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COMPOUND NUMBER: PF-06439535

PROTOCOL NO.: B7391003

PROTOCOL TITLE: 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

Study Centers: A total of 159 centers randomized patients into the study: Australia (3), Brazil (11), Bulgaria (1), Chile (3), Croatia (1)**,** Czech Republic (3), France (4), Germany (13), Greece (8), Hungary (7), India (5), Italy (3), Japan (13), Korea (4), Malaysia (2), Netherlands (2), Philippines (2), Poland (9), Romania (7), Russian Federation (17), South Africa (3), Spain (6), Taiwan (1), Thailand (5), Turkey (9), Ukraine (10), and United States (US) (7).

Study Initiation Date and Primary Completion or Final Completion Dates: 20 April 2015 (First Subject First Visit), 08 May 2017 (Primary Completion Date), 22 December 2017 (Last Subject Last Visit).

Phase of Development:

Phase 3

Study Objectives:

Primary Objective

- To compare the confirmed objective response rate (ORR) by Week 19 following treatment with PF-06439535 in combination with paclitaxel and carboplatin to bevacizumab-European Union (EU) plus paclitaxel and carboplatin in patients who had not received previous treatment for advanced non-small cell lung cancer (NSCLC).

Secondary Objectives

- To evaluate the safety of PF-06439535 plus paclitaxel and carboplatin and bevacizumab-EU plus paclitaxel and carboplatin;
- To evaluate secondary measures of tumor control;
- To evaluate the population pharmacokinetics (PK) of PF-06439535 and bevacizumab-EU;
- To evaluate the immunogenicity of PF-06439535 and bevacizumab-EU.

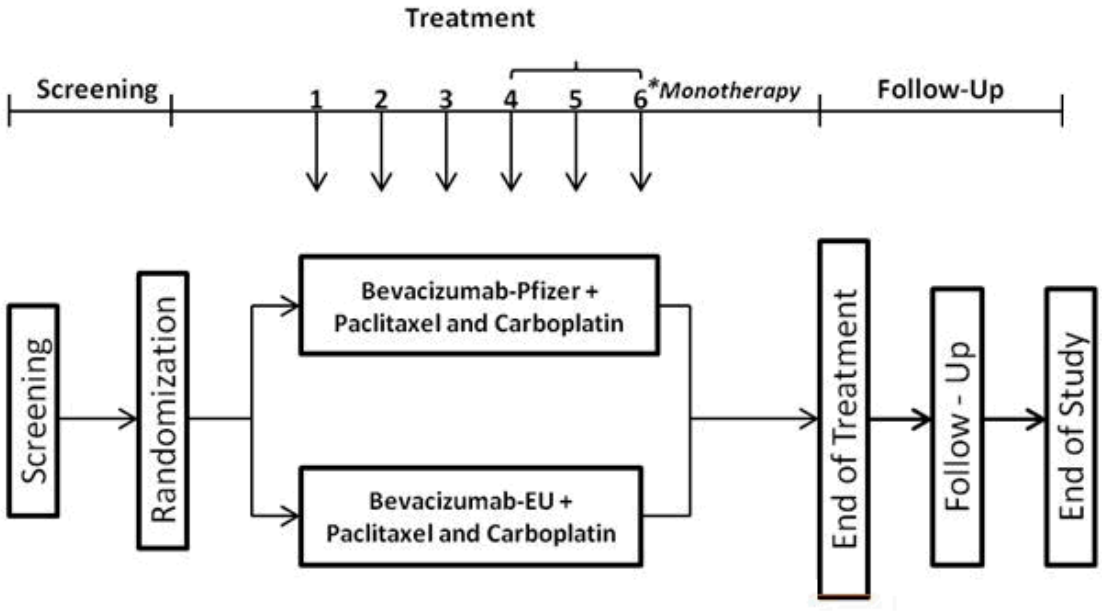
METHODS

Study Design:

This study was a multinational, double-blind, randomized, parallel-group Phase 3 clinical trial comparing the efficacy and safety of PF-06439535 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 were planned to be enrolled in each treatment arm for a total of approximately 710 patients at over 300 centers; up to approximately 10% additional patients may have been enrolled due to operational/logistical considerations. Patients were randomized (1:1) to receive at least 4 cycles and no more than 6 cycles of either PF-06439535 plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin, followed by the previously assigned blinded bevacizumab monotherapy. Randomization was stratified by region (according to the location of the drug depot supplying the site), sex (male/female) and smoking history (never/ever). The estimated duration of study participation was approximately 1 year. Last subject last visit (LSLV) was defined as up to 1 year from randomization of the last patient (End of Treatment) plus 28-day follow-up. The study was considered complete (End of Study) when the last patient had completed the LSLV. See study schema (Figure 1) for details.

Figure 1. Study Schema



Bevacizumab-Pfizer stands for PF-06439535.
Abbreviation: EU=European Union.
* Assigned bevacizumab monotherapy: Following completion of at least 4 cycles and no more than 6 cycles of chemotherapy.

The schedule of activities (SOA) is presented in Table 1.

Table 1. Schedule of Activities

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Protocol Activity/Cycle (1 Cycle=21 days)	**Screening**	**Treatment Period (Combination Therapy)** Blinded bevacizumab with chemotherapy						**Treatment Period (Monotherapy)** Blinded bevacizumab	**Treatment Period (Monotherapy)** Blinded bevacizumab	**End of Treatment/ Withdrawals[2]**
	≤28 days prior to randomization	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Through Cycle 17** (Up to week 52)	**Cycle 18+** 1 year post-randomization[1]	
Study Visit Window (Days)	**-4**	**0**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**
Pre-treatment Documentation										
Informed consent[3]	X									
Demography, medical/cancer history, mutation status[4]	X									
Complete physical examination[5]	X									
Brief physical examination[6]		X	X	X	X	X	X	X	Per local standard of care	X
Vital signs[7]	X	X	X	X	X	X	X	X	Per local standard of care	X
Baseline signs and symptoms[8]		X							Per local standard of care	
ECOG performance status	X	X	X	X	X	X	X	X	Per local standard of care	X
Inclusion/exclusion criteria[9]	X									
Laboratory Studies and Tests										
Hematology[10]	X	X	X	X	X	X	X	X	Per local standard of care	X
Blood chemistry[11]	X	X	X	X	X	X	X	X	Per local standard of care	X
Coagulation[12]	X								Per local standard of care	X
Pregnancy test[13]	(X)[13]	X	X	X	X	X	X	X	Per local standard of care	X
Urinalysis[14]	X	X	X	X	X	X	X	X	Per local standard of care	X
Serological tests[15]	(X)									
Immunogenicity (ADA/NAb)[16]		X	X	X	X		X	X		X
Pharmacokinetics[17]		X	X	X	X	X	X	X		X

Table 1. Schedule of Activities (Continued)

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Protocol Activity/Cycle (1 Cycle=21 days)	**Screening**	**Treatment Period (Combination Therapy)** Blinded bevacizumab with chemotherapy						**Treatment Period (Monotherapy)** Blinded bevacizumab	**Treatment Period (Monotherapy)** Blinded bevacizumab	**End of Treatment/ Withdrawals[2]**
	≤28 days prior to randomization	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Through Cycle 17** (Up to week 52)	**Cycle 18+** 1 year post-randomization[1]	
Study Visit Window (Days)	**-4**	**0**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±7**
Tumor Assessments										
Brain scan[18]	X	As clinically indicated and at time of confirmatory scan for PR/CR							Per local standard of care	
CT or MRI of chest, abdomen, and other disease sites[18]	X	Every 6 weeks (±7 days) until Week 25 (based on date of randomization); After Week 25, every 9 weeks (±7 days) until 1 year from randomization							Per local standard of care	X
Randomization										
Randomization[19]		X								
Drug Administration										
Paclitaxel and carboplatin[20]		X	X	X	X	Optional	Optional			
Blinded bevacizumab[21]		X	X	X	X	X	X	X	X	
Other Clinical Assessments										
12-lead ECG[22]	X									X
MUGA or ECHO[23]	X									X
Contraception check[24]	X	X	X	X	X	X	X	X	Per local standard of care	X
AEs[25]	X	Monitored continuously								
Prior medications/treatments[26]	X									
Concomitant treatments[27]		Monitored continuously								
Survival follow-up[28]		Every 2 months (±14 days) from last study drug administration								

Abbreviations: ADA=anti-drug antibody, AE=adverse event, ALK=anaplastic lymphoma kinase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CR=complete response, CRF=case report form, CT=computed tomography, ECG=electrocardiogram, ECHO=echocardiogram, ECOG=Eastern Cooperative Oncology Group, EGFR=epidermal growth factor receptor, EML4=echinoderm microtubule-associated protein-like 4, INR=international normalized ratio, LVEF=left ventricular ejection fraction, MRI=magnetic resonance imaging, MUGA=multi gated acquisition scan, NAb=neutralizing antibody, PK=pharmacokinetic(s), PR=partial response, SAE=serious adverse event.

