Online Resource

PF-06439535 (a Bevacizumab Biosimilar) Compared With Reference Bevacizumab (Avastin®), Both Plus Paclitaxel and Carboplatin, as First-Line Treatment for Advanced Non-Squamous Non-Small-Cell Lung Cancer: A Randomized, Double-Blind Study

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Eligibility Criteria

Inclusion Criteria

Eligible patients were expected to meet the following and all other qualifying criteria:

1. Male and female patients ≥18 years of age, or ≥ age of consent in the region.
2. Newly diagnosed Stage IIIB or IV non-small-cell lung cancer (NSCLC; according to Revised International System for Staging Lung Cancer Criteria of 2010) or recurrent NSCLC.
3. Histologically or cytologically confirmed diagnosis of predominately non-squamous NSCLC.
4. At least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
5. For patients with recurrent disease, at least 6 months must have elapsed since completing adjuvant or neoadjuvant treatment.
6. Screening scan (computed tomography [CT] or magnetic resonance imaging [MRI]) of the head, chest, abdomen (with adrenal glands), and other disease sites as clinically indicated, to assess disease burden.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Screening laboratory values within the following limits (where deviation of up to 10% was acceptable for any single value if, in the investigator's opinion, the patient did not have an increased safety risk):

   <u>Bone Marrow Function</u>

   - Absolute neutrophil count ≥1.5 × 10^9 cells/L (1500/mm^3);
   - Platelet count ≥100 × 10^9 cells/L (100,000/mm^3);
   - Hemoglobin ≥9.0 g/dL (90 g/L);

   <u>Renal Function</u>

- Serum or plasma creatinine ≤1.5 × upper limit of normal (ULN);
- Urine dipstick proteinuria <2+ (i.e., either 0, trace, or 1+). If urine dipstick was >1+, then a 24-hour urine test for protein must have demonstrated urinary excretion of ≤500 mg of protein per day or urine protein to creatinine (UPC) ratio <1;

Liver Function

- Total bilirubin ≤1.5 × ULN (<3 × ULN if Gilbert's disease);
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤3 × ULN (≤5 × ULN if liver metastases were present).

9. Recovery (to Grade 1 or baseline) from all clinically significant adverse effects of prior therapies (excluding alopecia).
10. Evidence of a personally signed and dated informed consent document indicating that the patient had been informed of all pertinent aspects of the study.
11. Patients who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
12. Eligible to receive study treatment of bevacizumab, paclitaxel, and carboplatin based on local standard of care, for the treatment of advanced or metastatic non-squamous NSCLC.
13. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy had to agree to use two highly effective methods of contraception throughout the study and for at least 6 months after receipt of the last dose of study treatment.

    Female patients who were not of childbearing potential (i.e., met at least one of the following criteria):

    - Had undergone a documented hysterectomy and/or bilateral oophorectomy;

- Had medically confirmed ovarian failure; or
- Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may have been confirmed by having a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

All other female patients (including females with tubal ligations) were considered to be of childbearing potential.

Exclusion Criteria

Patients were ineligible to participate in this study if any of the following criteria were met:

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. If mutation testing was performed, the results must have been reviewed and confirmed as negative for mutations before randomization.
4. History of other cancer within 5 years before screening for this study, with the exception of adequately treated ductal carcinoma in situ of the breast, cervical carcinoma in situ, or basal or squamous cell skin cancer.

5. Prior systemic therapy for NSCLC; prior neoadjuvant or adjuvant therapy was allowed if surgical resection for primary disease was performed.
6. History of local radiation for painful bone metastases in the last 2 weeks. Patients with bone metastases were eligible; however, those with symptomatic or painful bone metastases should not have received palliative local radiation for at least 2 weeks before randomization.
7. History of hemoptysis (>2.5 mL per event) in the last 3 months or severe bleeding. Evidence of current thrombotic or bleeding disorders. Therapeutic anticoagulation and/or coagulation abnormalities (e.g., international normalized ratio [INR] >1.5 and activated partial thromboplastin time [aPTT] greater than ULN unless on prophylactic anticoagulation).
8. Medically uncontrolled hypertension or systolic blood pressure (BP) >150 mmHg or diastolic BP >100 mmHg.
9. Peripheral motor or sensory neuropathy with value of ≥ Grade 2.
10. Major surgery or any investigational agents, within 4 weeks before the administration of the first dose of study treatment. Planned major surgery during the treatment period.
11. Any unhealed wound or bone fracture.
12. Active infection. Patients had to be off anti-infective agents.
13. Comorbidities that would have increased the risk of toxicity.
14. Concurrent administration of other anticancer therapies. Bisphosphonate or rank-ligand inhibitor therapy for pre-existing bone metastases or osteoporosis was allowed.
15. Known central nervous system (CNS) metastases, as evidenced by appropriate scans, clinical symptoms, cerebral edema, and/or progressive growth (if a

suspected CNS lesion was not confirmed by pathology). Treated and stable (asymptomatic; off steroids) brain metastases were allowed.

