PROTOCOL B7391003

A PHASE 3 RANDOMIZED, DOUBLE-BLIND STUDY OF PF-06439535 PLUS PACLITAXEL-CARBOPLATIN AND BEVACIZUMAB PLUS PACLITAXEL-CARBOPLATIN FOR THE FIRST-LINE TREATMENT OF PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

Statistical Analysis Plan (SAP)

Version: 4.0

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Date: 28 March 2017

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

This amendment is based on protocol amendment 3. Following are changes compared to the previous version of SAP.

Section 3 – Update the number of study reports, data versions, and planned analyses.

Section 6.3 – Updated the subgroup analyses for primary efficacy endpoint on.

Section 7.1 – Updated the method to handle data for objective response data.

Section 8.1 – clarify how to derive the best overall response for primary efficacy endpoint.

Section 8.2.3 – For secondary endpoint on DOR, PFS and OS, the one-sided p-value from log-rank test is replaced with 2-sided p-value from log-rank test stratified by region, gender and smoking history; clarified the covariates included in the Cox proportional hazard model; and updated the censoring algorithms.

Appendix 1 – Added the assessment windows for derivation of time point response.

2. INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for study B7391003 (Pfizer compound PF-06439535). This SAP is based on the final approved protocol amendment 3 for study B7391003 dated Jun. 10th, 2016.

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

2.1. Study Design

This is a multinational, double-blind, randomized, parallel-group Phase 3 clinical trial evaluating the efficacy and safety of bevacizumab-Pfizer plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin in first-line treatment for patients with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

Approximately 355 patients will be enrolled in each treatment arm for a total of approximately 710 patients at over 300 centers. Patients will be randomized (1:1) to receive either treatment of bevacizumab-Pfizer plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin. Randomization will be stratified by region (according to the location of the drug depot supplying the site), sex (male/female) and smoking history (never/ever).

2.2. Study Objectives

2.2.1. Primary Objectives

The primary objective of this study is to compare the confirmed objective response rate (ORR) by Week 19 following treatment with bevacizumab-Pfizer in combination with paclitaxel and carboplatin to bevacizumab-EU plus paclitaxel and carboplatin in patients who have not received previous treatment for advanced NSCLC.

[redacted].

2.2.2. Secondary Objectives

- *To evaluate the safety of bevacizumab-Pfizer plus paclitaxel and carboplatin and bevacizumab-EU plus paclitaxel and carboplatin;*
- *To evaluate the secondary measures of tumor control;*
- *To evaluate the population pharmacokinetics (PK) of bevacizumab-Pfizer and bevacizumab-EU;*
- *To evaluate the immunogenicity of bevacizumab-Pfizer and bevacizumab-EU.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis is planned for this study.

Primary completion date CSR: The data cut-off date for the primary efficacy analysis for equivalence will be when the last available patient has completed Week 19 tumor assessment and had the opportunity to subsequently confirm the response at the Week 25 tumor assessment, or early discontinued (withdrawal, lost to follow up, death, etc). All analyses described in Section 8 will be carried out for this data snapshot.

Week 55 CSR: The data cut-off for the Week 55 CSR will be when the last available patient has completed 1-year (Week 55) assessment or early discontinued. There are no plans to repeat the primary endpoint analysis of objective response rate (ORR) in the Week 55 CSR; the analysis of other efficacy endpoints (descriptive statistics for the secondary efficacy endpoints), the safety analyses, and other analyses (PK analysis and immunogenicity assessment) as described in Section 8 will be updated with this data snapshot.

If there are any patients who did not complete their last follow-up by the time of the data snapshot for Week 55 CSR (eg, a patient may come in for another follow-up visit after he/she completed the week 55 visit), then listings for these remaining data will be presented in a separate report.

These planned analyses are summarized as follows:

Data Version	Planned Analyses
First data snapshot (Week 19 with confirmation data at Week 25)	• All possible analyses specified in Section 8 of this document.
Week 55 data snapshot (Week 55)	• Repeat efficacy analyses for the secondary efficacy endpoints (Section 8.2.3). • Repeat the PK analysis (Section 8.2.4). • Repeat the immunogenicity analysis (Section 8.2.5). • Repeat safety analyses (Section 8.2.6).