Table 1. Schedule of Activities (Continued)

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1. One (1) year post-randomization: Patients who continued to receive study treatment after 1 year had assessments performed according to local standard of care; reduced data collection, although tumor assessment and safety data collection were required.
2. End of Treatment/withdrawals: When patients discontinued all study treatment, patients were require to be evaluated 28 (+7) days after last dose or prior to the start of new anti-cancer therapy if initiated within 28 days after the last dose.
3. Informed consent: Had to be obtained prior to undergoing any study specific procedure and could occur prior to the 28-day screening period.
4. Demographics and medical/cancer history: Included information on prior anti-tumor regimens (including chemotherapy and radiation therapy and duration of treatment), mutation test results, if known, and progression or relapse date. Testing for mutations was not required, however, patient records were reviewed for known sensitizing EGFR mutations (for example, exon 19 deletion or exon 21 L858R) or EML4-ALK translocation positive mutations. If mutation testing was performed, samples were required to be tested by local approved laboratories, and the results were required to be reviewed and confirmed as negative for mutations prior to randomization.
5. Physical examination: Included head, ears, eyes, nose, mouth, skin, neck, heart and lung examinations, lymph nodes, abdomen, musculoskeletal, neurological systems, and weight. Height was recorded at Screening only. Genitourinary examination was only required if directed by signs or symptoms.
6. Brief physical examination: Performed as directed by signs and symptoms on Day 1 (pre-dose) of each cycle after Screening.
7. Vital signs: Temperature was required to be taken using the same method throughout the study. Blood pressure, heart rate, and respiratory rate were required to be taken with the patient in the supine or sitting position after the patient had been resting quietly for at least 5 minutes and prior to dosing on dosing days. Weight was required to be taken at the beginning of each cycle and was to be used for dose calculation. On days of an infusion, vital signs were required to be taken within 30 minutes before the first infusion and within 30 minutes of the end of the last infusion.
8. Baseline signs and symptoms: Observed after Screening and before Cycle 1, Day 1 pre-dose were recorded as part of medical history or as brief physical examination findings.
9. Inclusion/exclusion criteria: Eligibility criteria were reviewed to confirm eligibility prior to randomization.
10. Hematology: Tests included hemoglobin, white blood cells, platelets, and absolute neutrophil count. Results of tests had to be reviewed prior to each cycle of therapy.
11. Chemistry: Tests included ALT, AST, alkaline phosphatase, total bilirubin, serum or plasma creatinine, sodium, potassium, total calcium, BUN or urea, magnesium, and albumin, and results had to be reviewed prior to each cycle of therapy.
12. Coagulation: Tests included INR for prothrombin time (or prothrombin time if INR was not available) and activated partial thromboplastin time. Tests may have been performed more frequently if clinically indicated. Results of tests had to be reviewed prior to dosing on Cycle 1 Day 1.
13. Pregnancy test: For female patients of childbearing potential, a serum or urine pregnancy test with sensitivity of at least 25 mIU/mL was performed by the local certified laboratory, and 2 negative tests were required before receiving the first dose of investigational product. The second negative test was required to be done during the first 5 days of the menstrual period, immediately preceding the first dose of any study treatment.
14. Urinalysis: If the results of the dipstick urine protein indicated ≥2+ proteinuria, follow-up was required to be performed with a quantitative urine protein analysis according to local standard practices with data captured on the AE CRF if AE criteria were met. The results of the dipstick had to be reviewed prior to each cycle of therapy.
15. Serological tests (optional): If testing was performed, samples had to be tested by local approved laboratories, and the results had to be reviewed and eligibility confirmed prior to randomization.
16. Immunogenicity: Blood sampling for ADA/NAb prior to blinded bevacizumab. If AEs were considered possibly related to ADA formation, an additional sample may have been collected at the time of the immunogenicity-related AEs.
17. PK: Blood sampling for drug concentration prior to blinded bevacizumab. Post-dose samples were also collected at 1 hour (±0.5 hour) after the end of blinded bevacizumab for Cycles 1 and 5 (if patient received Cycle 5). If ADA/NAb sampling was conducted at the time of immunogenicity related AEs, a serum sample for drug concentration was also collected at that same time point.

Table 1. Schedule of Activities (Continued)

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18. Tumor assessments: Assessments had to include CT with contrast or MRI of head, chest, abdomen (including adrenals) and other disease sites such as pelvis if clinically indicated. Tumor assessments were not scheduled based on cycle length or number of cycles received. Assessment delay to conform to treatment delays was not permitted. The same method of tumor assessments was to be used throughout the trial. A confirmatory scan was required approximately 6 weeks (+7 days) for a CR/PR.
19. Randomization: Unless clinically indicated, screening physical examination and laboratory assessments including blood chemistry, hematology, and urinalysis, were not required to be repeated for randomization if they were performed ≤7 days prior to Cycle 1, Day 1, and results met eligibility criteria. Eligibility criteria were reviewed and Sponsor confirmation of eligibility must have been received prior to randomization. Randomization was required on Day 1 of first dose (but no more than 1 day prior).
20. Paclitaxel and carboplatin administration: Per dosing algorithm for a total of at least 4 cycles and no more than 6 cycles. Premedication was to be administered according to the local label or institutional guidelines. Dose delay (up to 2 weeks) and dose reduction were permitted per local guidelines.
21. Blinded bevacizumab: 15 mg/kg by intravenous infusion on Day 1 of each of the 3-week (21-day) cycles.
22. ECG: 12-lead ECG was obtained at Screening, as clinically indicated, and at the End of Treatment Visit.
23. MUGA or ECHO: To assess LVEF; the original methodology used for each patient had to be used throughout the trial.
24. Contraception check: Male patients who were able to father children and female patients who were of childbearing potential needed to affirm that they met the criteria for correct use of 2 of the selected methods of contraception.
25. AEs: Patients had to be followed for AEs from the first day of study treatment through the patient's last visit and at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable", whichever was later as assessed by the investigator. SAEs were required to be monitored and reported from the time that the patient provided informed consent through and including 28 calendar days after the last study treatment. SAEs considered related to study treatments were to be reported whenever they occurred even after 28 days after the last study treatment.
26. Prior medication/treatments: Medications and non-drug treatments delivered prior to initial dosing were recorded from 28 days prior to the start of study treatment.
27. Concomitant treatments: Recorded from initial dosing and monitored continuously by the investigator until at least 28 days following the last dose of study treatment to coincide with the safety evaluation period. Patients discontinuing the active treatment phase were to enter the follow-up phase during which survival and new anti-cancer therapy information were to be collected until the study was completed or was terminated early.
28. Survival follow-up: After discontinuation from treatment, survival status was to be collected by telephone contact every 2 months (±14 days) until death or 1 year from patient randomization.

Number of Patients (Planned and Analyzed): Approximately 355 patients were planned to be enrolled in each treatment arm for a total of approximately 710 patients; up to approximately 10% additional patients may have been enrolled due to operational/logistical considerations.

Overall, a total of 719 patients were randomized to the study, 358 patients to the PF-06439535 group and 361 patients to the bevacizumab-EU group. Of these, 714 patients received at least 1 dose of study drug or chemotherapy, 356 patients were assigned to the PF-06439535 group and 358 patients were assigned to the bevacizumab-EU group.

Diagnosis and Main Criteria for Inclusion and Exclusion: Male and female patients ≥18 years of age, or ≥age of consent in the region, who had histologically or cytologically confirmed diagnosis of predominately non-squamous NSCLC and newly diagnosed Stage IIIB or IV NSCLC (according to Revised International System for Staging Lung Cancer Criteria of 2010) or recurrent NSCLC were eligible to participate in the study. Patients who had 1) small cell lung cancer (SCLC) or combination of SCLC and NSCLC, squamous-cell tumors and mixed adenosquamous carcinomas of predominantly squamous nature, 2) evidence of a tumor that compressed or invaded major blood vessels or tumor cavitation that was likely to bleed, 3) known sensitizing epidermal growth factor receptor (EGFR) mutations (for example, exon 19 deletion or exon 21 L858R) or echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) translocation positive mutations, 4) prior systemic therapy for NSCLC (except for neoadjuvant or adjuvant therapy prior to surgical resection for primary disease), were ineligible to participate in this study.

Study Treatment: On treatment days when both bevacizumab and paclitaxel-carboplatin were administered, the order of administration was: 1) paclitaxel, 2) carboplatin, 3) bevacizumab. Bevacizumab monotherapy was administered following completion of at least 4 cycles and no more than 6 cycles of chemotherapy.

Premedication to ameliorate the toxicities associated with the chemotherapy were to be administered according to the local label or institutional guidelines.

Paclitaxel:

Following premedication, paclitaxel was administered as the first drug when chemotherapy was administered. Paclitaxel at a dose of 200 mg/m^2 was administered by intravenous (IV) infusion over 3 hours on Day 1 in each cycle (21-day cycle). In the absence of progressive disease (PD), patients received paclitaxel treatment for at least 4 cycles but no more than 6 cycles. Dose reduction for toxicity was allowed.

Carboplatin:

Carboplatin was administered by IV infusion over a minimum of 15 minutes, and could be administered immediately after the paclitaxel infusion had completed. Patients were administered carboplatin for at least 4 cycles and no more than 6 cycles. Dose reduction for toxicity was allowed.

Bevacizumab:

Blinded bevacizumab was administered once at the start of every 21-day cycle. The initial dose was 15 mg/kg delivered over 90 minutes as an IV infusion. If the first infusion was well tolerated, the second infusion may have been administered over 60 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions may have been administered over 30 minutes. If during the shortened infusions, infusion related reactions (IRRs) occurred, the duration of the infusion could be increased at the discretion of the investigator. For the infusion of bevacizumab in patients over 110 kg, the dilution volume and infusion time were to be increased. The concentration of bevacizumab solution was required to be kept within the range of 1.4 mg/mL to 16.50 mg/mL.

Infusions were not allowed to be administered as an IV push or bolus injection. Infusions were not allowed to be administered or mixed with dextrose solutions.

Assigned blinded bevacizumab monotherapy could be administered after chemotherapy had been discontinued until Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 defined disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred, or End of Treatment, whichever came first.

Efficacy, Safety, Pharmacokinetic and Immunogenicity Endpoints:

Efficacy Endpoints:

The primary efficacy endpoint is:

- ORR, evaluating the best response achieved by Week 19 and subsequently confirmed by 6 weeks thereafter, in accordance with RECIST version 1.1.

