population-level summary: Summary of the positive ADA and NAb percentage for PF-06439535 (CN) and bevacizumab-EU treatment respectively.

2.2. Study Design

This is a double-blind, randomized, parallel-group clinical bridging trial evaluating the efficacy and safety of PF-06439535 (CN) plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin in first-line treatment for participants with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

Approximately 108 participants will be enrolled in each treatment arm for a total of approximately 216 participants at over 30 centers in China, with the aim to achieve a target sample size of 200. Participants will be randomized (1:1) to receive either PF-06439535 (CN) plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin for at least 4 and no more than 6 cycles, followed by the assigned blinded bevacizumab monotherapy until investigator assessed disease progression defined by RECIST 1.1, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, or Week 25, whichever comes first. At Week 25, all of the participants who continue to demonstrate clinical benefit in the opinion of the investigator, will receive PF-06439535 (CN) monotherapy for up to 2 years from randomization in this study, or until no further benefit from treatment (eg, investigator assessed disease progression, unacceptable toxicity, death, withdrawal of consent, lost to follow-up), whichever occurs first. Randomization will be stratified by sex (male/female) and smoking history (yes/no).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

- ORR, evaluating best overall responses achieved by Week 19 and subsequently confirmed by Week 25, in accordance with Response Evaluations Criteria in Solid Tumors (RECIST) version 1.1

3.2. Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness, and relationship to investigational product of adverse events, including cardiotoxicity and infusion related reactions, and laboratory abnormalities;

- Trough (collected at Cycle 1, Cycle 5) and apparent peak (collected at Cycle 1, Cycle 5 and End of Treatments) PF-06439535 (CN) and bevacizumab-EU concentrations;

- Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing antibodies (NAb) (collected at Cycle 1, Cycle 5 and End of Treatments).

3.3. Other Endpoint(s)

No other endpoints are planned in this protocol.

3.4. Baseline Variables

3.4.1. Covariates

In the statistical analysis models for primary efficacy on ORR as described in Section 6.1.1, the following covariates from the CRF will be used to explore their impact on the outcome variable based on ITT population:

- Gender (male/female);
- Smoking history (yes/no).

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3.4.3. Other Baseline Variables

Demographic and baseline characteristics such as participant age, sex, height, weight, ethnicity, prior therapy, medical history, and ECOG performance status, which are collected during screening, will serve as baseline variables and will be tabulated and summarized using descriptive statistics.

3.5. Safety Endpoints

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of investigational product through a minimum of 28 calendar days after the last administration of investigational product or start of new anticancer therapy, whichever occurs first.

The safety analyses will be carried out in the safety population. The following safety endpoints will be summarized descriptively:

- Treatment emergent adverse events (TEAE), treatment related adverse events, bevacizumab-related adverse events, CTCAE Grade 3 or higher adverse events and serious adverse events;
- Adverse events leading to delays, dose reduction and permanent discontinuation;
- Left ventricular ejection fraction (LVEF) as assessed by Multiple-gated acquisition (MUGA) or echocardiogram (ECHO).

3.5.1. Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) to determine System Organ Class and Preferred Term. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be used to grade severity.

Treatment emergent adverse event (TEAE) is defined as any adverse event that occurs after the beginning of the investigational product during the on-treatment period.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.6.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

Tier 2 events: These are events that are not tier 1 but are "common." A Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is defined as a Tier 2 event if there are at least 10% occurrence in any treatment group.

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4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following populations are defined:

Defined Population for Analysis	Description
Intent-to-Treat Population	The Intent to Treat (ITT) Population is defined as all participants who are randomized to investigational product. The ITT population will be used for participant accountability and all efficacy analyses.
Per Protocol Population	The Per Protocol (PP) Population is defined as all participants who are randomized and received the investigational product (PF-06439535 (CN) or bevacizumab) as planned and have no major protocol deviations. The PP population will be used for sensitivity analyses of the primary efficacy endpoint. The list of participants in PP population will be determined based on blinded data review prior to database release.
Safety Population	The safety population is defined as all participants who are randomized and receive at least one dose of investigational product. The safety population will be used for the safety analyses including ADA and NAb analyses.
Pharmacokinetics Population	Participants in the per protocol population who have at least one post dose drug concentration measurement, and have no major protocol deviations which could influence the pharmacokinetic assessment will be included in the PK analysis.

4.1. Treatment Misallocations

If a patient was:

- Randomized but not treated: the patient will be accounted for in the patient disposition table and listing. The patient will be reported under the randomized treatment group for efficacy analysis. The patient will not be included in safety analyses.