[redacted]

The study is considered complete (End of Study) when the last patient has completed the last subject last visit (LSLV). LSLV is defined as up to 1 year from randomization of the last patient (End of Treatment) plus 28 day follow-up.

This study will use an external data monitoring committee (EDMC). The EDMC will be responsible for ongoing monitoring of the efficacy and safety of patients in the study according to its charter. Detailed information about those entities is described in the DMC charter.

Limited team members will be unblinded at the time of the primary efficacy analysis. A separate document will be created to capture the details of the unblinding plan. Site personnel and patients will remind blinded until the completion of the study.

4. HYPOTHESES, DECISION RULES AND SAMPLE SIZE

4.1. Statistical Hypotheses

Two one-sided hypothesis tests will be carried out in the study for ORR in order to show that bevacizumab-Pfizer is equivalent to bevacizumab-EU.

For both US and Japan, equivalence will be tested based on relative risk (RR), with following hypothesis:

$$\textit{TEST 1: } H_{0a}: \theta_1 / \theta_2 > R_{ub} \textit{ vs. } H_{1a}: \theta_1 / \theta_2 \leq R_{ub}$$

$$\textit{TEST 2: } H_{0b}: \theta_1 / \theta_2 < R_{lb} \textit{ vs. } H_{1b}: \theta_1 / \theta_2 \geq R_{lb}$$

Where θ_1 is the ORR for patients randomized to bevacizumab-Pfizer, θ_2 is the ORR for patients randomized to bevacizumab-EU, R_{ub} is the largest acceptable ratio for equivalence, and R_{lb} is the smallest acceptable ratio for equivalence. Note: $R_{lb} = 1 / R_{ub}$. For US, $R_{ub}=1.37$ and $R_{lb}=0.73$ and for Japan, $R_{ub}=1.371$ and $R_{lb}=0.729$.For the EU, equivalence will be tested based on risk difference (RD), with following hypothesis:

$$\textit{TEST 1: } H_{0a}: \theta_1 - \theta_2 > R_{ub} \textit{ vs. } H_{1a}: \theta_1 - \theta_2 \leq R_{ub}$$

$$\textit{TEST 2: } H_{0b}: \theta_1 - \theta_2 < R_{lb} \textit{ vs. } H_{1b}: \theta_1 - \theta_2 \geq R_{lb}$$

Where R_{ub} is the largest acceptable difference for equivalence, and R_{lb} is the smallest acceptable difference for equivalence. Note: $R_{lb} = -R_{ub}=-0.13$.

4.2. Statistical Decision Rules

For the US, equivalence will be considered established if the 90% confidence interval of the risk ratio falls into the margins (0.73, 1.37).

For Japan, equivalence will be considered established if the 95% confidence interval of the risk ratio falls into the margins (0.729, 1.371).

[redacted]

For the EU equivalence will be considered established if the 95% confidence interval of the risk difference falls into the margins (-0.13, 0.13).

For all other regions the primary hypothesis will be analyzed based on a US scenario unless otherwise requested by local regulators.

4.3. Sample Size

Based on the results of a meta-analysis combining Sandler (2006),[1] Johnson (2004),[2] and Niho (2012),[3] the objective response rate (ORR) to bevacizumab + chemotherapy combination therapy was estimated to be approximately 41%, and the response rate to chemotherapy alone was estimated to be 21%. The relative risk (RR) for ((bevacizumab + chemotherapy)/ chemotherapy alone) was estimated to be 2.17 with 95% CI (1.74, 2.70). The margin
(0.73, 1.37) maintained 43% of two-sided 95% CI lower bound of the effect size based on the historical ORR data based on the meta-analysis treatment estimate of bevacizumab + chemotherapy over chemotherapy alone based on a log scale (or about 50% on the linear scale).