The secondary efficacy endpoints are:

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

PK Endpoints:

The secondary PK endpoints are:

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

Immunogenicity Endpoints:

The secondary immunogenicity endpoints are:

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

Safety Endpoints:

The secondary safety endpoints are:

- Safety characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events, including cardiotoxicity and infusion-related reactions, and laboratory abnormalities at 1 year from randomization.

Safety Evaluations:

Safety evaluations were assessed by adverse event (AE) and serious adverse event (SAE) monitoring, clinical safety laboratory assessments, vital signs, physical examinations, and 12-lead electrocardiogram (ECG) monitoring.

Statistical Methods:

Efficacy:

Analysis Populations:

The Intent-to-Treat (ITT) population was defined as all patients who were randomized to study treatment. The ITT population was used for patient accountability and all efficacy analyses.

The Per-Protocol (PP) population was defined as all patients who were randomized and received the study treatment (PF-06439535 or bevacizumab-EU) as planned and had no major protocol deviations. The PP population was used for sensitivity analyses of the primary and secondary endpoints.

Analyses of the Primary Efficacy Endpoint:

The two 1-sided hypotheses were tested in this study for ORR in order to show that PF-06439535 was equivalent to bevacizumab-EU.

For the US Food and Drug Administration (FDA), equivalence was considered established if the 90% confidence interval (CI) of the risk ratio falls into the margins of (0.73, 1.37).

For Japan Pharmaceuticals and Medical Devices Agency (PMDA), equivalence was considered established if the 95% CI of the risk ratio falls into the margins of (0.729, 1.371).

For the EU European Medicines Authority (EMA), equivalence was considered established if the 95% CI of the risk difference falls into the margins of (-13%, 13%).

The primary efficacy analysis for the primary endpoint in the ITT population was based on the Miettinen and Nurminen (1985) method without strata. Estimated risk ratio and risk difference and the asymptotic 95% and 90% CIs in ORR between PF-06439535 and bevacizumab-EU were computed. These values were used to determine equivalence based on the criteria defined above.

The same analysis based on PP population was also performed as a sensitivity analysis.

Descriptive statistics (frequency and percentage) for complete response (CR), partial response (PR), and ORR were presented by treatment group, with 95% CI being determined based on the F-distribution.

Analyses of the Secondary Efficacy Endpoints

For PFS, survival (time to death), and DOR, a Cox proportional hazard model was used for analysis; the model included treatment and the covariates (region, gender and smoking history). The hazard ratios and the 95% CIs of the hazard ratios based on the model were presented.

All analyses described in this section were performed with the ITT population. As sensitivity analyses, these analyses were also repeated with the PP population.

- Duration of Response (DOR)

DOR was defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of PD or to death due to any cause in the absence of documented PD. DOR was only calculated for the subgroup of patients with a confirmed objective response achieved by Week 19 from ITT population, the same analysis was repeated for PP population as a sensitivity analysis.

Censoring for the DOR endpoint was assigned on the date of the last tumor assessment if no assessment of tumor progression was identified and the patient did not die while on study. If there was no adequate disease assessment at baseline, the endpoint was to be censored on the date of randomization with duration of 1 day. When a patient had missing tumor assessment(s) but remained as a CR or PR responder at the time of data analysis, the endpoint was to be censored at the time of the last available tumor assessment where CR or PR was declared.

The Kaplan-Meier method was used to estimate the DOR rate at 1-year. The 2-sided 95% CIs of the rate using the Greenwood's formula was reported. Kaplan-Meier curves were also plotted for each of the 2 treatment groups at 1-year together with a 2-sided log-rank test stratified by region, gender and smoking history to compare the DOR curve between the 2 treatment groups at 1-year. The Kaplan-Meier method was also 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 were to be reported when estimable.

- Progression-free Survival (PFS) and PFS Rates

PFS was defined as the time from date of randomization to first progression of disease or death due to any cause, whichever occurred first. The tumor assessment was based on investigator assessment in accordance with RECIST version 1.1.

Similar Kaplan-Meier analyses, as described for DOR, were carried out for PFS.

- Survival and Survival Rates

Survival (time to death) was defined as the time from date of randomization to death due to any causes. Patients were censored for this endpoint on the date last known alive. Date of last known alive could be determined from survival follow-up data, onset date of AE, concomitant medication or any other documented assessments. The Kaplan-Meier method was used to estimate 1-year survival rates, the 2-sided 95% CIs of 1-year survival rate was also reported. Kaplan-Meier curves were also plotted for each of the 2 treatment groups at 1-year together with a 2-sided log-rank test stratified by region, gender and smoking history to compare the survival distribution between the 2 treatment groups at the 3 time points.

Safety:

The safety population was defined as all patients who were randomized and received at least 1 dose of study treatment. Safety evaluations were summarized in accordance with sponsor's reporting standards.

Pharmacokinetics:

Patients in the PP population who had at least 1 drug concentration measurement post administration of treatment were included in the PK analysis.

The drug concentration-time data were summarized by descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum) according to treatment. A listing of all concentrations sorted by treatment, patient identification number (ID) and nominal time post-dose was generated. The concentration listing also included the actual sampling times. Deviations from the nominal time were given in a separate listing.

Immunogenicity:

The safety population was used for ADA and NAb analyses. The percentage of patients with positive ADA and NAb was summarized for each treatment and each visit. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response were also described, if data permitted.

RESULTS

Patient Disposition and Demography:

The ITT population was comprised of 719 patients who were randomized to double-blind treatment, 358 patients to the PF-06439535 group and 361 patients to the bevacizumab-EU group (Table 2). Of these, 714 patients were included in the safety population and received at least 1 dose of study drug or chemotherapy, 356 patients were assigned to the PF-06439535 group and 358 patients were assigned to the bevacizumab-EU group.
Five (5) patients did not receive any blinded bevacizumab and paclitaxel/carboplatin, including 2 patients randomized to the PF-06439535 group, and 3 patients randomized to the bevacizumab-EU group.

Efficacy evaluations were performed using the ITT population (the primary population). The PP population was used for sensitivity analyses of the primary and secondary efficacy endpoints. PK parameters were analyzed using the PK population. The safety population was used for all safety endpoints, including ADA and NAb analyses. There were comparable numbers of patients in the 2 treatment groups.

Table 2. Patient Disposition

Number (%) of Patients	PF-06439535	Bevacizumab-EU	Total
Randomized[a]	358	361	719
Treated	356 (99.4)	358 (99.2)	714 (99.3)
Study			
Discontinued	356 (99.4)	358 (99.2)	714 (99.3)
Randomized not treated	2 (0.6)	3 (0.8)	5 (0.7)
Treatment			
Discontinued[b]	356 (99.4)	358 (99.2)	714 (99.3)
Analyzed for efficacy			
ITT population	358 (100.0)	361 (100.0)	719 (100.0)
PP population	351 (98.0)	355 (98.3)	706 (98.2)
PK population	351 (98.0)	354 (98.1)	705 (98.1)
Analyzed for safety			
Safety population[c]	356 (99.4)	358 (99.2)	714 (99.3)
AEs	356 (100.0)	358 (100.0)	714 (100.0)
Laboratory data	342 (96.1)	348 (97.2)	690 (96.6)

Abbreviations: AE=adverse event, EU=European Union, ITT=Intent-to-Treat, PK=pharmacokinetic, PP=Per-Protocol.

a. The number of randomized patients was used as the denominator for percentages except for safety data.
b. Treatment was defined as all 3 agents (blinded bevacizumab, paclitaxel and carboplatin).
c. The number of safety population was used as the denominator for percentages of AEs and laboratory data.

Of the 719 patients randomized to the study, 467 were male and 252 were female. The mean (SD) age was 61.3 (9.2) years, 58.4% were 45 to 64 years of age, 36.6% were ≥65 years of age, and the remaining 5.0% were 18 to 44 years of age. The majority of patients were of White race (88.7%), 10.6% were of Asian race and included patients from the Indian subcontinent, China, Japan and Korea.

Histopathological classifications for the primary diagnosis of the 719 randomized patients were adenocarcinoma (699 [97.2%] patients), large cell carcinoma (11 [1.5%] patients), mixed adenocarcinoma (7 [1.0%] patients), and other (2 [0.3%] patients including 1 neuroendocrine carcinoma and 1 other-non-squamous NSCLC). The majority of patients had newly diagnosed Stage IV disease and 13.2% of patients presented at Screening with recurrent disease. Of the 719 patients who were randomized to the study, 129 (17.9%) patients had received prior resection of primary disease (not including biopsies), 35 (4.9%) patients had received prior systemic therapy, and 47 (6.5%) patients had received prior

radiation therapy, for their primary diagnosis, which were comparable for both treatment groups. Of the 719 patients who were randomized to the study, the most common previous systemic therapies were cisplatin (28 [3.9%] patients) and vinorelbine (20 [2.8%] patients), both of which were reported with comparable proportions in the 2 treatment groups. The most frequently reported histology classification was adenocarcinoma (348 [97.2%] and 351 [97.2%] patients for the PF-06439535 and bevacizumab-EU groups, respectively), and the median duration of disease since primary diagnosis of NSCLC was 1.2 months (range: 0.2 to 210.9 months) and 1.3 months (range: 0.1 to 137.9 months) for the PF-06439535 and bevacizumab-EU groups, respectively.

Efficacy, Pharmacokinetic, and Immunogenicity Results:

Primary Efficacy Endpoint:

The primary efficacy endpoint of the study was ORR defined as the percent of patients within each treatment group who achieved a best overall response (BOR) of CR or PR by Week 19, in accordance with RECIST version 1.1, and subsequently confirmed on a follow-up tumor assessment by Week 25. The primary endpoint of ORR was based on the Sponsor's derived BOR using tumor measurements reported by the investigator in the case report form (CRF).