16. Active uncontrolled cardiac disease, such as cardiomyopathy, congestive heart failure (CHF) New York Heart Association (NYHA) functional classification of ≥3, unstable angina, or myocardial infarction within 12 months before first dose of study treatment. Clinically significant cardiovascular disease, peripheral vascular disease, transient ischemic attack, cerebrovascular accident.
17. History of severe hypersensitivity reaction to any of the products to be administered during the study, including mammalian cell-derived drug products, taxanes, bevacizumab, murine proteins, or excipients in their formulations.
18. Clinical contraindication to treatment with steroids preventing use as part of paclitaxel premedication.
19. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant.
20. Immunocompromised patients, including known seropositivity for human immunodeficiency virus (HIV).
21. Known or demonstrated hepatitis infection as listed below. Testing to demonstrate eligibility was required only in countries where regulations mandated testing. In all other countries, testing was required to be considered if a patient was at risk for having undiagnosed infection (for example, because of a history of injection drug use or geographic location).
    - Hepatitis B infection as detected by positive testing for hepatitis B surface antigen (HBsAg), and detectable viral load.
    - Hepatitis C infection as detected by positive hepatitis C antibody (HCAb) and detectable viral load.

22. Participation in other clinical studies involving investigational drug(s) within 4 weeks before randomization and/or during study participation. Patients participating in observational studies not involving investigational drug(s) and/or long-term follow-up of studies involving investigational drug(s) in which treatment had been completed ≥4 weeks before randomization were not excluded.
23. Other severe acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration, or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.
24. Patients who were investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who were sponsor employees directly involved in the conduct of the trial.
25. Prior treatment with immunotherapy or bevacizumab.

The listing above represents the final eligibility criteria for the study, and is reflective of Final Protocol Amendment 3, 10 June 2016.

Table S1 Patient enrollment by country (intent-to-treat population)

	PF-06439535 group (N=358)	**Bevacizumab-EU group (N=361)**
Australia	3 (0.8)	3 (0.8)
Brazil	7 (2.0)	7 (1.9)
Bulgaria	1 (0.3)	0
Chile	5 (1.4)	5 (1.4)
Croatia	1 (0.3)	0
Czech Republic	2 (0.6)	4 (1.1)
France	1 (0.3)	7 (1.9)
Germany	17 (4.7)	16 (4.4)
Greece	8 (2.2)	10 (2.8)
Hungary	30 (8.4)	22 (6.1)
India	14 (3.9)	16 (4.4)
Italy	2 (0.6)	3 (0.8)
Japan	8 (2.2)	11 (3.0)
Korea	4 (1.1)	1 (0.3)
Malaysia	2 (0.6)	1 (0.3)
Netherlands	2 (0.6)	2 (0.6)
Philippines	1 (0.3)	1 (0.3)
Poland	23 (6.4)	17 (4.7)
Romania	30 (8.4)	32 (8.9)
Russia	88 (24.6)	88 (24.4)
South Africa	1 (0.3)	2 (0.6)
Spain	6 (1.7)	4 (1.1)
Taiwan	1 (0.3)	0
Thailand	5 (1.4)	10 (2.8)
Turkey	15 (4.2)	17 (4.7)
Ukraine	76 (21.2)	76 (21.1)
United States	5 (1.4)	6 (1.7)

Bevacizumab-EU reference bevacizumab sourced from the European Union; *N* number of patients randomized

Data are presented as number (%) of patients

Table S2 Reasons for discontinuation from treatment (safety population)