A sample size of 656 patients (328 per treatment arm) provides approximately 85% power for achieving equivalence in relative risk (RR) under the specified margin with 5% type I error[1] rate assuming an ORR of 38% in both treatment arms. Considering a possible ~7.5% attrition rate for patients reaching evaluation for ORR, a total sample size of approximately 710 patients (355 per treatment arm) will be randomized to achieve the target sample size of 656. This target sample size of 656 patients will provide approximately a power of 90% given above assumptions and assuming ORR=41%.

A sample size of 656 patients (328 per treatment arm) provides approximately 86% power for achieving equivalence in risk difference (RD) under specified margin of (-13%, 13%) with 2.5% type I error rate assuming an ORR of 38% in both treatment arms. This target sample size of 656 patients will provide approximately a power of 84% given above assumptions and assuming ORR=41%.

A sample size of 656 patients (328 per treatment arm) will also provide approximately 74% power for achieving equivalence in relative risk (RR) under specified margin of (0.729, 1.371) with 2.5% type I error rate assuming an ORR of 38% in both treatment arms. This target sample size of 656 patients will provide approximately a power of 82% given above assumptions and assuming ORR=41%.

Unless otherwise specified, analysis for all other geographical regions will follow US-specific analysis using risk ratio approach.

[1] For two-sided tests of superiority the alpha level is divided between the lower bound and the upper bound of the test statistic, ie, for an alpha level of 5%, 2.5% is allocated to the upper bound and 2.5% is allocated to the lower bound, under a single null hypothesis of no difference. However, in equivalence tests, there are two null hypotheses, that is, the true response rate of the biosimilar is either clinically greater than the reference product or is clinically less than the reference product; the two null hypotheses cannot be true at the same time. Thus, the alpha level for the TOST method is determined by the one sided error rate of each individual test.

[redacted].

5. ANALYSIS POPULATIONS

5.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population is defined as all patients who are randomized to study treatment. The ITT population will be used for patient accountability and all efficacy analyses. Patients will be assigned to treatment groups "as randomized" for efficacy analyses, but "as treated" for all other analyses. For these other analyses, if there are any cases where patients received both drugs, they will be assigned to the treatment initially given.

5.2. Per-Protocol Population

The Per-Protocol (PP) Population is defined as all patients who are randomized and received the study treatment (bevacizumab-Pfizer or bevacizumab-EU) as planned and have no major protocol deviations. The PP population will be used for sensitivity analyses of the primary and secondary objectives. The list of patients who will be excluded from this population and reason for exclusion will be determined prior to unblinding for the primary efficacy analysis.

5.3. Safety Population

The safety population is defined as all patients who are randomized and receive at least one dose of study treatment. The safety population will be used for the safety analyses including ADA and NAb analyses.

5.4. Pharmacokinetics Population

Patients in the PP population who have at least one post-dose drug concentration measurement will be included in the PK analysis.

5.5. 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 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 as a major protocol deviation. Patient profiles on safety (demographics, adverse events, laboratory data, anti-drug antibody, concomitant medications) may be generated for further assessments.

[redacted].

5.6. 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.

6. ENDPOINTS AND COVARIATES

6.1. Endpoints

6.1.1. Primary Endpoint

- *Objective Response Rate (ORR), evaluating the best response achieved by Week 19 and subsequently confirmed by 6 weeks thereafter, in accordance with Response Evaluations Criteria in Solid Tumors (RECIST)[4] version 1.1.*

6.1.2. Secondary Endpoints

- *Safety characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events, including cardiotoxicity and infusion-related reactions* (IRR)*, and laboratory abnormalities;*

- *Duration of response (DOR), 1 year progression-free survival (PFS) rate and 1-year survival rate from randomization;*

- *Peak and trough bevacizumab-Pfizer and bevacizumab-EU concentrations at selected cycles up to 1 year from randomization;*

- *Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing antibodies (NAb) up to 1 year from randomization.*

6.2. Covariates

In the statistical analysis models for primary efficacy on ORR and secondary endpoints on DOR, PFS and OS, as described in Section 8.2.2 and 8.2.3, the following covariates from the CRF will be used to explore their impact on the outcome variable based on ITT population:

- Region (according to the location of the drug depot supplying the site). Regions might be combined into aggregated levels to facilitate related analyses.;

- Gender (male/female);

- Smoking history (never or ever (includes ex-smoker and smoker).