- Treated but not randomized: the patient will be reported under the treatment they actually received for the safety analyses. The patient will not be included in efficacy analyses.

- Randomized but received incorrect treatment: if patient received the incorrect treatment they will be reported under the treatment they first/actually received for safety analyses; and they will be reported under the randomized treatment group for efficacy analysis. The patient will be excluded from the PP population if this is deemed a major protocol deviation. Patient profiles on safety (demographics, adverse

events, laboratory data, anti-drug antibody, concomitant medications) may be generated for further assessments.

4.2. Protocol Deviations

Protocol deviations will be determined on an ongoing basis per blinded data review. Any patient with a major protocol deviation as determined by the study team will be excluded from the PP population.

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary completion date (PCD) for this study is defined as the last date on which all participants have completed Week 25 visit (ie, the last participant randomized has completed the Week 25 visit) or have otherwise died, withdrawn consent or been lost to follow-up. A database snapshot (containing data up to and including the Week 25 visit but before Week 25 dosing for every participant) will be performed after the PCD and a study report will be developed using this data to support the new drug application. All analyses described in Section 6 will be performed using this data snapshot. While the study participants, sites, investigators will remain blinded until the official database release (the final database release at the end of study), the core study team members will be unblinded at this time in order to prepare an unblinded clinical study report for regulatory submission. Details for blinding/unblinding will be described in a separate Data Blinding Plan.

The study is considered complete (End of Study) when the last participant has completed the last subject last visit (LSLV) (as per the study protocol) and the database is locked. Data collected after Week 25 until the end of study will be summarized in a supplemental study report which will describe safety results during the monotherapy extension period and will be considered as supplemental to the study report for the PCD.

5.1. Hypotheses and Decision Rules

This study is designed as a bridging study from the global studies in support of an abbreviated clinical program in China. This study is descriptive in nature, and no statistical hypotheses and testings will be done and no decision rule will be applied. The data from this study will be combined with all the global project package and the Chinese healthy volunteer PK study results to support the new drug application (NDA) submission.

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The criterion about the observed point estimate of RR to be greater than (>) the lower bound of the 90% CI of global study was only used to justify the sample size in this bridging study. We will not use this criterion as a decision rule for the efficacy equivalence declaration between PF-06439535 (CN) and bevacizumab-EU, as the point estimate of RR will be very sensitive to many factors in clinical trial operation. And we should combine the descriptive estimation with all other global data package to make a robust and solid conclusion.

5.2. General Methods

This study includes two treatment period, the blinded treatment period up to Week 25 and the extension period from Week 25. As described in the study design, during the blinded treatment period, "treatment arm" is defned as follows:

- PF-06439535 (CN) treatment arm: PF-06439535 (CN) plus paclitaxel and carboplatin up to cycle 6 and following PF-06439535 (CN) monotherapy until Week 25.
- bevacizumab-EU treatment arm: bevacizumab-EU plus paclitaxel and carboplatin up to cycle 6 and following bevacizumab-EU monotherapy until Week 25.

In the extension period, "treatment arm" refers to PF-06439535 (CN) monotherapy from Week 25 until up to 2 years from randomization.

In general, efficacy, safety, PK and immunogenicity as of Week 25 visit will be analyzed (analyses specified in Section 6) by treatment group in the study report for the PCD. In the supplemental study report, safety will be summarized across all participants, and PK and immunogenicity (which are to be collected at end of treatment/withdrawal visit) listed. For the supplemental report, only very limited safety summaries will be done (a subset of analyses as described in Section 6.6).

5.2.1. Analyses for Binary Endpoints

Descriptive statistics (frequency and percentage) and 90% confidence interval for CR, PR and ORR by treatment group will be constructed. Miettinen and Nurminen (1985)[6] method without strata will be used as the primary analysis method for the binomial distributed efficacy endpoint ORR. Estimated risk ratio, risk difference and the asymptotic 90% CI in ORR between bevacizumab-Pfizer and bevacizumab-EU will be computed.

5.2.2. Analyses for Continuous Endpoints

Descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided for continuous variables.

5.2.3. Analyses for Categorical Endpoints

The number and percentage of patients in each category will be provided for categorical variables. For Tier-1 and Tier-2 adverse events, besides the number and percentage summary for each category, the risk difference (RD) and 95% CI on RD calculated using the exact method by Chan and Zhang (1999)[7] will be provided for each event.