A summary of the BOR and ORR for the ITT population is provided in Table 3. In the PF-06439535 treatment group, 9 patients (2.5%) had CR, 153 patients (42.7%) had PR, 154 patients (43.0%) had stable disease, and 15 patients (4.2%) had PD. In the bevacizumab-EU treatment group, the corresponding numbers of patients were 4 (1.1%) had CR, 157 (43.5%) had PR, 167 (46.3%) had stable disease, and 14 (3.9%) had PD. Overall, 46 patients (6.4%) were considered not evaluable for response (27 [7.5%] and 19 [5.3%] in the PF-06439535 and bevacizumab-EU groups, respectively) due to early death, unevaluable tumor assessment, or early study discontinuations, and were treated as non-responders in the ORR calculation.

Similarity between PF-06439535 and bevacizumab-EU was statistically demonstrated for the primary efficacy endpoint, ORR, based on the pre-specified criteria for each of the 3 Health Authorities. The analysis of ORR showed an un-stratified risk ratio of 1.0146 (PF-06439535 versus bevacizumab-EU), with a 95% CI of (0.8628, 1.1933) and a 90% CI of (0.8856, 1.1625), and an un-stratified risk difference of 0.6531% (PF-06439535 versus bevacizumab-EU), with a 95% CI of (-6.6080%, 7.9082%), all of which fell entirely within the equivalence margins.

The BOR distribution and the analysis of ORR for patients in the PP population were consistent with that of the ITT population.

Table 3. Summary of Best Overall Response and ORR (Week 19) (Unstratified) - ITT Population

	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Best overall response, n (%)			
Complete response (CR)	9 (2.5)	4 (1.1)	13 (1.8)
Partial response (PR)	153 (42.7)	157 (43.5)	310 (43.1)
Stable disease	154 (43.0)	167 (46.3)	321 (44.6)
Progressive disease	15 (4.2)	14 (3.9)	29 (4.0)
Not evaluable[a]	27 (7.5)	19 (5.3)	46 (6.4)
Objective response rate (CR + PR), n (%)	162 (45.3)	161 (44.6)	323 (44.9)
95% exact CI[b]	(40.01, 50.57)	(39.40, 49.89)	(41.25, 48.64)
Treatment comparison (versus bevacizumab-EU)			
Un-stratified risk difference in ORR (%)[c]	0.6531		
95% CI of difference (%)[c]	(-6.6080, 7.9082)		
Treatment comparison (versus bevacizumab-EU)			
Un-stratified risk ratio[d]	1.0146		
95% CI of risk ratio[d]	(0.8628, 1.1933)		
90% CI of risk ratio[d]	(0.8856, 1.1625)		

ORR was defined as the percentage of patients within each treatment group who achieved complete response or partial response by Week 19 of the study in accordance with RECIST version 1.1 which was subsequently confirmed by Week 25.
Abbreviations: CI=confidence interval, CR=complete response, EMA=European Medicines Authority, EU=European Union, FDA=Food and Drug Administration, ITT=Intent-to-Treat, n/N=number of patients with observation/total number of patients, ORR=objective response rate, PMDA=Pharmaceuticals and Medical Devices Agency, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors, US=United States.

a. Not evaluable: Early death, unevaluable tumor assessment, and early study discontinuations.
b. Exact method based on F-distribution was used.
c. Calculated based on 2-sided Miettinen and Nurminen method without strata for risk difference for confirmed response. EU EMA equivalence margins (95% CI in -13% to 13%).
d. Calculated based on 2-sided Miettinen and Nurminen method without strata for risk ratio for confirmed response. US FDA equivalence margins (90% CI in 0.73 to 1.37) and Japan PMDA equivalence margins (95% CI in 0.729 to 1.371).

Secondary Efficacy Endpoints:

Duration of Response (DOR)

The percentage of all patients who achieved objective response (CR or PR) by Week 19 and subsequently confirmed by Week 25 in the ITT population was comparable between the 2 treatment groups (162 [45.3%] patients in the PF-06439535 group compared with 161 [44.6 %] patients in the bevacizumab-EU group) (Table 3). The probability of not having subsequent progression or death at Week 55 after a confirmed objective response was 32.0% (95% CI: 24.2%, 40.1%) in the PF-06439535 group, and 30.7% (95% CI: 23.2%, 38.6%) in the bevacizumab-EU group (Table 4).

Using a Cox proportional hazards model with region, sex and smoking history as strata, the hazard ratio when comparing DOR between PF-06439535 and bevacizumab-EU was 0.800, with a 95% CI of (0.608, 1.051). The stratified log-rank test resulted in a 2-sided p-value of 0.1077 indicating no statistically significant difference between the 2 treatment groups (Table 4).

The analysis of DOR for patients in the PP population showed consistent results to that of the primary ITT population.

Table 4. Duration of Objective Response (Week 55) - Patients in ITT Population Who Had an Objective Response Achieved by Week 19

Number (%) of Patients	PF-06439535 (N=162)	Bevacizumab-EU (N=161)	Total (N=323)
Patients with event	107 (66.0)	119 (73.9)	226 (70.0)
Type of event			
Progressive disease	101 (62.3)	110 (68.3)	211 (65.3)
Death	6 (3.7)	9 (5.6)	15 (4.6)
Number censored	55 (34.0)	42 (26.1)	97 (30.0)
Probability of being event free (95% CI[a]) at 55 weeks	0.320 (0.242, 0.401)	0.307 (0.232, 0.386)	0.315 (0.261, 0.371)
Kaplan-Meier estimates of time to event (weeks) Quartiles (95% CI)[b]			
Q1	25.3 (20.7, 27.1)	18.7 (17.9, 21.3)	21.3 (18.7, 24.4)
Median	36.3 (31.6, 43.6)	28.7 (27.0, 36.3)	35.9 (28.7, 36.6)
Q3	69.1 (55.0, 86.1)	62.1 (51.3, 76.6)	65.6 (58.1, 76.6)
Stratified analysis[c]			
Comparison versus bevacizumab-EU			
Hazard ratio[d]	0.800		
95% CI[d]	0.608, 1.051		
2-sided p-value[e]	0.1077		

A hazard ratio=1 indicated no difference in PD/death between PF-06439535 and bevacizumab-EU;
>1 indicated an increase in PD/death in PF-06439535;
<1 indicated an increase in PD/death in bevacizumab-EU.
Abbreviations: CI=confidence interval, CR=complete response, EU=European Union, ITT=Intent-to-Treat, N=number of patients who achieved confirmed objective response (CR or PR) by Week 19, PD=progressive disease, PR=partial response, Q1=25th percentile, Q3=75th percentile.

a. Estimated from the Kaplan-Meier curve; calculated from the product-limit method.
b. Based on the Brookmeyer and Crowley method.
c. Stratified by smoking, sex, and region.
d. Based on the Cox proportional hazards model stratified by smoking, sex, and region.
e. Two-sided p-value from the log-rank test stratified by smoking, sex, and region.

One (1) Year Progression-Free Survival (PFS) Rate

The percentages of patients who progressed/died or were censored in the ITT population were comparable between the 2 treatment groups. There were 228 (63.7%) and 255 (70.6%) patients who had objective progression or had died without objective progression in the PF-06439535 group and the bevacizumab-EU group, respectively

(Table 5). The probability of being progression free at Week 55 was 32.3% (95% CI: 26.9%, 37.8%) in the PF-06439535 group and 30.5% (95% CI: 25.3%, 35.8%) in the bevacizumab-EU group (Table 5).

Using a Cox proportional hazards model with region, gender and smoking history as strata, the hazard ratio when comparing PFS between PF-06439535 and bevacizumab-EU was 0.931, with a 95% CI of (0.777, 1.116). The stratified log-rank test resulted in a 2-sided p-value of 0.4492.

The analysis of PFS for patients in the PP population showed results consistent with the primary ITT population.

Table 5. Summary of Progression-Free Survival (Week 55) - ITT Population

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Patients with event	228 (63.7)	255 (70.6)	483 (67.2)
Type of event			
Progressive disease	192 (53.6)	219 (60.7)	411 (57.2)
Death	36 (10.1)	36 (10.0)	72 (10.0)
Number censored	130 (36.3)	106 (29.4)	236 (32.8)
Probability of being event free (95% CI[a]) at 55 weeks	0.323 (0.269, 0.378)	0.305 (0.253, 0.358)	0.314 (0.276, 0.352)
Kaplan-Meier estimates of time to event (week) Quartiles (95% CI)[b]			
Q1	23.4 (18.9, 24.3)	24.0 (19.3, 24.3)	23.9 (20.3, 24.1)
Median	41.3 (33.1, 42.3)	33.6 (33.0, 37.0)	34.3 (33.1, 41.1)
Q3	71.9 (59.7, 88.3)	68.9 (56.9, 75.0)	69.0 (60.9, 75.0)
Stratified analysis[c] Comparison versus bevacizumab-EU			
Hazard ratio[d]	0.931		
95% CI[d]	0.777, 1.116		
2-sided p-value[e]	0.4492		

A hazard ratio=1 indicated no difference in PD/death between PF-06439535 and bevacizumab-EU;
>1 indicated an increase in PD/death in PF-06439535;
<1 indicated an increase in PD/death in bevacizumab-EU.
Abbreviations: CI=confidence interval, EU=European Union, ITT=Intent-to-Treat, N=total number of patients, PD=progressive disease, Q1=25th percentile, Q3=75th percentile.
a. Estimated from the Kaplan-Meier curve; calculated from the product-limit method.
b. Based on the Brookmeyer and Crowley method.
c. Stratified by smoking, sex and region.
d. Based on the Cox proportional hazards model stratified by smoking, sex and region.
e. Two-sided p-value from the log-rank test stratified by smoking, sex and region.