6.3. Subgroup Analyses

In addition, the following factors at screening will be used in the subgroup analyses for primary efficacy endpoint on ORR based on ITT population and a forest plot will be presented.

- Smoking history (never or ever (includes ex-smoker and smoker))

[redacted]

- Gender (male/female)
- Region (according to the location of the drug depot supplying the site). Regions might be combined into aggregated levels to facilitate related analyses.
- Age (≥65, <65)
- Race (White, Black, Asian, Other)
- Disease Stage (IIIB, IV, recurrent)
- Prior radiation therapy (Yes, No)
- Any prior systemic therapy, including adjuvant/neoadjuvant (Yes, No)
- ECOG PS (0, 1)

7. HANDLING OF MISSING VALUES

7.1. 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 responsewill 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.

7.2. Time to Event Data

For the time-to-event endpoints (DOR, PFS, or survival), the missing data handling method will be censoring. Censoring mechanisms for these endpoints are described in Section 8.2.3.

7.3. 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);

[redacted]

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous 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 C_{max} from the same patient. If the concentration value in the pre-dose sample in a patient is >5% of C_{max} from the same patient, the patient will be excluded from the PK data summary.

7.4. 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). For overall survival and PFS, if conventions result in a negative duration, duration will be reset to 1 day.

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.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

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.

8.1. Statistical Methods

For primary efficacy endpoint of objective response rate, secondary endpoints on DOR, PFS and overall survival (OS), outcome will be derived based on investigator tumor assessments.

8.1.1. Analysis of Response Data

Miettinen and Nurminen (1985)[4] 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 95% and 90% CI in ORR between bevacizumab-Pfizer and bevacizumab-EU will be computed and used in the hypothesis testing.

8.1.2. Analysis of Time to Event Data

The time to event endpoints (DOR, PFS, and survival) will be assessed by the Kaplan-Meier method. Time to event curves between the two treatment groups will be compared with a log-rank test along with the corresponding hazard ratio. PFS rate and survival rate will be estimated along with the corresponding 95% CI.

[redacted]

8.2. Statistical Analyses

8.2.1. Standard Analyses

8.2.1.1. Subject 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.

8.2.1.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics such as patient age, sex, height, weight, ethnicity, prior therapy, medical history, ECOG performance status and screening LVEF results *will be tabulated and summarized using descriptive statistics.* These endpoints will be summarized descriptively by treatment group for the ITT population.

8.2.1.3. Study Treatment Exposure

Following endpoints will be summarized by treatment groups for both chemotherapy and bevacizumab-Pfizer/bevacizumab-EU:

- Duration of treatment: number of cycles.

8.2.1.4. Prior and Concomitant Medications

Collected prior and concomitant medications will be summarized by treatment group for the safety population.

8.2.2. Analyses of the Primary Efficacy Endpoint

The primary efficacy endpoint is the best objective response rate achieved by Week 19 and subsequently confirmed, based on the investigator reported assessment.

To assess the best overall response, the response from each patient at different time point (time point response) will need to be derived, based on the clustered investigator reported tumor assessments following the assessment window as presented in Appendix 1, unless it is certain that the tumor assessments were from different visits. The best overall response per patient will then 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. The following table presents some typical scenarios for deriving the best overall response.

[redacted]

Table 1. 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.

The primary analysis for this endpoint will be based on the Miettinen and Nurminen (1985)[4] method without strata. Estimated risk ratio and risk difference and the asymptotic 95% and 90% CI in ORR between bevacizumab-Pfizer and bevacizumab-EU will be computed. This analysis will be carried out by the BINOMIAL procedure in SAS (Appendix 3). The risk ratio, risk difference and its associated 95% and 90% CI will be used in the hypothesis test as described in Section 4. This analysis will be based on the ITT population. Same analysis based on PP population will also be performed as a sensitivity analysis.