5.3. Methods to Manage Missing Data

5.3.1. Objective Response Data

Objective response (CR or PR) will be derived based on investigator reported tumor assessments. At each time point, missing response data will be considered as non-evaluable; the time point response will be used to derive the best objective response in accordance with RECIST 1.1. In the best objective response rate calculation, if a patient has missing tumor outcome across all visits or if he/she had non-evaluable best overall response following RECIST 1.1, the patient will be considered as non-responder, and will be included in the denominator but will not be included in the numerator.

5.3.2. Pharmacokinetic Concentrations

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 the listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

Deviations, missing concentrations and anomalous values

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

In drug concentration summary tables, 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 anomalously by the PK analyst.

For patients with a quantifiable concentration value for the pre-dose PK sample collected before treatment initiation, the concentration-time data without any adjustment will be included in PK data summary if the pre-dose concentration value is ≤5% of peak concentration (Cycle 1) from the same patient. If the concentration value in the pre-dose sample in a patient is >5% of peak concentration (Cycle 1) from the same patient, the patient will be excluded from the PK data summary.

5.3.3. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of resolution cannot be prior to date of onset; if replacing resolution date with the 1st of the month results in a negative duration, the resolution date will be set to the onset date). Pfizer standards are similarly used if both month and day are missing (January 1 unless negative time duration).

If the start date is missing for an AE, the AE is considered to be treatment emergent unless the collection date is prior to the treatment start date.

6. ANALYSES AND SUMMARIES

While every effort has been made to pre-specify all analyses in this statistical analysis plan, should any additional exploratory analyses be found to be necessary, the analyses and the reasons for them will be detailed in the clinical study report.

6.1. Primary Endpoint

6.1.1. Objective Response Rate (ORR) Achieved by Week 19

6.1.1.1. Main Analysis

- Estimand strategy: Compound estimand using hypothetical strategy for new anti-cancer medications and treatment policy strategy for the other intercurrent events (Section 2.1.1).

- Analysis set: Intent to Treat Population (Section 4).

- Analysis methodology: Miettinen and Nurminen (1985)[6] method without strata will be used as the primary analysis method for the efficacy endpoint ORR (Section 5.2.1).

- Intercurrent events and missing data: All response data after start of new anti-cancer medications will be excluded and the other intercurrent events will not be considerd (Section 2.1.1); missing response data will be considered as non-evaluable (Section 5.3.1).

- The best overall response per patient will be derived from the time point response in accordance with RECIST 1.1. The confirmation assessment for CR or PR must be at least 4 weeks later; the minimum criterion for SD duration is 5 weeks from the date of randomization. Table 2 presents some typical scenarios for deriving the best overall response.

- Estimated risk ratio and risk difference and the asymptotic 90% CI in ORR between PF-06439535 (CN) and bevacizumab-EU will be computed. The Miettinen and Nurminen analysis method without strata will be carried out by the BINOMIAL procedure. A sample of the SAS codes with PROC BINOMIAL is provided in the

appendix of this document (Appendix 3). The primary analysis will be based on the ITT population.

- In addition, descriptive statistics will also be presented for the best overall response by Week 19 (confirmed by Week 25) by treatment group.

Table 2. Derivation of the Best Overall Response

Assessment 1	Assessment 2	Assessment 3	Assessment 4	Overall Response
CR	CR	PD		CR *
CR	NE	CR	PD	CR *
PR	CR	CR	PD	CR *
PR	CR	PD		PR *
PR	PR	PD		PR *
PR	NE	PR	PD	PR *
PR	PR	CR	PD	PR *
CR	PR			Not allowed **. SD/PD/PR. Review of the CR is recommended.
CR	PD			SD ***
PR	PD			SD ***
SD or NE	CR	PD		SD ***
SD or NE	PR	PD		SD ***
SD	PD			SD ***
PD				PD
NE	PD			PD
NE	NE	PD		Assume no response

* The best overall response is CR/PR, if the assessments with PR/CR is ≥4 weeks apart (NE is allowed between the assessments of PR/CR); otherwise, it is SD if the minimum criteria for SD duration is met, else it is PD.