One (1) -Year Survival Rate

The percentage of patients who died due to all causes in the ITT population was comparable between the 2 treatment groups. There were 144 (40.2%) and 149 (41.3%) patients who died in the PF-06439535 group and the bevacizumab-EU group, respectively (Table 6). The

probability of being alive at Week 55 was 65.8% (95% CI: 60.5%, 70.6%) in the PF-06439535 group, and 64.1% (95% CI: 58.6%, 69.0%) in the bevacizumab-EU group (Table 6).

Using a Cox proportional hazards model with region, sex and smoking history as strata, the hazard ratio when comparing OS between PF-06439535 and bevacizumab-EU, was 0.918, with a 95% CI of (0.729, 1.157). The stratified log-rank test resulted in a 2-sided p-value of 0.4726, indicating no statistically significant difference between the 2 treatment groups (Table 6).

The analysis of OS for patients in the PP population showed consistent results to that of the primary ITT population.

Table 6. Summary of Overall Survival (Week 55) - ITT Population

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Patients with event	144 (40.2)	149 (41.3)	293 (40.8)
Number censored	214 (59.8)	212 (58.7)	426 (59.2)
Probability of being event-free (95% CI[a]) at 55 weeks	0.658 (0.605, 0.706)	0.641 (0.586, 0.690)	0.650 (0.612, 0.684)
Kaplan-Meier estimates of time to event (weeks) Quartiles (95% CI)[b]			
Q1	40.3 (34.0, 49.0)	42.9 (36.3, 47.9)	41.1 (37.4, 46.0)
Median	84.4 (71.7, NE)	77.4 (69.3, 102.1)	83.0 (73.4, 98.7)
Q3	NE	NE	NE
Stratified analysis[c] Comparison versus bevacizumab-EU			
Hazard ratio[d]	0.918		
95% CI[d]	0.729, 1.157		
2-sided p-value[e]	0.4726		

A hazard ratio=1 indicated no difference in death between PF-06439535 and bevacizumab-EU;
>1 indicated an increase in death in PF-06439535;
<1 indicated an increase in death in bevacizumab-EU.
Abbreviations: CI=confidence interval, EU=European Union, ITT=Intent-to-Treat, N=total number of patients, NE=not evaluable, Q1=25th percentile, Q3=75th percentile.
a. Estimated from the Kaplan-Meier curve; calculated from the product-limit method.
b. Based on the Brookmeyer and Crowley method.
c. Stratified by smoking, sex, and region.
d. Based on the Cox proportional hazards model stratified by smoking, sex, and region.
e. Two-sided p-value from the log-rank test stratified by smoking, sex, and region.

Secondary Pharmacokinetic Endpoints:

Patients received chemotherapy of carboplatin and paclitaxel for at least 4 (unless shorter due to death, withdrawal of consent, or early termination of the trial) and no more than 6 cycles. Mean trough (pre-dose) and apparent peak (1 hour post end of infusion) concentrations were comparable between the 2 treatment groups for all time points measured from Baseline (defined as Hour 0, Cycle 1 Day 1) through Cycle 5 Day 1 (Table 7)

Table 7. Summary of Serum Concentration of PF-06439535 and Bevacizumab-EU Versus Time - PK Population

Visit	Planned Time Post Infusion Start	N	NALQ	Mean	SD	CV (%)	Median	Minimum	Maximum
Concentration Units: ng/mL, Treatment Group: PF-06439535									
Cycle 1 Day 1	0 h	333	6[a]	68.08	705.53	1036	0.0000	0.000	11300
	2 h 30 min	319	309	280000	103260	37	282000	0.000	546000
Cycle 2 Day 1	0 h	310	308	54350	44479	82	49050	0.000	460000
Cycle 3 Day 1	0 h	206	206	81090	48671	60	77450	4040	495000
Cycle 4 Day 1	0 h	277	277	100900	54979	54	94700	1000	475000
Cycle 5 Day 1	0 h	257	256	105300	48469	46	101000	0.000	494000
	1 h 30 min	192	192	360700	131170	36	372500	19700	636000
Concentration Units: ng/mL, Treatment Group: Bevacizumab-EU									
Cycle 1 Day 1	0 h	338	7[a]	116.4	1032.1	886	0.0000	0.000	12300
	2 h 30 min	326	321	302200	100360	33	300000	0.000	525000
Cycle 2 Day 1	0 h	326	324	58930	49452	84	52650	0.000	522000
Cycle 3 Day 1	0 h	211	211	83350	32384	39	79700	5270	259000
Cycle 4 Day 1	0 h	299	298	99750	50531	51	96500	0.000	697000
Cycle 5 Day 1	0 h	271	271	110000	65416	59	106000	5610	723000
	1 h 30 min	201	201	377200	142250	38	387000	28700	1010000

Summary statistics were calculated by setting concentration values below the lower limit of quantification (250 ng/mL) to 0.
Samples with a time deviation of >20% or any positive time deviation from the 0 h planned time point were excluded from this table.
Abbreviations: C_{max}=maximum concentration, CV=coefficient of variation, EU=European Union, h=hour(s), min=minutes, N=number of observations (non-missing concentrations), NALQ=number of observations above lower limit of quantification (250 ng/mL), PK=pharmacokinetic, SD=standard deviation.
a. Patients with pre-dose concentrations >5% of C_{max} on Cycle 1 Day 1 were excluded from this table.

Secondary Immunogenicity Endpoints:

A summary of Baseline and overall post-treatment ADA incidences are presented in Table 8. One (1, 0.3%) patient in the PF-06439535 group and 3 (0.8%) patients in the bevacizumab-EU group tested positive for ADA (titer ≥2.29) at Baseline. For the overall post-treatment assessment, 5 (1.5%) patients in the PF-06439535 group and 5 (1.4%) patients in the bevacizumab-EU group were reported ADA positive.

Table 8. Summary of ADA Incidence by Treatment Group - Safety Population

Visit	Criteria	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Cycle 1 (prior to treatment)	n	352	353	705
	Positive	1 (0.3)	3 (0.8)	4 (0.6)
	Negative	350 (99.4)	350 (99.2)	700 (99.3)
	Not tested	1 (0.3)	0	1 (0.1)
Overall (post-treatment)	n	339	350	689
	Positive	5 (1.5)	5 (1.4)	10 (1.5)
	Negative	334 (98.5)	345 (98.6)	679 (98.5)

Percentages were based on the number of patients at each visit. All samples were taken prior to dosing.
For calculation of the overall incidence of post-treatment ADA, n=number of patients with at least 1 post Cycle 1 ADA sample tested. Patients with a positive ADA sample at any time post Cycle 1 were defined as having an overall positive ADA status.
ADA positive sample was defined as ADA titer ≥2.29, ADA negative sample was defined as ADA titer <2.29.
Abbreviations: ADA=anti-drug antibody, EU=European Union, N=the number of patients who received study drug, n=the number of patients evaluated at each visit.

All ADA positive samples were tested subsequently in the single NAb assay. A summary of Baseline and overall post-treatment NAb incidences are presented in Table 9. At Baseline, 1 (PF-06439535 treatment group) out of the 4 patients who tested positive for ADA was reported positive for NAb (titer ≥1.70). For the overall post-treatment assessment, of the 5 patients who reported positive ADA status in the PF-06439535 group, none were reported as NAb positive; of the 5 patients who reported positive ADA status in the bevacizumab-EU group, 3 (0.9%) patients reported NAb positive.

Table 9. Summary of NAb Incidence by Treatment Group - Safety Population

Visit	Criteria	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Cycle 1 (prior to treatment)	n	352	353	705
	Positive	1 (0.3)	0	1 (0.1)
	Negative	0	3 (0.8)	3 (0.4)
	Not tested	351 (99.7)	350 (99.2)	701 (99.4)
Overall (post-treatment)	n	339	350	689
	Positive	0	3 (0.9)	3 (0.4)
	Negative	339 (100.0)	347 (99.1)	686 (99.6)

Percentages were based on the number of patients at each visit. All samples were taken prior to dosing.
For calculation of the overall incidence of post-treatment NAb, n=number of patients with at least 1 post Cycle 1 Day 1 ADA sample tested.
Patients with a positive NAb sample at any time post Cycle 1 Day 1 dose were defined as having an overall positive NAb status; while patients without a NAb positive sample at any cycle post Cycle 1 Day 1 dose were defined as having an overall negative NAb status.
NAb positive samples were defined as NAb titer ≥1.70. NAb negative samples were defined as NAb titer <1.70.
Abbreviations: ADA=anti-drug antibody, EU=European Union, N=the number of patients who received study drug, n=the number of patients evaluated at each visit, NAb=neutralizing antibody.

Safety Results:

All patients who were randomized and received at least 1 dose of study treatment were included in the safety population. Of the 719 randomized patients, 714 received at least 1 dose of the study treatment (356 patients in the PF-06439535 group and 358 patients in the bevacizumab-EU group). Overall, the mean (SD) duration of treatment for patients in the PF-06439535 group and the bevacizumab-EU group was 35.2 (27.19) weeks and 34.9 (25.96) weeks, respectively.

The majority of all patients experienced at least 1 treatment-emergent adverse events (TEAE, all causalities), with 344 (96.6%) patients in the PF-06439535 group and 347 (96.9%) patients in the bevacizumab-EU group reporting a total of 2442 and 2470 TEAEs, respectively. Bevacizumab-related AEs were those AEs related to bevacizumab (with or without causal relationship to chemotherapy) according to the investigator's assessment. Approximately half of all patients experienced at least 1 bevacizumab-related TEAE, with 190 (53.4%) patients in the PF-06439535 group and 199 (55.6%) patients in the bevacizumab-EU group reporting a total of 625 and 574 bevacizumab-related TEAEs, respectively.