The Miettinen and Nurminen method will also be carried out with additional stratification variables described in Section 6.2, to assess whether these factors will affect the risk ratio / risk difference of ORR between the 2 treatment groups. This analysis will be performed based on both ITT population. Reference SAS code is available in the appendix.

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

[redacted]

8.2.3. Analyses of the Secondary Efficacy Endpoint

For DOR, PFS and survival (time to death), a Cox proportional hazard models may be performed; the model will include treatment and the covariates specified in Section 6.2. The hazard ratios and the 95% CIs of the hazard ratios based on the model will be presented.

DOR

Duration of response (DOR) is defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of Progressive Disease (PD) or to death due to any cause in the absence of documented PD. Censoring for the DOR endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified and the patient does not die while on study. If no adequate disease assessment at baseline, the endpoint will be censored on the date of randomization with duration of 1 day. When a patient has missing tumor assessment(s) but remains as a CR or PR responder at the time of data analysis, the endpoint will be censored at the time of the last available tumor assessment where CR or PR is declared. *DOR will only be calculated for the subgroup of patients with a* confirmed *objective response* achieved by week 19 from ITT population*; same analysis will be repeated for PP population as a sensitivity analysis.*

The Kaplan-Meier method will be used to estimate the DOR rate at 1-year. The 2-sided 95% CIs of the rate using the Greenwood's formula will be reported. Kaplan-Meier curves will also be plotted for each of the two treatment group at 1-year together with a 2-sided log-rank test stratified by region, gender and smoking history (as specified in Section 6.2) to compare the DOR curve between the two treatment groups at 1-year. The Kaplan-Meier method will also be used to obtain the estimates of median DOR associated with each treatment group. The 2-sided 95% CIs for the 25^{th}, 50^{th} and 75^{th} percentiles of the DOR time using the Brookmeyer and Crowley method will be reported when estimable.

At the time of the first data cut off (Week 19 and confirmed at Week 25), all above mentioned analyses will be performed for secondary endpoints. The DOR endpoint will be censored based on the following algorithms:

- If a Patients last known, 1) to be alive, 2) not to have started new (non-protocol) anti-cancer treatment, and 3) to be progression-free, and who have a baseline and at least one on-study disease assessment, are censored at the date of the last objective disease assessment that verified lack of progressive disease (even if there is unacceptably long interval between the assessments).

- If no assessment of tumor progression is identified by the investigator assessment and the patient does not die, the endpoint will be censored on the date of the last available tumor assessment.

- If radiotherapy or surgery is used to manage any target lesion or the patient starts a new anti-cancer therapy prior to the documented PD, the endpoint will be censored on the date of the last available tumor assessment prior to the start of the new anti-cancer therapy.

[redacted].

Patients with documentation of progressive disease or death after an unacceptably long interval (> 14 weeks) since the last tumor assessment will be censored at the time of last objective assessment verifying lack of disease progression prior to the event.PFS and PFS Rates

PFS is defined as the time from date of randomization to first progression of disease (PD) or death due to any cause, whichever occurred first. The analysis of this endpoint will be based on ITT population and same analysis based on PP population will also be performed as a sensitivity analysis. The tumor assessment will be based on investigator assessment in accordance with RECIST 1.1. The PFS endpoint will be censored based on the following algorithms:

- If a Patients last known, 1) to be alive, 2) not to have started new (non-protocol) anti-cancer treatment, and 3) to be progression-free, and who have a baseline and at least one on-study disease assessment, are censored at the date of the last objective disease assessment that verified lack of disease progression (even if there is unacceptably long interval between the assessments).

- If no assessment of tumor progression is identified by the investigator assessment and the patient does not die, the endpoint will be censored on the date of the last available tumor assessment.

- If no evaluation of disease is performed after randomization, the endpoint will be censored on the date of randomization with duration of 1 day. (If patient died prior to the first scheduled disease assessment, death will be considered as an event).

- If radiotherapy or surgery is used to manage any target lesion or the patient starts a new anti-cancer therapy prior to the documented PD, the endpoint will be censored on the date of the last available tumor assessment prior to the start of the new therapy.