** If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

*** Unconfirmed responses are considered as stable disease, if the minimum criterion for SD duration is met.

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6.2. Secondary Endpoint(s)

6.2.1. Safety Endpoints

- Estimand strategy: Treatment policy strategy will be used (Section 2.1.2.1).
- Analysis set: Safety Population (Section 4).
- Analysis methodology: Descriptive statistics summary will be done for safety endpoints, and the risk difference (RD) and 95% CI on RD will be calculated for Tier-1 and Tier-2 adverse events (Section 5.2.3).
- Intercurrent events and missing data: All safety data collected during the on-treatment period will be included in the analyses without regard to intercurrent events (Section 2.1.2.1); missing safety data will be imputed per Pfizer standard (Section 5.3.3).
- Detailed summaries and analyses for safety endpoints please refer to Section 6.6.

6.2.2. Pharmacokinetic Endpoints

- Estimand strategy: Hypothetical strategy will be used (Section 2.1.2.2).
- Analysis set: Pharmacokinetics Population (Section 4).
- Analysis methodology: Descriptive statistics will be used to summarize the PK concentration data (Section 5.2.2).
- Intercurrent events and missing data: All PK data after intercurrent events as defined in Section 2.1.2.2 will be excluded; missing PK data will be imputed as described in Section 5.3.2.
- The drug concentration-time data will be summarized by descriptive statistics (N (number of observations for non-missing concentrations), NALQ (Number of observations Above Lower limit of Quantification), mean, standard deviation, CV%, median, minimum and maximum) according to treatment. A listing of all concentrations sorted by treatment, subject ID and nominal time postdose will be generated. The concentration listing will also include the actual sampling times. Deviations from the nominal time will be given in a separate listing.
- The detailed procedures for the population PK analysis, if conducted, including the model implementation and evaluation, will be described in the Population Modeling Analysis Plan (PMAP). The results of the analysis, will be summarized in a Population Modeling and Analysis Report (PMAR) separated from the clinical study report (CSR).

6.2.3. Immunogenicity Endpoints

- Estimand strategy: Treatment policy strategy will be used (Section 2.1.2.3).
- Analysis set: Safety Population (Section 4).
- Analysis methodology: Descriptive statistics summary will be done for positive ADA and NAb (Section 5.2.3).
- Intercurrent events and missing data: All data collected will be included in the analyses without regard to intercurrent events (Section 2.1.2.3); No imputation will be done for immunogenicity data.
- The percentage of participants with positive ADA and NAb will be summarized for each treatment. For participants with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. In addition, efforts will be made, as appropriate, to examine possible correlations of the ADA response with clinical data on the PK, safety and/or efficacy of each product.
- Because the observed incidence of ADA is highly dependent on multiple factors including the assays used for ADA detection, timing of sample collection and immune status of the participants, the incidence of ADA observed in the planned study may differ from the incidence reported in historical clinical trials.

6.3. Other Endpoint(s)

No other endpoints are planned in this protocol.

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6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline characteristics such as participant age, sex, height, weight, ethnicity, prior therapy, medical history, and ECOG performance status, which are collected during screening, will serve as baseline variables and will be tabulated and summarized using descriptive statistics.

6.5.2. Study Conduct and Participant Disposition

A subject disposition table will be provided. Subject disposition will be summarized by treatment group and will include the number and percentage of patients, randomized, treated, and analyzed for safety and efficacy. The percentage of patients who are ongoing and discontinued in the treatment and follow up periods will be presented.

The percentages will use the number of randomized patients in each treatment group as the denominator. The disposition summary will be based on the ITT population.

6.5.3. Study Treatment Exposure

Administration for each investigational product will be described in terms of the total number of cycles administered, the median (range) of cycles administered, duration of treatment (weeks).

6.5.4. Prior and Concomitant Medications

Collected prior and concomitant medications will be coded by the World Health Organization (WHO) medical dictionary; and these data will be summarized by treatment group for the safety population.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

All analyses described below will be based on TEAEs (as defined in Section 3.5.1) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

The Pfizer standard 3 tier adverse events reporting approach will be employed:

- For Tier-1 and Tier-2 adverse events, besides the number and percentage summary for each category, the risk difference (RD) between PF-06439535 (CN) and bevacizumab-EU and 95% CI on RD will be provided for each event. For Tier-1 events, p-value will also be provided. Both summary tables and graphical plots for risk difference will be presented, and the output will be sorted in descending point estimate of the risk difference.

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Adverse events as defined in Section 3.5 will be summarized by System Organ Class and Preferred Term and severity for each treatment group. CTCAE Grade 3 or higher adverse events will be additionally summarized separately by treatment group. A summary of AEs by preferred term and maximum CTCAE grade will be presented, in decreasing order of frequency.

Adverse events recorded on the CRF as infusion related reactions (IRRs) will be summarized separately for the 2 treatment arms.