Serious Adverse Event

Treatment –emergent SAEs are summarized in Table 10 (all causalities) and Table 11 (treatment-related). Overall, 81 (22.8%) patients in the PF-06439535 group and 80 (22.3%) patients in the bevacizumab-EU group experienced at least 1 SAE (all causalities). Among them, 23 (6.5%) patients in the PF-06439535 group and 17 (4.7%) patients in the bevacizumab-EU group experienced at least 1 bevacizumab-related SAE. The most frequently reported SAEs were pneumonia (8 [2.2%] patients in the PF-06439535 group and

6 [1.7%] patients in the bevacizumab-EU group), febrile neutropenia (5 [1.4%] patients in the PF-06439535 group and 7 [2.0%] patients in the bevacizumab-EU group), and neutropenia (4 [1.1%] patients in the PF-06439535 group and 6 [1.7%] patients in the bevacizumab-EU group). The most frequently reported bevacizumab-related SAEs were neutropenia, which was reported by 1 (0.3%) patient in the PF-06439535 group and 3 (0.8%) patients in the bevacizumab-EU group, and pulmonary embolism, which was reported by 2 (0.6%) patients in the PF-06439535 group and 2 (0.6%) patients in the bevacizumab-EU group.

Table 10. Treatment-Emergent Serious Adverse Events – All Causality

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Number of Patients Evaluable for AEs	PF-06439535 (N = 356)	Bevacizumab-EU (N = 358)	Total (N = 714)
Number (%) of Patients with SAEs by SOC and MedDRA[a] Preferred Term	n (%)	n (%)	n (%)
With any AEs	81 (22.8)	80 (22.3)	161 (22.5)
Blood and Lymphatic System Disorders	**12 (3.4)**	**18 (5.0)**	**30 (4.2)**
Anaemia	2 (0.6)	5 (1.4)	7 (1.0)
Febrile neutropenia	5 (1.4)	7 (2.0)	12 (1.7)
Leukopenia	2 (0.6)	0	2 (0.3)
Neutropenia	4 (1.1)	6 (1.7)	10 (1.4)
Pancytopenia	1 (0.3)	1 (0.3)	2 (0.3)
Thrombocytopenia	3 (0.8)	3 (0.8)	6 (0.8)
Cardiac Disorders	**7 (2.0)**	**8 (2.2)**	**15 (2.1)**
Acute coronary syndrome	1 (0.3)	1 (0.3)	2 (0.3)
Acute myocardial infarction	1 (0.3)	1 (0.3)	2 (0.3)
Angina unstable	1 (0.3)	0	1 (0.1)
Cardiac arrest	1 (0.3)	1 (0.3)	2 (0.3)
Cardiac failure	1 (0.3)	0	1 (0.1)
Cardio-respiratory arrest	0	2 (0.6)	2 (0.3)
Cardiovascular insufficiency	1 (0.3)	1 (0.3)	2 (0.3)
Myocardial infarction	1 (0.3)	1 (0.3)	2 (0.3)
Right ventricular failure	0	1 (0.3)	1 (0.1)
Gastrointestinal Disorders	**8 (2.2)**	**14 (3.9)**	**22 (3.1)**
Abdominal pain	0	1 (0.3)	1 (0.1)
Colitis	0	1 (0.3)	1 (0.1)
Colitis ischaemic	1 (0.3)	0	1 (0.1)
Constipation	0	2 (0.6)	2 (0.3)
Diarrhoea	2 (0.6)	2 (0.6)	4 (0.6)
Enterocolitis	1 (0.3)	0	1 (0.1)
Faecaloma	0	1 (0.3)	1 (0.1)
Gastritis	1 (0.3)	0	1 (0.1)
Haemorrhoidal haemorrhage	1 (0.3)	0	1 (0.1)
Ileus	0	1 (0.3)	1 (0.1)
Intestinal obstruction	0	1 (0.3)	1 (0.1)
Nausea	0	2 (0.6)	2 (0.3)
Neutropenic colitis	0	1 (0.3)	1 (0.1)
Peptic ulcer	1 (0.3)	0	1 (0.1)
Rectal haemorrhage	0	1 (0.3)	1 (0.1)
Small intestinal perforation	0	1 (0.3)	1 (0.1)
Subileus	0	1 (0.3)	1 (0.1)
Vomiting	1 (0.3)	1 (0.3)	2 (0.3)
General Disorders and Administration Site Conditions	**12 (3.4)**	**11 (3.1)**	**23 (3.2)**
Asthenia	4 (1.1)	1 (0.3)	5 (0.7)
Chest pain	1 (0.3)	1 (0.3)	2 (0.3)
Death	2 (0.6)	3 (0.8)	5 (0.7)
Disease progression	4 (1.1)	5 (1.4)	9 (1.3)
General physical health deterioration	1 (0.3)	0	1 (0.1)
Pain	2 (0.6)	1 (0.3)	3 (0.4)
Hepatobiliary Disorders	**3 (0.8)**	**0**	**3 (0.4)**
Cholangitis acute	2 (0.6)	0	2 (0.3)

Table 10. Treatment-Emergent Serious Adverse Events – All Causality (Continued)

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Number (%) of Patients with SAEs by SOC and MedDRA[a] Preferred Term	PF-06439535	Bevacizumab-EU	Total
Cholelithiasis	1 (0.3)	0	1 (0.1)
Immune System Disorders	**0**	**1 (0.3)**	**1 (0.1)**
Anaphylactic reaction	0	1 (0.3)	1 (0.1)
Infections and Infestations	**18 (5.1)**	**19 (5.3)**	**37 (5.2)**
Anal infection	1 (0.3)	0	1 (0.1)
Appendictis perforated	0	1 (0.3)	1 (0.1)
Bacteraemia	1 (0.3)	0	1 (0.1)
Disseminated tuberculosis	0	1 (0.3)	1 (0.1)
Enterocolitis infectious	0	1 (0.3)	1 (0.1)
Febrile infection	1 (0.3)	0	1 (0.1)
Gastroenteritis	4 (1.1)	0	4 (0.6)
Infection	0	1 (0.3)	1 (0.1)
Infectious pleural effusion	0	1 (0.3)	1 (0.1)
Lower respiratory tract infection	1 (0.3)	2 (0.6)	3 (0.4)
Lung abscess	0	1 (0.3)	1 (0.1)
Lung infection	1 (0.3)	1 (0.3)	2 (0.3)
Oral fungal infection	0	1 (0.3)	1 (0.1)
Pleural infection	0	1 (0.3)	1 (0.1)
Pneumonia	8 (2.2)	6 (1.7)	14 (2.0)
Respiratory tract infection	2 (0.6)	0	2 (0.3)
Sepsis	0	2 (0.6)	2 (0.3)
Septic shock	0	1 (0.3)	1 (0.1)
Sinusitis	1 (0.3)	0	1 (0.1)
Soft tissue infection	0	1 (0.3)	1 (0.1)
Urinary tract infection	1 (0.3)	2 (0.6)	3 (0.4)
Injury, Poisoning and Procedural Complications	**1 (0.3)**	**3 (0.8)**	**4 (0.6)**
Femur fracture	1 (0.3)	0	1 (0.1)
Fracture	0	1 (0.3)	1 (0.1)
Infusion related reaction	0	1 (0.3)	1 (0.1)
Subarachnoid haemorrhage	0	1 (0.3)	1 (0.1)
Investigations	**2 (0.6)**	**1 (0.3)**	**3 (0.4)**
Alanine aminotransferase increased	1 (0.3)	0	1 (0.1)
Blood bilirubin increased	1 (0.3)	0	1 (0.1)
Neutrophil count decreased	1 (0.3)	1 (0.3)	2 (0.3)
Metabolism and Nutrition Disorders	**5 (1.4)**	**2 (0.6)**	**7 (1.0)**
Decreased appetite	0	1 (0.3)	1 (0.1)
Dehydration	0	1 (0.3)	1 (0.1)
Hypercalcaemia	1 (0.3)	0	1 (0.1)
Hyperkalaemia	0	1 (0.3)	1 (0.1)
Hyponatraemia	4 (1.1)	0	4 (0.6)
Musculoskeletal and Connective Tissue Disorders	**0**	**3 (0.8)**	**3 (0.4)**
Bone pain	0	2 (0.6)	2 (0.3)
Myalgia	0	1 (0.3)	1 (0.1)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	**2 (0.6)**	**4 (1.1)**	**6 (0.8)**
Bone cancer metastatic	0	1 (0.3)	1 (0.1)
Neoplasm progression	2 (0.6)	2 (0.6)	4 (0.6)

Table 10. Treatment-Emergent Serious Adverse Events – All Causality (Continued)