	PF-06439535 group (N=356)	**Bevacizumab-EU group (N=358)**
Primary reason for discontinuation from bevacizumab treatment[a]		
Adverse event	63 (17.7)	49 (13.7)
Completed	54 (15.2)	39 (10.9)
Global deterioration of health status	14 (3.9)	12 (3.4)
Lost to follow-up	3 (0.8)	5 (1.4)
Objective progression or relapse	176 (49.4)	207 (57.8)
Other	4 (1.1)	8 (2.2)
Protocol violation	2 (0.6)	2 (0.6)
Study terminated by sponsor[b]	0	1 (0.3)
Patient died	18 (5.1)	22 (6.1)
Patient refused continued treatment for reason other than adverse event	21 (5.9)	13 (3.6)
Total[c]	**355 (99.7)**	**358 (100.0)**
Primary reason for discontinuation from paclitaxel treatment		
Adverse event	47 (13.2)	51 (14.2)
Completed[d]	250 (70.2)	245 (68.4)
Global deterioration of health status	10 (2.8)	8 (2.2)
Lost to follow-up	1 (0.3)	3 (0.8)
Objective progression or relapse	25 (7.0)	26 (7.3)
Other	3 (0.8)	4 (1.1)
Protocol violation	1 (0.3)	2 (0.6)
Patient died	13 (3.7)	13 (3.6)
Patient refused continued treatment for reason other than adverse event	6 (1.7)	6 (1.7)
Total	**356 (100.0)**	**358 (100.0)**

Primary reason for discontinuation from carboplatin treatment		
Adverse event	43 (12.1)	45 (12.6)
Completed[d]	253 (71.1)	250 (69.8)
Global deterioration of health status	11 (3.1)	8 (2.2)
Lost to follow-up	1 (0.3)	3 (0.8)
Objective progression or relapse	25 (7.0)	26 (7.3)
Other	3 (0.8)	4 (1.1)
Protocol violation	1 (0.3)	2 (0.6)
Patient died	13 (3.7)	14 (3.9)
Patient refused continued treatment for reason other than adverse event	6 (1.7)	6 (1.7)
Total	**356 (100.0)**	**358 (100.0)**

Bevacizumab-EU reference bevacizumab sourced from the European Union; *N* number of patients who received study treatment

Data are presented as number (%) of patients

Final data after study completion on 22 December 2017

[a] PF-06439535 and bevacizumab-EU discontinuations may have occurred concurrently with chemotherapy discontinuations

[b] One patient in the bevacizumab-EU group was indicated as "study terminated by sponsor" by the investigator; however, this patient was considered to have met definition of study completion

[c] One patient in the PF-06439535 group received paclitaxel and carboplatin but withdrew before receiving PF-06439535

[d] Patients had completed 4–6 cycles of paclitaxel and carboplatin

Table S3 All-causality treatment-emergent adverse events of special interest (safety population)

Category	System organ class and MedDRA preferred term[a]	PF-06439535 group (N=356)	Bevacizumab-EU group (N=358)
Arterial thromboembolic events	**Total**		
	Total	8 (2.2)	7 (2.0)
	Cardiac disorders		
	Acute myocardial infarction	1 (0.3)	1 (0.3)
	Myocardial infarction	1 (0.3)	1 (0.3)
	Silent myocardial infarction	0	1 (0.3)
	Nervous system disorders		
	Cerebral ischemia	2 (0.6)	0
	Cerebrovascular insufficiency	1 (0.3)	0
	Ischemic stroke	0	3 (0.8)
	Vascular disorders		
	Embolism arterial	2 (0.6)	1 (0.3)
	Peripheral artery thrombosis	1 (0.3)	0
	Arterial occlusive disease	0	1 (0.3)
Bleeding/hemorrhage (including pulmonary hemorrhage)	**Total**		
	Total	83 (23.3)	69 (19.3)
	Gastrointestinal disorders		

	Hematochezia	3 (0.8)	1 (0.3)
	Hemorrhoidal hemorrhage	2 (0.6)	0
	Gingival bleeding	17 (4.8)	16 (4.5)
	Anal hemorrhage	1 (0.3)	0
	Lip hemorrhage	1 (0.3)	0
	Lower gastrointestinal hemorrhage	1 (0.3)	0
	Melena	1 (0.3)	0
	Mouth hemorrhage	1 (0.3)	0
	Rectal hemorrhage	1 (0.3)	1 (0.3)
	Hematemesis	0	1 (0.3)
	Injury, poisoning and procedural complications		
	Procedural hemorrhage	1 (0.3)	0
	Subarachnoid hemorrhage	0	1 (0.3)
	Nervous system disorders		
	Cerebral hemorrhage	1 (0.3)	0
	Hemorrhagic stroke	1 (0.3)	0
	Renal and urinary disorders		
	Hematuria	8 (2.2)	9 (2.5)
	Respiratory, thoracic and mediastinal disorders		