- Patients with documentation of progression or death after an unacceptably long interval (> 14 weeks) since the last tumor assessment will be censored at the time of last objective assessment verifying lack of disease progression prior to the event.

- If no adequate disease assessment at baseline, the endpoint will be censored on the date of randomization with duration of 1 day.

Similar analyses, as described for DOR, will be carried out for PFS.

Survival and Survival Rates

Survival *(time to death) is defined as the time from date of randomization to death due to any causes.* Patients will be censored for this endpoint on the date known alive. Date of last known alive could be determined from onset date of AE, concomitant medication or any other documented assessments. The Kaplan-Meier method will be used to estimate 1-year survival rates, the 2-sided 95% CIs of 1-year survival rate will also be reported. Kaplan-Meier curves will also be plotted for each of the two treatment group at 1-year

[redacted].

together with a 2-sided log-rank test stratified by region, gender and smoking history (as specified in Section 6.2) to compare the survival distribution between the 2 treatment groups at the three timepoints. The analysis will be carried out based on ITT population and same analysis will be repeated based on PP population as a sensitivity analysis.

8.2.4. Analyses of Pharmacokinetic Endpoints

The drug concentration-time data will be summarized by descriptive statistics (mean, standard deviation, 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.

Population PK assessment will be conducted using a nonlinear mixed effect modeling approach. All patients who are treated with bevacizumab-Pfizer or bevacizumab-EU, have no major protocol deviations that can influence the PK assessment and provide at least one post-dose drug concentration measurement will be included in the population PK analysis. A structural PK model based on prior information will be used. The population PK analysis will estimate typical value and variability for parameters including clearance (CL) and volume of distribution (Vd). Also, the influence of selected potential covariates on the PK parameters will be explored; the potential covariates to be explored will include drug product, selected demographics (eg, body weight, sex), and ADA status.

Details of the population PK data analysis will be reported in a Population Modeling Analysis Report that is separate from the Clinical Study Report.

8.2.5. Immunogenicity Assessment

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies will be summarized for each treatment. For patients 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 patients, the incidence of ADA observed in the planned study may differ from the incidence reported in historical clinical trials.

This analysis will be carried out with the safety population.

8.2.6. Safety Analyses

Patients who start treatment are assessed for toxicities up to at least 28 days after final dose of treatment or start of new anti-cancer therapy (whichever comes first). Toxicities observed beyond 28 days and recorded in the database per sponsor's agreement will be included in the summaries.

[redacted].

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

- Treatment emergent Adverse Events (TEAE), bevacizumab- related AE, Serious Adverse Events (SAE), and treatment related SAE;
- Adverse events leading to delays, dose reduction and permanent discontinuation;
- Echocardiogram (ECHO) or MUGA.

Treatment emergent adverse events (TEAE) is defined as any adverse event that occurs after the beginning of the study treatment (on or after Study Day 1) or any pre-existing adverse event that worsens after the beginning of the study treatment and at least 28 days after final dose of study treatment or start of new anticancer therapy (whichever comes first). Whether an adverse event is related to the study treatment will be determined by the investigator.

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

- Tier-1 events will be identified by the medical team on an ongoing basis and the final list of events will be determined before database lock. Frequency and percentage of patients with each treatment group, risk difference (RD), 95% CI on RD Tier-2 events will be those events that occur in >= 10% patients in at least one treatment group. The frequency and percentage of patients, RD and 95% CI of RD will be provided for each event.
- Tier-3 events will be all other events that are neither Tier-1 nor Tier-2. Only frequency and percentage of patients will be provided.

The 3-tier AE summary tables will be generated for all TEAEs and then for those that are related to the study treatment.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA)[6] to determine System Organ Class and Preferred Term. Common Terminology Criteria for Adverse Events (CTCAE)[7], version 4.03, will be used to grade severity. Adverse events 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.

Selected adverse events and syndromes will be summarized using grouped MedDRA codes in addition to presentation of individual AE preferred terms. Among these groupings will be the following categories of adverse events:

- Signs and symptoms of anaphylaxis will be captured and summarized in accordance with guidance provided by the *Second Symposium on the Definition of Anaphylaxis.*
- Clinically significant decrease in LVEF.