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Number (%) of Patients with SAEs by SOC and MedDRA[a] Preferred Term	**PF-06439535**	**Bevacizumab-EU**	**Total**
Tumor necrosis	0	1 (0.3)	1 (0.1)
Nervous System Disorders	**5 (1.4)**	**5 (1.4)**	**10 (1.4)**
Cerebral haemorrhage	1 (0.3)	0	1 (0.1)
Cerebral ischaemia	1 (0.3)	0	1 (0.1)
Dizziness	0	1 (0.3)	1 (0.1)
Haemorrhagic stroke	1 (0.3)	0	1 (0.1)
Headache	1 (0.3)	0	1 (0.1)
Ischaemic stroke	0	3 (0.8)	3 (0.4)
Mononeuropathy	0	1 (0.3)	1 (0.1)
Paraesthesia	1 (0.3)	0	1 (0.1)
Renal and Urinary Disorders	**2 (0.6)**	**1 (0.3)**	**3 (0.4)**
Proteinuria	1 (0.3)	0	1 (0.1)
Renal cyst	1 (0.3)	0	1 (0.1)
Urinary retention	0	1 (0.3)	1 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	**19 (5.3)**	**14 (3.9)**	**33 (4.6)**
Acute respiratory failure	0	1 (0.3)	1 (0.1)
Chronic obstructive pulmonary disease	0	1 (0.3)	1 (0.1)
Cough	0	1 (0.3)	1 (0.1)
Dyspnoea	2 (0.6)	2 (0.6)	4 (0.6)
Epistaxis	2 (0.6)	1 (0.3)	3 (0.4)
Haemoptysis	2 (0.6)	2 (0.6)	4 (0.6)
Pneumonitis	1 (0.3)	0	1 (0.1)
Pneumothorax	2 (0.6)	1 (0.3)	3 (0.4)
Pulmonary embolism	7 (2.0)	2 (0.6)	9 (1.3)
Pulmonary haemorrhage	3 (0.8)	3 (0.8)	6 (0.8)
Pulmonary oedema	0	1 (0.3)	1 (0.1)
Respiratory failure	1 (0.3)	0	1 (0.1)
Vascular Disorders	**5 (1.4)**	**3 (0.8)**	**8 (1.1)**
Brachiocephalic vein thrombosis	1 (0.3)	0	1 (0.1)
Embolism arterial	1 (0.3)	1 (0.3)	2 (0.3)
Haemorrhage	1 (0.3)	0	1 (0.1)
Hypertensive crisis	0	1 (0.3)	1 (0.1)
Ischaemia	1 (0.3)	0	1 (0.1)
Shock haemorrhagic	0	1 (0.3)	1 (0.1)
Subgaleal haematoma	1 (0.3)	0	1 (0.1)

Abbreviations: AE=adverse event, EU=European Union, MedDRA=Medical Dictionary for Regulatory Activities, SAE=serious adverse event, SOC=system organ class.

a. MedDRA version 20.1 coding dictionary applied.

Table 11. Treatment-Emergent Serious Adverse Events – Bevacizumab-Related[a]

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Number (%) of Patients	PF-06439535 (N = 356)	Bevacizumab-EU (N = 358)	Total (N = 714)
Number (%) of Patients with SAEs by SOC and MedDRA[b] Preferred Term			
With any AEs	23 (6.5)	17 (4.7)	40 (5.6)
Blood and Lymphatic System Disorders	**5 (1.4)**	**7 (2.0)**	**12 (1.7)**
Anaemia	2 (0.6)	1 (0.3)	3 (0.4)
Febrile neutropenia	2 (0.6)	1 (0.3)	3 (0.4)
Leukopenia	1 (0.3)	0	1 (0.1)
Neutropenia	1 (0.3)	3 (0.8)	4 (0.6)
Thrombocytopenia	1 (0.3)	2 (0.6)	3 (0.4)
Cardiac Disorders	**1 (0.3)**	**0**	**1 (0.1)**
Acute myocardial infarction	1 (0.3)	0	1 (0.1)
Gastrointestinal Disorders	**3 (0.8)**	**2 (0.6)**	**5 (0.7)**
Abdominal pain	0	1 (0.3)	1 (0.1)
Colitis ischaemic	1 (0.3)	0	1 (0.1)
Gastritis	1 (0.3)	0	1 (0.1)
Small intestinal perforation	0	1 (0.3)	1 (0.1)
Vomiting	1 (0.3)	0	1 (0.1)
General Disorders and Administration Site Conditions	**3 (0.8)**	**0**	**3 (0.4)**
Asthenia	2 (0.6)	0	2 (0.3)
Death	1 (0.3)	0	1 (0.1)
Infections and Infestations	**3 (0.8)**	**3 (0.8)**	**6 (0.8)**
Appendictis perforated	0	1 (0.3)	1 (0.1)
Enterocolitis infectious	0	1 (0.3)	1 (0.1)
Pleural infection	0	1 (0.3)	1 (0.1)
Pneumonia	2 (0.6)	0	2 (0.3)
Sepsis	0	1 (0.3)	1 (0.1)
Urinary tract infection	1 (0.3)	0	1 (0.1)
Investigations	**1 (0.3)**	**0**	**1 (0.1)**
Neutrophil count decreased	1 (0.3)	0	1 (0.1)
Metabolism and Nutrition Disorders	**2 (0.6)**	**1 (0.3)**	**3 (0.4)**
Decreased appetite	0	1 (0.3)	1 (0.1)
Dehydration	0	1 (0.3)	1 (0.1)
Hyponatraemia	2 (0.6)	0	2 (0.3)
Nervous System Disorders	**1 (0.3)**	**0**	**1 (0.1)**
Cerebral haemorrhage	1 (0.3)	0	1 (0.1)
Renal and Urinary Disorders	**1 (0.3)**	**0**	**1 (0.1)**
Proteinuria	1 (0.3)	0	1 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	**7 (2.0)**	**5 (1.4)**	**12 (1.7)**
Cough	0	1 (0.3)	1 (0.1)
Dyspnoea	1 (0.3)	0	1 (0.1)
Epistaxis	2 (0.6)	1 (0.3)	3 (0.4)
Haemoptysis	2 (0.6)	0	2 (0.3)
Pulmonary embolism	2 (0.6)	2 (0.6)	4 (0.6)
Pulmonary haemorrhage	1 (0.3)	1 (0.3)	2 (0.3)
Vascular Disorders	**2 (0.6)**	**1 (0.3)**	**3 (0.4)**
Brachiocephalic vein thrombosis	1 (0.3)	0	1 (0.1)
Embolism arterial	0	1 (0.3)	1 (0.1)
Haemorrhage	1 (0.3)	0	1 (0.1)

Table 11. Treatment-Emergent Serious Adverse Events – Bevacizumab-Related[a] (Continued)

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Abbreviations: AE=adverse event, EU=European Union, MedDRA=Medical Dictionary for Regulatory Activities, SAE=serious adverse event, SOC=system organ class.

a. AEs related to bevacizumab with or without causal relationship to chemotherapy.
b. MedDRA version 20.1 coding dictionary applied.

Non-Serious Adverse Events:

Treatment-emergent non-serious AEs in ≥5% of patients are summarized in Table 12 (all causality) and Table 13 (bevacizumab-related). The most frequently reported non-serious AEs were alopecia (166 [46.6%] patients in the PF-06439535 group and 165 [46.1%] patients in the bevacizumab-EU group), and anaemia (102 [28.7%] patients in the PF-06439535 group and 106 [29.6%] patients in the bevacizumab-EU group). The most frequently reported bevacizumab-related non-serious AEs were hypertension (45 [12.6%] patients in the PF-06439535 group and 40 [11.2%] patients in the bevacizumab-EU group), and anaemia (28 [7.9%] patients in the PF-06439535 group and 30 [8.4%] patients in the bevacizumab-EU group).

Table 12. Treatment-Emergent Non-Serious Adverse Events in ≥5% of Patients of Any Treatment Group – All Causality

Page 1 of 2

Number (%) of Patients	PF-06439535 (N = 356)	Bevacizumab-EU (N = 358)	Total (N = 714)
Number (%) of Patients with AEs by SOC and MedDRA[a] Preferred Term			
With any AEs	328 (92.1)	333 (93.0)	661 (92.6)
Blood and Lymphatic System Disorders	**153 (43.0)**	**166 (46.4)**	**319 (44.7)**
Anaemia	102 (28.7)	106 (29.6)	208 (29.1)
Leukopenia	26 (7.3)	30 (8.4)	56 (7.8)
Neutropenia	59 (16.6)	66 (18.4)	125 (17.5)
Thrombocytopenia	55 (15.4)	66 (18.4)	121 (16.9)
Gastrointestinal Disorders	**128 (36.0)**	**126 (35.2)**	**254 (35.6)**
Constipation	39 (11.0)	27 (7.5)	66 (9.2)
Diarrhoea	46 (12.9)	48 (13.4)	94 (13.2)
Nausea	71 (19.9)	69 (19.3)	140 (19.6)
Vomiting	41 (11.5)	33 (9.2)	74 (10.4)
General Disorders and Administration Site Conditions	**126 (35.4)**	**124 (34.6)**	**250 (35.0)**
Asthenia	46 (12.9)	43 (12.0)	89 (12.5)
Fatigue	73 (20.5)	71 (19.8)	144 (20.2)
Pyrexia	24 (6.7)	23 (6.4)	47 (6.6)
Injury, Poisoning and Procedural Complications	**19 (5.3)**	**22 (6.1)**	**41 (5.7)**
Infusion related reaction	19 (5.3)	22 (6.1)	41 (5.7)
Investigations	**116 (32.6)**	**107 (29.9)**	**223 (31.2)**
Alanine aminotransferase increased	49 (13.8)	39 (10.9)	88 (12.3)
Aspartate aminotransferase increased	44 (12.4)	37 (10.3)	81 (11.3)
Blood alkaline phosphatase increased	29 (8.1)	32 (8.9)	61 (8.5)
Blood creatinine increased	16 (4.5)	21 (5.9)	37 (5.2)
Platelet count decreased	23 (6.5)	19 (5.3)	42 (5.9)
Weight decreased	36 (10.1)	29 (8.1)	65 (9.1)
Metabolism and Nutrition Disorders	**48 (13.5)**	**46 (12.8)**	**94 (13.2)**
Decreased appetite	48 (13.5)	46 (12.8)	94 (13.2)
Musculoskeletal and Connective Tissue Disorders	**110 (30.9)**	**115 (32.1)**	**225 (31.5)**
Arthralgia	40 (11.2)	43 (12.0)	83 (11.6)
Bone pain	25 (7.0)	23 (6.4)	48 (6.7)
Myalgia	54 (15.2)	49 (13.7)	103 (14.4)
Pain in extremity	16 (4.5)	23 (6.4)	39 (5.5)
Nervous System Disorders	**156 (43.8)**	**172 (48.0)**	**328 (45.9)**
Headache	30 (8.4)	37 (10.3)	67 (9.4)
Neuropathy peripheral	53 (14.9)	65 (18.2)	118 (16.5)
Paraesthesia	40 (11.2)	31 (8.7)	71 (9.9)
Peripheral sensory neuropathy	34 (9.6)	46 (12.8)	80 (11.2)
Polyneuropathy	23 (6.5)	19 (5.3)	42 (5.9)
Renal and Urinary Disorders	**28 (7.9)**	**34 (9.5)**	**62 (8.7)**
Proteinuria	28 (7.9)	34 (9.5)	62 (8.7)
Respiratory, Thoracic and Mediastinal Disorders	**86 (24.2)**	**94 (26.3)**	**180 (25.2)**
Cough	41 (11.5)	47 (13.1)	88 (12.3)
Dyspnoea	32 (9.0)	35 (9.8)	67 (9.4)