6.6.1.1. Anaphylaxis

Subjects with adverse events occurring within 24 hours or 1 day after study drug administration of each visit and falling under anaphylactic reaction Standardised MedDRA Query (SMQ), angioedema SMQ or Hypersensitivity SMQ will be assessed for potential anaphylactic reaction.

AEs that were categorized as the SMQs of Anaphylactic Reaction, Hypersensitivity, and 2 categories combined will be summarized for all causality TEAEs and bevacizumab related with or without causal relationship to chemotherapy TEAEs. For patients that were ADA positive, their all causality TEAEs categorized as the Anaphylactic Reaction, and Hypersensitivity SMQs were also summarized.

The subjects with IRRs and having an AE that is in the anaphylaxis and hypersensitivity SMQ will be summarized for subjects overall, by ADA status (positive or negative), and by visit. This summary will appear in the PCD CSR Table 'Summary of Anti-Drug Antibody (ADA) and Clinical Outcomes Associated with Immunogenicity (COAI)* by Visit and Overall - Safety Population'.

6.6.2. Laboratory Data

Hematology and chemistry laboratory data will be summarized by treatment and visit. The laboratory results will be graded according to NCI CTCAE v4.03 severity grade. The frequencies of the worst severity grade observed will be displayed by investigational product. Shift tables of baseline against each post baseline visit will be provided for selected laboratory tests to examine the distribution of laboratory toxicities. For parameters for which an NCI CTCAE scale does not exist, the frequency of participants with values below, within, and above the normal ranges will be summarized by treatment and visit.

Change from baseline will be additionally summarized by treatment group and visit. Baseline is defined as the most recent measurement prior to the beginning of the investigational product.

6.6.3. Vital Signs

Vital signs will be presented in listing format only.

6.6.4. LVEF assessed by MUGA or ECHO

Multiple-gated acquisition (MUGA) or Echocardiogram (ECHO) will be used to assess left ventricular ejection fraction (LVEF) of each participant. LVEF will be summarized by treatment and visit. Absolute decline in LVEF and shift summary from baseline will be summarized by treatment and visit. Baseline is defined as the most recent measurement prior to the beginning of the investigational product.

6.6.5. Physical Examination

Physical examination at screening phase will be collected in the CRF and will be listed in a data listing.

7. INTERIM ANALYSES

There will be no interim analyses in this study.

8. REFERENCES

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9. APPENDICES

Appendix 1. Assessment Windows to Derive the Time Point Response

To derive the time point response for each patient, the assessment windows in Table 3 will be used to cluster the assessments.

Table 3. Assessment Windows

Assessments	Scheduled Assessment Day	Start Day of Assessment Window	End day of Assessment Window
1	42	22	63
2	84	64	105
3	126	106	147
4	168	148	200

Appendix 2. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Method
ORR	Main analysis	ITT	All responses data after start of new anti-cancer medications will be excluded and the other intercurrent events will not be considerd. Missing response data will be considered as non-evaluable.	Miettinen and Nurminen without strata
CCI	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 3. Sample Code for the Miettinen and Nurminen Method Without Strata

Appendix 3.1. For Risk Ratio

First, manipulate study data to form the following structure. The variable Count in the sample would be corresponding to the ORR count in the primary efficacy analysis.

```
Data test;
Input   group $     resp $      count;
Cards;
  pfe          yes        210
  pfe          no         180
  eu           yes        202
  eu           no         188
;
run;
```

Then, apply the following codes to obtain the asymptotic 90% CI:

```
proc binomial data=test alpha=0.9;
        eqv/as ratio margin=1.33;
        po group;
        ou resp;
        weight count;
run;
quit;
```

Appendix 3.2. For Risk Difference

First, manipulate study data to form the same structure as in Appendix 3.1.

Then, apply the following codes to obtain the asymptotic 90% CI:

```
proc binomial data=test alpha=0.9;
        eqv/as diff margin=0.13;
        po group;
        ou resp;
        weight count;
run;
quit;
```