[redacted].

ECHO or MUGA will be summarized by treatment and visit. Change from baseline and percent change from baseline will be summarized by treatment and visit for selected continuous variables. Baseline is Day 1 and if Day 1 value is missing, the closest measurement prior to Day 1 will be used.

Shift tables of baseline against each post-baseline visit may *be provided for selected laboratory tests to examine the distribution of laboratory toxicities.*

Physical examination at screening phase will be collected in the CRF and will be listed in a data listing. Vital signs will be presented in listing format only.

Patient listings will be produced for all safety endpoints.

[redacted]

9. REFERENCE

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6. http://www.meddra.org/

7. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). In: Version 4. NIH Publication No. 09-5410. Washington, DC; 2010: 194 pages.

[redacted].

10. 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 2 will be used to cluster the assessments.

Table 2. 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

[redacted].

Appendix 2. Summary of Key Efficacy Analyses

The key efficacy analyses are summarized in.

Table 3. Summary of Key efficacy analysis

Endpoint	Analysis Set	Statistical Method	Covariates	Missing Data	Analyses type
ORR	ITT	Miettinen and Nurminen without strata	Treatment	Non-responder imputation	Primary analysis
ORR	PP	Miettinen and Nurminen without strata	Treatment	Non-responder imputation	Sensitivity analysis
ORR	ITT	Miettinen and Nurminen with strata	Treatment and other covariates	Non-responder imputation	Secondary analysis
ORR	PP	Miettinen and Nurminen with strata	Treatment and other covariates	Non-responder imputation	Secondary analysis
DOR	ITT	Kaplan-Meier	Treatment	Censoring	Secondary analysis
DOR	PP	Kaplan-Meier	Treatment	Censoring	Secondary analysis
PFS	ITT	Kaplan-Meier	Treatment	Censoring	Secondary analysis
PFS	PP	Kaplan-Meier	Treatment	Censoring	Secondary analysis
Survival	ITT	Kaplan-Meier	Treatment	Censoring	Secondary analysis
Survival	PP	Kaplan-Meier	Treatment	Censoring	Secondary analysis

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=1.37;
        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 95% CI:

```
proc binomial data=test alpha=0.95;
        eqv/as diff margin=0.13;
        po group;
        ou resp;
        weight count;
run;
quit;
```


[redacted].

Appendix 4. Sample Code for the Miettinen and Nurminen Method With Strata

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;
```


[redacted].

```
/* 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;
```


[redacted]

```
 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;
```


[redacted].

```
        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;
```


[redacted].

```
            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);
```


[redacted].

```
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) */
```


[redacted].

```
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;
```


[redacted].

```
/*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;
```


[redacted].

```
        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);
```


[redacted].

Appendix 5. Sample Code for DOR, PFS and Survival

Analysis dataset event derivations

CNSR = 0 for patients who have an Event, and a value of 1 for patients who were censored.
AVAL is in weeks. AVAL is derived as: [ADT (date of event) – RANDDT +1] / 7 for patients with events where RANDDT is randomization date.

SAS code analogous to the following will be used:

```
proc lifetest data = adtte outsurv=survpl alpha=0.05 alphaqt=0.05;
    where aval ne . and cnsr ne . and trtpn ne .;
    strata trtpn;
    time aval * cnsr(1);
run;
quit;
```

The Kaplan-Meier Estimate of PFS at 25 weeks and 55 weeks will be derived using the TIMELIST= option in PROC LIFETEST

```
proc phreg data = adtte;
   where aval ne . and cnsr ne . and trtpn ne . and strata1 ne . and strata2 ne .;
   model aval * cnsr(1) = trtpn / alpha = 0.05 rl ties= efron;
   strata strata1 strata2;
run ;
quit;

proc lifetest data=adtte ;
    where aval ne . and cnsr ne . and trtpn ne . and strata1 ne . and strata2 ne .;
    time aval * cnsr(1);
    strata strata1 strata2/ group=trtpn;
run;
quit;
```