	Epistaxis	41 (11.5)	33 (9.2)
	Hemoptysis	15 (4.2)	13 (3.6)
	Laryngeal hemorrhage	1 (0.3)	0
	Pulmonary hemorrhage	3 (0.8)	3 (0.8)
	Skin and subcutaneous tissue disorders		
	Petechiae	0	1 (0.3)
	Vascular disorders		
	Hemorrhage	1 (0.3)	0
	Subgaleal hematoma	1 (0.3)	1 (0.3)
	Shock hemorrhagic	0	1 (0.3)
Cardiac disorders	**Total**		
	Total	29 (8.1)	29 (8.1)
	Cardiac disorders		
	Bundle branch block right	2 (0.6)	0
	Extrasystoles	2 (0.6)	0
	Mitral valve incompetence	2 (0.6)	0
	Tricuspid valve incompetence	2 (0.6)	0
	Tachycardia	4 (1.1)	3 (0.8)
	Left ventricular dysfunction	3 (0.8)	2 (0.6)
	Cardiac arrest	2 (0.6)	1 (0.3)
	Ventricular extrasystoles	2 (0.6)	1 (0.3)

	Angina unstable	1 (0.3)	0
	Degenerative aortic valve disease	1 (0.3)	0
	Diastolic dysfunction	1 (0.3)	0
	Left atrial dilatation	1 (0.3)	0
	Mitral valve sclerosis	1 (0.3)	0
	Sinus tachycardia	1 (0.3)	0
	Ventricular flutter	1 (0.3)	0
	Cardiac failure	2 (0.6)	2 (0.6)
	Acute coronary syndrome	1 (0.3)	1 (0.3)
	Acute myocardial infarction	1 (0.3)	1 (0.3)
	Cardiac septal hypertrophy	1 (0.3)	1 (0.3)
	Cardiovascular insufficiency	1 (0.3)	1 (0.3)
	Left ventricular hypertrophy	1 (0.3)	1 (0.3)
	Myocardial infarction	1 (0.3)	1 (0.3)
	Pericardial effusion	1 (0.3)	1 (0.3)
	Supraventricular extrasystoles	1 (0.3)	1 (0.3)
	Arrhythmia	1 (0.3)	2 (0.6)
	Arteriosclerosis coronary artery	0	1 (0.3)
	Bradycardia	0	1 (0.3)
	Cardiomyopathy	0	1 (0.3)
	Metabolic cardiomyopathy	0	1 (0.3)

	Mitral valve disease	0	1 (0.3)
	Myocardial ischemia	0	1 (0.3)
	Palpitations	0	1 (0.3)
	Pericarditis	0	1 (0.3)
	Right ventricular failure	0	1 (0.3)
	Silent myocardial infarction	0	1 (0.3)
	Sinus bradycardia	0	1 (0.3)
	Supraventricular tachycardia	0	1 (0.3)
	Cardio-respiratory arrest	0	2 (0.6)
	Atrial fibrillation	0	3 (0.8)
Congestive heart failure	**Total**		
	Total	4 (1.1)	9 (2.5)
	Cardiac disorders		
	Cardiac failure	2 (0.6)	2 (0.6)
	Right ventricular failure	0	1 (0.3)
	Investigations		
	Ejection fraction decreased	2 (0.6)	5 (1.4)
	Respiratory, thoracic and mediastinal disorders		
	Pulmonary edema	0	1 (0.3)
Hypertension, only Grade 3 or higher	**Total**		

	Total	34 (9.6)	32 (8.9)
	Investigations		
	Blood pressure increased	1 (0.3)	0
	Blood pressure systolic increased	0	1 (0.3)
	Vascular disorders		
	Hypertension	33 (9.3)	31 (8.7)
	Hypertensive crisis	0	1 (0.3)
Proteinuria/nephrotic syndrome	**Total**		
	Total	28 (7.9)	34 (9.5)
	Renal and urinary disorders		
	Nephrotic syndrome	1 (0.3)	1 (0.3)
	Proteinuria	28 (7.9)	34 (9.5)
Venous thromboembolic events	**Total**		
	Total	13 (3.7)	11 (3.1)
	Respiratory, thoracic and mediastinal disorders		
	Pulmonary embolism	10 (2.8)	6 (1.7)
	Pulmonary infarction	0	1 (0.3)
	Vascular disorders		
	Brachiocephalic vein occlusion	1 (0.3)	0
	Brachiocephalic vein thrombosis	1 (0.3)	0