CCI

Appendix 4.1. For Risk Ratio

```
%macro MNRRFunc(RR=);

/* calculate ML estimate of R1 and R0*/

r0s=0;
r1s=0;

/* initial value of weights sum */
wsum=0;
%do j=1 %to &size;
wsum=wsum+w&j;
%end;

/* paper equation (12) */

%do j= 1 %to &size;

AA=(&&nt&j+&&nc&j)*&RR;
BB=-(&&nt&j*&RR+&&yt&j+&&nc&j+&&yc&j*&RR);
CC= &&yc&j+&&yt&j;

r0&j=(-BB-sqrt(BB*BB-4*AA*CC))/(2*AA);
r1&j=r0&j*&RR;

/* rounding the boundary values */
if r0&j>1 then r0&j=1;if r0&j<0 then r0&j=0;
if r1&j>1 then r1&j=1;if r1&j<0 then r1&j=0;

r0s=r0s+r0&j*w&j/wsum;
r1s=r1s+r1&j*w&j/wsum;
%end;
/* end of calculate ML estimate of R1 and R0*/

/* update the weights W, paper equation (18) */

%do j=1 %to &size;
w&j=1/((1-r1s)/(1-r0s)/&&nt&j+&RR/&&nc&j);
%end;

wsum=0;
%do j=1 %to &size;
wsum=wsum+w&j;
%end;
```

```
/* calculate the variance V, paper equation (11) */
vsum=0;
%do j=1 %to &size;
v&j=(r1&j*(1-r1&j)/&&nt&j+(&RR**2)*r0&j*(1-
r0&j)/&&nc&j)*((&&nt&j+&&nc&j)/(&&nt&j+&&nc&j-1));
if v&j=0 then do;
                    r0&j=0.001;
          r1&j=0.001;
                    v&j=(r1&j*(1-r1&j)/&&nt&j+(&RR**2)*r0&j*(1-
r0&j)/&&nc&j)*((&&nt&j+&&nc&j)/(&&nt&j+&&nc&j-1));
                    end;
vsum=vsum+w&j**2*v&j/wsum**2;
%end;

/* calculate the score and the limits, paper equation (17)  */
t=0;
%do j=1 %to &size;
t=t+((&&yt&j/&&nt&j*w&j)-(&&yc&j/&&nc&j*w&j*&RR))/wsum/sqrt(vsum);
%end;

ZA1=t+probit(1-&alpha/2); /* upper limit */
ZA2=t-probit(1-&alpha/2); /* lower limit */

%mend;

/** Use bisection method and iterative procedure to find the limits for RR **/

%macro RRrootfinding(parainput=,size=,alpha=);

/* read in parameters from input dataset to global variables */
proc sql noprint;
  select nt, nc, yt, yc
    into :nt1 - :nt&size, :nc1 - :nc&size, :yt1 - :yt&size, :yc1 - :yc&size
        from &parainput;

/* main part of the macro */
data MNRR;

/* set machine epsilon for bisection method*/
eps=0.000001;

/* read parameters from global variables*/
%do j=1 %to &size;
 nt&j=&&nt&j;
 nc&j=&&nc&j;
```

```
 yt&j=&&yt&j;
 yc&j=&&yc&j;
 /* following parameters are used to define the searching range */
 /* 0.5 and 1 is added to avoid cases when cells has value 0 */
 c1s&j=&&yt&j+0.5;
 n1s&j=&&nt&j+1;
 c0s&j=&&yc&j+0.5;
 n0s&j=&&nc&j+1;

%end;

/* set initial values for weights */
 %do j=1 %to &size;
 w&j= 1/(1/&&nt&j+1/&&nc&j);
 %end;


/**max RR and Min RR for searching*/;
b1=0;b0=0.01;
%do j=1 %to &size;
        b1=max(b1,(c1s&j/n1s&j)/(c0s&j/n0s&j),(c0s&j/n0s&j)/(c1s&j/n1s&j));
        b0=min(b0,(c1s&j/n1s&j)/(c0s&j/n0s&j),(c0s&j/n0s&j)/(c1s&j/n1s&j));