Table 12. Treatment-Emergent Non-Serious Adverse Events in ≥5% of Patients of Any Treatment Group – All Causality (Continued)

Page 2 of 2			
Number (%) of Patients with AEs by SOC and MedDRA[a] Preferred Term	**PF-06439535**	**Bevacizumab-EU**	**Total**
Epistaxis	40 (11.2)	32 (8.9)	72 (10.1)
Skin and Subcutaneous Tissue Disorders	**171 (48.0)**	**173 (48.3)**	**344 (48.2)**
Alopecia	166 (46.6)	165 (46.1)	331 (46.4)
Rash	9 (2.5)	21 (5.9)	30 (4.2)
Vascular Disorders	**60 (16.9)**	**62 (17.3)**	**122 (17.1)**
Hypertension	60 (16.9)	62 (17.3)	122 (17.1)

Abbreviations: AE=adverse event, EU=European Union, MedDRA=Medical Dictionary for Regulatory Activities, SOC=system organ class.
a. MedDRA version 20.1 coding dictionary applied.

Table 13. Treatment-Emergent Non-Serious Adverse Events in ≥5% of Patients of Any Treatment Group – Bevacizumab-Related[a]

Number (%) of Patients	**PF-06439535 (N = 356)**	**Bevacizumab-EU (N = 358)**	**Total (N = 714)**
Number (%) of Patients with AEs by SOC and MedDRA[b] Preferred Term			
With any AEs	127 (35.7)	125 (34.9)	252 (35.3)
Blood and Lymphatic System Disorders	**38 (10.7)**	**44 (12.3)**	**82 (11.5)**
Anaemia	28 (7.9)	30 (8.4)	58 (8.1)
Neutropenia	15 (4.2)	19 (5.3)	34 (4.8)
General Disorders and Administration Site Conditions	**31 (8.7)**	**23 (6.4)**	**54 (7.6)**
Fatigue	31 (8.7)	23 (6.4)	54 (7.6)
Investigations	**18 (5.1)**	**14 (3.9)**	**32 (4.5)**
Alanine aminotransferase increased	18 (5.1)	14 (3.9)	32 (4.5)
Renal and Urinary Disorders	**21 (5.9)**	**27 (7.5)**	**48 (6.7)**
Proteinuria	21 (5.9)	27 (7.5)	48 (6.7)
Respiratory, Thoracic and Mediastinal Disorders	**30 (8.4)**	**26 (7.3)**	**56 (7.8)**
Epistaxis	30 (8.4)	26 (7.3)	56 (7.8)
Vascular Disorders	**45 (12.6)**	**40 (11.2)**	**85 (11.9)**
Hypertension	45 (12.6)	40 (11.2)	85 (11.9)

Abbreviations: AE=adverse event, EU=European Union, MedDRA=Medical Dictionary for Regulatory Activities, SOC=system organ class.
a. AEs related to bevacizumab with or without causal relationship to chemotherapy.
b. MedDRA version 20.1 coding dictionary applied.

Withdrawals Due to AEs:

There were 85 (23.9%) patients in the PF-06439535 group and 86 (24.0%) patients in the bevacizumab-EU group who were permanently discontinued from any treatment (ie, discontinued from bevacizumab and/or paclitaxel and/or carboplatin) due to AEs. The most frequently reported AE that led to permanent discontinuation from any treatment was polyneuropathy (8 [2.2%] patients in the PF-06439535 group and 5 [1.4%] patients in the bevacizumab-EU group). There were 33 (9.3%) patients in the PF-06439535 group and 25 (7.0%) patients in the bevacizumab-EU group who were permanently discontinued from any treatment (ie, discontinued from bevacizumab and/or paclitaxel and/or carboplatin) due to bevacizumab-related AEs. The most frequently reported bevacizumab-related AE that led to permanent discontinuation from any treatment was proteinuria (5 [1.4%] patients in the PF-06439535 group and 2 [0.6%] patients in the bevacizumab-EU group).

Death:

Deaths occurring during the safety reporting period (during the treatment period and up to 28 days after the last dose or the start of subsequent anti-cancer therapy [whichever was earlier]) are presented as Grade 5 TEAEs. In the PF-06439535 group, out of 356 patients who received study treatment, there were 21 (5.9%) patients with Grade 5 TEAEs within the safety reporting period. In the bevacizumab-EU group, out of 358 patients who received study treatment, there were 24 (6.7%) patients with Grade 5 TEAEs within the safety reporting period. There was 1 bevacizumab-related Grade 5 event (pulmonary hemorrhage) in the bevacizumab-EU group and 6 bevacizumab-related Grade 5 events (acute myocardial infarction, pneumonia, hemoptysis, pulmonary hemorrhage, hemorrhage, and death) in the PF-06439535 group. The events of acute myocardial infarction, pneumonia and pulmonary hemorrhage in the PF-06439535 group were also related to paclitaxel and carboplatin. Bevacizumab-related fatal events were consistent with the complications of underlying disease and known safety profile of Avastin. Overall, the incidence of Grade 5 events (all cause deaths) was similar between the 2 treatment groups.

Severity of Adverse Events

In total, there were 343 (48.0%) patients (171 [48.0%] patients in the PF-06439535 group and 172 [48.0%] patients in the bevacizumab-EU group) with a TEAE reported at Grade 3 or higher, with a comparable incidence between the 2 treatment groups. The most frequently reported Grade 3 or higher TEAEs were hypertension (33 [9.3%] patients in the PF-06439535 group and 31 [8.7%] patients in the bevacizumab-EU group), followed by neutropenia (26 [7.3%] patients in the PF-06439535 group and 32 [8.9%] patients in the bevacizumab-EU group), and anemia (19 [5.3%] patients in the PF-06439535 group and 18 [5.0%] patients in the bevacizumab-EU group).

In the PF-06439535 group, there were 53 (14.9%) patients, 5 (1.4%) patients, and 6 (1.7%) patients who had bevacizumab-related TEAEs with maximum CTCAE Grade 3, Grade 4, and Grade 5, respectively. In the bevacizumab-EU group, the corresponding numbers of patients were 35 (9.8%), 14 (3.9%), and 1 (0.3%), respectively. The most frequently reported Grade 3 and Grade 4 bevacizumab-related TEAEs were hypertension,

with 23 (6.5%) patients (Grade 3: 23) in the PF-06439535 group, and 14 (3.9%) patients (Grade 3: 14) in the bevacizumab-EU group followed by neutropenia with 6 (1.7%) patients (Grade 3: 4 [1.1%]; Grade 4: 2 [0.6%]) in the PF-06439535 group and 8 (2.2%) patients (Grade 3: 2 [0.6%]; Grade 4: 6 [1.7%]) in the bevacizumab-EU group) and anemia, with 5 (1.4%) patients (Grade 3: 5) in the PF-06439535 group and 4 (1.1%) patients (Grade 3: 4) in the bevacizumab-EU group.

Clinical Laboratory Abnormalities

The number and percentage of patients with laboratory abnormalities were 303 (88.6%) in the PF-06439535 group and 304 (87.4%) in the bevacizumab-EU group, respectively.

Four (4) patients (2 in the PF-06439535 group, and 2 in the bevacizumab-EU group) had elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) defined as ≥3 × upper limit of normal (ULN) and elevated total bilirubin of ≥2 × ULN which were considered as clinically significant.

CONCLUSIONS:

- Study B7391003 met its primary objective, based on the analysis of the primary efficacy endpoint ORR in patients who received PF-06439535 in combination with paclitaxel and carboplatin versus those who received bevacizumab-EU in combination with paclitaxel and carboplatin in first-line treatment of advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

- Similarity between PF-06439535 and bevacizumab-EU was statistically demonstrated for the primary efficacy endpoint, ORR (defined as the percent of patients within each treatment group that achieved CR or PR by Week 19 and subsequently confirmed on a follow-up tumor assessment by Week 25) based on the pre-specified equivalence margins required by US FDA, EU EMA and Japan PMDA.

- Sensitivity analyses for ORR using stratification factors, and sensitivity analyses using the PP population supported the results of the primary endpoint analysis.

- No statistically significant or clinically meaningful differences between the 2 treatment groups were observed for the secondary efficacy endpoints, which included DOR, 1-year PFS rate, and 1-year survival rate.

- Both treatments showed comparable safety profiles. No clinically meaningful safety differences were identified between the 2 treatment groups. No new safety signal was identified.

- Trough and apparent peak serum bevacizumab concentrations were comparable for both treatments.

- The observed rate of ADA and NAb was low, with comparable percentages of patients with ADA and NAb observed for the 2 treatment groups. Given the low number of patients with ADA, the association between immunogenicity and safety could not be

evaluated. The patients with ADA did not experience serious IRRs or anaphylactic reactions.