	Deep vein thrombosis	1 (0.3)	1 (0.3)
	Paget-Schroetter syndrome	0	1 (0.3)
	Subclavian vein thrombosis	0	1 (0.3)
	Thrombophlebitis superficial	0	1 (0.3)
	Venous thrombosis	0	1 (0.3)
Gastrointestinal perforation	**Total**		
	Total	0	3 (0.8)
	Gastrointestinal disorders		
	Small intestinal perforation	0	1 (0.3)
	Infections and infestations		
	Appendicitis perforated	0	1 (0.3)
	Peritonitis	0	1 (0.3)
Wound-healing complications	**Total**		
	Total	1 (0.3)	0
	Infections and infestations		
	Wound abscess	1 (0.3)	0

Bevacizumab-EU reference bevacizumab sourced from the European Union; *N* number of patients evaluable for adverse events

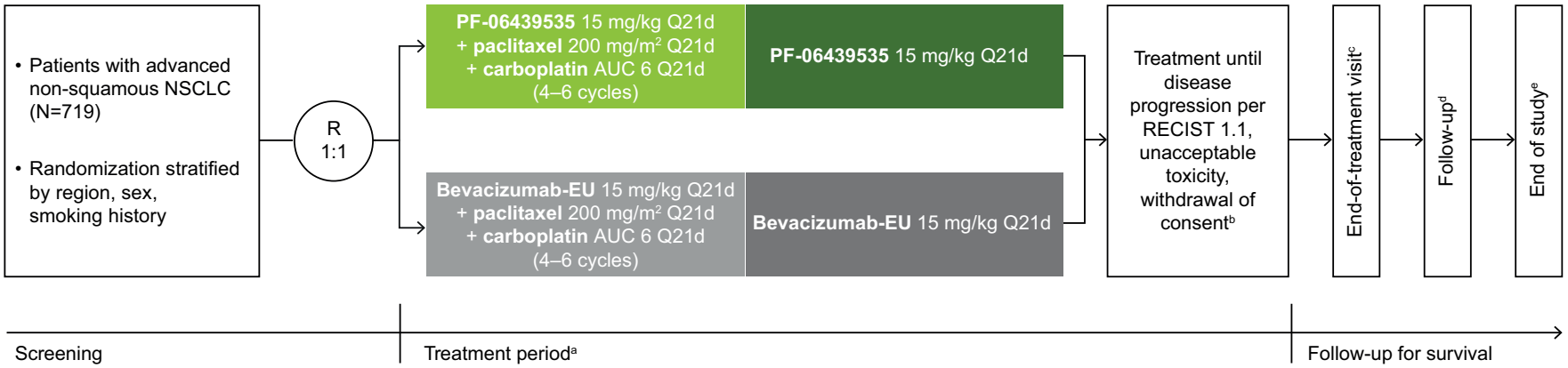
Data are presented as number (%) of patients

Final data after study completion on 22 December 2017

Data collected up to 28 days after the last dose of study drug or to start of subsequent anticancer therapy, whichever came first

[a] Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 coding dictionary applied

Fig. S1 Study schema



PF-06439535 or bevacizumab-EU: 15 mg/kg by intravenous infusion on Day 1 of each 21-day cycle. Initial dose delivered over 90 minutes. 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

Paclitaxel: 200 mg/m^2 by intravenous infusion over 3 hours on Day 1 of each 21-day cycle. Dose reduction for toxicity allowed

Carboplatin: AUC of 6 mg/mL·min by intravenous infusion over a minimum of 15 minutes on Day 1 of each 21-day cycle. Dose reduction for toxicity allowed

On treatment days when PF-06439535 or bevacizumab-EU was administered in combination with chemotherapy, the order of administration was: paclitaxel, carboplatin, and PF-06439535 or bevacizumab-EU. All patients were to be pre-medicated before paclitaxel administration to prevent severe hypersensitivity reaction

[a] Patients who continued to receive study treatment after 1 year had assessments performed according to local standard of care. Data collection was reduced, although tumor assessment and safety data collection were required

[b] Additional reasons for discontinuing treatment with PF-06439535 or bevacizumab-EU included investigator discretion, death, or the end of the study being reached

[c] Patients discontinuing all study treatment were required to be evaluated 28 (+7) days after last dose or before the start of new anticancer therapy if initiated within 28 days after the last dose

[d] After discontinuation from treatment, survival status was collected by telephone contact every 2 months (±14 days) until death or 1 year from patient randomization

[e] Last subject last visit was defined as up to 1 year from randomization of the last available patient plus 28-day follow-up

AUC area under the concentration–time curve; *bevacizumab-EU* reference bevacizumab sourced from the European Union; *NSCLC* non-small-cell lung cancer; *Q21d* every 21 days; *R* randomization; *RECIST 1.1* Response Evaluation Criteria in Solid Tumors version 1.1