 %end;
 b1=b1*100;
 b0=b0/100;


/*Upper Limits, using bisection method */;

Uroot1=b0; RR=Uroot1; %MNRRFunc(RR=RR);y1=ZA1;
Uroot3=b1; RR=Uroot3; %MNRRFunc(RR=RR);y3=ZA1;

y2=(b1+b0)/2;
i=0;

if y1*y3>0 then do;
                                put  "f does not have opposite sign at endpoints";
                                Uroot2=.;
end;

else do while (i<1000 and abs(y2)>eps);
                                i=i+1;
                        Uroot2=(Uroot1+Uroot3)/2;

                        RR=Uroot2; %MNRRFunc(RR=RR); y2=ZA1;
                RR=Uroot1; %MNRRFunc(RR=RR); y1=ZA1;
```

```
            RR=Uroot3; %MNRRFunc(RR=RR); y3=ZA1;

           if y1*y2<0 then do;
                              Uroot3=Uroot2;
                              y3=y2;
                       end;

                       else do;
                           Uroot1=Uroot2;
                                 y1=y2;
                       end;
              end;

/*Lower Limits, using bisection method */;

 %do j=1 %to &size;
 w&j= 1/(1/&&nt&j+1/&&nc&j);
 %end;

Lroot1=b0; RR=Lroot1; %MNRRFunc(RR=RR); y11=ZA2;
Lroot3=b1; RR=Lroot3; %MNRRFunc(RR=RR); y33=ZA2;

y22=(b0+b1)/2;
i=0;

if y11*y33>0 then do;
            put  "f does not have opposite sign at endpoints" ;
                              Lroot2=.;
end;

else do while (i<1000 and abs(y22)>eps);
                                    i=i+1;
                         Lroot2=(Lroot1+Lroot3)/2;
            RR=Lroot2; %MNRRFunc(RR=RR); y22=ZA2;
            RR=Lroot1; %MNRRFunc(RR=RR); y11=ZA2;
            RR=Lroot3; %MNRRFunc(RR=RR); y33=ZA2;

           if y11*y22<0 then do;
               Lroot3=Lroot2;
                              y33=y22;
                       end;

                       else do;
                           Lroot1=Lroot2;
                                 y11=y22;
                       end;
```

```
            end;

keep nt1 nt2 nc1 nc2 yc1 yc2 yt1 yt2 Lroot2 Uroot2;
run;
%mend;
/* provide feed in data to the macro*/
/* each line represent values in each stratum */
/* with total n in each arm (nt and nc) and responder in each arm (yt and yc) */
/* following example only contains one strata with 4 levels */
data data;
input nt nc yt yc;
cards;
100 110 60 70
120 110 80 70
120 115 70 70
130 120 75 75
;
run;
/* calculated CI based on RR with MN method with strata*/
/* parameter Size is the total levels of strata.If two strata is considered, each with 2 and 3
levels, */
/* there will be 6 lines in the input dataset, and size=6  */
%RRrootfinding(parainput=data,size=4,alpha=0.05);
```

Appendix 4.2. For Risk Difference

```
%macro MNRDfunc(RD=);

/* force the restricted difference not equal to zero*/
if &RD=0 then RD=0.001; else RD=&RD;

/* calculate ML estimate of R1 and R0*/
r0s=0;
r1s=0;

/* initial value of weights sum */
wsum=0;
%do j=1 %to &size;
wsum=wsum+w&j;
%end;


/* paper equation (27),(28) */
%do j= 1 %to &size;

L0=&&yc&j*RD*(1-RD);
L1=(RD*&&nc&j-&&nc&j-&&nt&j-2*&&yc&j)*RD+(&&yt&j+&&yc&j);
```

```
L2=(&&nt&j+2*&&nc&j)*RD-&&nc&j-&&nt&j-(&&yt&j+&&yc&j);
L3=&&nt&j+&&nc&j;
**********************;
q=(L2**3)/(27*(L3**3))-(L1*L2)/(6*L3*L3)+L0/(2*L3);
p=q/abs(q)*sqrt((L2*L2)/(9*L3*L3)-L1/(3*L3));
a=(1/3)*(arcos(-1)+arcos( q/(p**3)));
**************************;
r0&j=2*p*cos(a)-L2/(3*L3);
r1&j=r0&j+RD;

/* rounding the boundary values */
if r0&j>1 then r0&j=1;if r0&j<0 then r0&j=0;
if r1&j>1 then r1&j=1;if r1&j<0 then r1&j=0;

r0s=r0s+r0&j*w&j/wsum;
r1s=r1s+r1&j*w&j/wsum;

%end;
/* end of calculate ML estimate of R1 and R0*/

/* update the weights W, paper equation (16) */

%do j=1 %to &size;
w&j=1/(r1s*(1-r1s)/r0s/(1-r0s)/&&nt&j+1/&&nc&j);
%end;

wsum=0;
%do j=1 %to &size;
wsum=wsum+w&j;
%end;

/* calculate the variance V, paper equation (8) */
vsum=0;
%do j=1 %to &size;
v&j=(r1&j*(1-r1&j)/&&nt&j+r0&j*(1-
r0&j)/&&nc&j)*((&&nt&j+&&nc&j)/(&&nt&j+&&nc&j-1));
if v&j=0 then do;
                r0&j=0.001;
        r1&j=0.001;
                v&j=(r1&j*(1-r1&j)/&&nt&j+r0&j*(1-
r0&j)/&&nc&j)*((&&nt&j+&&nc&j)/(&&nt&j+&&nc&j-1));
                end;
vsum=vsum+w&j**2*v&j/wsum**2;
%end;

/* calculate the score and the limits, paper equation (15) */
```

```
t=0;
%do j=1 %to &size;
t=t+w&j*(&&yt&j/&&nt&j-&&yc&j/&&nc&j)/wsum/sqrt(vsum);
%end;
t=t-RD/sqrt(vsum);

Zmnd1=t-probit(1-&alpha/2);
Zmnd2=t+probit(1-&alpha/2);

%mend;


/** Use bisection method and iterative procedure to find the limits for RD **/

%macro RDrootfinding(parainput=,size=,alpha=);


/* read in parameters from input dataset to global variables */
proc sql noprint;
  select nt, nc, yt, yc
    into :nt1 - :nt&size, :nc1 - :nc&size, :yt1 - :yt&size, :yc1 - :yc&size
        from &parainput;

/* main part of the macro */
data MNRD;

/* set machine epsilon for bisection method*/
eps=0.000001;

/* read parameters from global variables*/
%do j=1 %to &size;
 nt&j=&&nt&j;
 nc&j=&&nc&j;
 yt&j=&&yt&j;
 yc&j=&&yc&j;
%end;

/* set initial values for weights */
 %do j=1 %to &size;
 w&j= 1/(1/&&nt&j+1/&&nc&j);
 %end;


/**max RR and Min RR for searching*/;
b1=-0.999;
b0=0.999;
```

```
/*Lower Limits, using bisection method */;
Lroot1=b0;RD=Lroot1;%MNRDfunc(RD=RD); y1=Zmnd1;
Lroot3=b1;RD=Lroot3;%MNRDfunc(RD=RD); y3=Zmnd1;

i=0;y2=2*eps;

if y1*y3>0 then do;
        put  "f does not have oposite sign at endpoints" ;
        Lroot2=.;
end;


else do while (i<1000 and abs(y2)>eps);
      i=i+1;
      Lroot2=(Lroot1+Lroot3)/2;
      RD=Lroot2; %MNRDfunc(RD=RD); y2=Zmnd1;
      RD=Lroot1; %MNRDfunc(RD=RD); y1=Zmnd1;
      RD=Lroot3; %MNRDfunc(RD=RD); y3=Zmnd1;

        if y1*y2<0 then do;
                Lroot3=Lroot2;
                        y3=y2;
   end;
   else do;
                        Lroot1=Lroot2;
                        y1=y2;
   end;
end;

/*Upper Limits, using bisection method */;
   Uroot1=b0; RD=Uroot1; %MNRDfunc(RD=RD); y11=Zmnd2;
   Uroot3=b1; RD=Uroot3; %MNRDfunc(RD=RD); y33=Zmnd2;

    y22=2*eps;
        i=0;

        if y11*y33>0 then do;
                put  "f does not have oposite sign at endpoints" ;
                Uroot2=.;
        end;

        else do while (i<1000 and abs(y22)>eps);
        i=i+1;
        Uroot2=(Uroot1+Uroot3)/2;
```

```
        RD=Uroot2; %MNRDfunc(RD=RD); y22=Zmnd2;
        RD=Uroot1; %MNRDfunc(RD=RD); y11=Zmnd2;
        RD=Uroot3; %MNRDfunc(RD=RD); y33=Zmnd2;

        if y11*y22<0 then do;
         Uroot3=Uroot2;
                        y33=y22;
                end;
      else do;
                        Uroot1=Uroot2;
                        y11=y22;
                end;
          end;
keep nt1 nt2 nc1 nc2 yc1 yc2 yt1 yt2 Lroot2 Uroot2;
run;
%mend;

/* provide feed in data to the macro*/
/* each line represent values in each stratum */
/* with total n in each arm (nt and nc) and responder in each arm (yt and yc) */
/* following example only contains one strata with 4 levels */
data data;
input nt nc yt yc;
cards;
100 110 60 70
120 110 80 70
120 115 70 70
130 120 75 75
;
run;
/* calculated CI based on RD with MN method with strata*/
/* parameter Size is the total levels of strata.If two strata is considered, each with 2 and 3
levels, */
/* there will be 6 lines in the input dataset, and size=6  */

%RDrootfinding(parainput=data,size=4,alpha=0.05);
```