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

Compound:	PF-06439535
Compound Name:	Not Applicable
United States (US) Investigational New Drug (IND) Number:	117,038
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Protocol Number:	B7391003
Phase:	3

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 3	10 June 2016	• For European Union (EU) change primary analysis from risk ratio (RR) to risk difference (RD) per Committee for Medicinal Products for Human Use (CHMP) request • Schedule of activities (SoA) Table 1 and Table 2 merged to clarify treatment periods and required procedures, remove redundancies and streamline text by referring to specific protocol sections rather than repeating instructions • Bevacizumab background and adverse event profile updated to reflect recent updates to Investigator Brochure based on updated prescribing information • Inclusion criterion 2: clarify criterion for intended study population • Inclusion criterion 6: window around baseline scan removed; specified in SoA • Inclusion criterion 8: addition of plasma creatinine and UPC ratio • Inclusion criterion 13: postmenopausal language revised per protocol template • Exclusion criterion 3: added language that was previously in body of protocol, to require review of mutation testing results prior to randomization, if testing is performed • Exclusion criterion 5: clarified language to exclude prior systemic therapy except prior neoadjuvant or adjuvant therapy if accompanied by surgery • Exclusion criterion 6: reduced window for prior radiotherapy from 4 weeks to 2 weeks

		• Exclusion criterion 7: clarify allowed anticoagulation/NSAID therapy • Exclusion criterion 10: radiotherapy removed since previously addressed in exclusion criterion 6 • Exclusion criterion 12: language revised to exclude active infections and remove window for prior anti-infective agents • Exclusion criterion 15: language added to define and allow treated and stable brain metastases • Exclusion criterion 19: contraception language removed as previously stated in inclusion criterion 13. • Exclusion criterion 21: clarification to exclude active hepatitis B and C infection instead of past infection • Exclusion criterion 25: added prior immunotherapy and bevacizumab • Remove language regarding investigator's judgment in the following criterion: exclusion criteria 2 (tumor involving major blood vessels): "in the opinion of the investigator"; 13 (comorbidities) "as per the investigator's discretion"; 21 (hepatitis infection) "based on investigator clinical judgment" • Addition of time window for protocol required testing (Screening); clarification of timeframe for vital sign (within 30 minutes) and randomization (no more than 1 day prior to Day 1) • Clarification of head CT/MRI requirement at time of confirmation scan • Inclusion of ECG in SOA as separate footnote that was previously inadvertently

		omitted • Removal of redundancy around birth control requirements for female partners of study subjects to reflect updated protocol template language • Clarifications to bevacizumab dose adjustment guidelines/ Table 3 • Drug administration and dosing section added to clarify dose calculations and dosing algorithms for all three study drugs, including threshold for protocol deviations • Carboplatin: clarify formulas used to calculate the dose • Concomitant medications: language added to allow use of bisphosphonates and Rank-Ligand inhibitors (previously stated in eligibility section) • Update of footnotes, references, template updates and typographical or clerical errors • Removal of redundancies to improve readability, address discrepancies among redundant sections, and to provide more clarity. • Clarification of enrollment, secondary endpoints, last subject last visit, end of treatment, and end of trial • Inclusion of wording for early unblinding for PK per sponsor requirement • Appendix 3 – Tumor staging added for reference
Amendment 2	06 July 2015	Changes incorporate feedback from investigators, regulatory agencies, and protocol template updates: • Clarification of Study Design language.

		• Update to global sample size, statistical considerations, and addition of Japan specific statistical analysis. • Removal of HBsAb test from SOA and protocol body. • Changed 5% to 10% throughout protocol regarding bevacizumab dose reductions due to change in weight. • Change of Partial Thromboplastin Time to Activated Partial Thromboplastin Time in SOA and protocol body. • Clarification of disease sites for tumor assessments in SOA and protocol body. • Clarification of mutation testing language. • Addition of reference to eligibility form to SOA Randomization section and protocol body. • SOA footnote #18 addition of dose delay language. • Clarification of survival follow-up language in SOA and protocol body. • Clarification of disease sites for CT and MRI throughout protocol. • Addition of clarification 'based on investigator clinical judgment' to exclusion criteria 21. • Addition of platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel and carboplatin, pegylated liposomal doxorubicin or topotecan, to bevacizumab US indications per update to USPI in November 2014.

		• Simplification of injection site information. • Addition of maximum allowed doses for carboplatin. • Clarification of inclusion criteria #6. • Clarification of exclusion criteria #2. • Clarification of exclusion criteria #15. • Addition of exclusion criteria regarding local radiation for painful bone metastases within the past 4 weeks. • Addition of inclusion criteria to require that patients be eligible to receive study treatment of bevacizumab, paclitaxel, and carboplatin for the treatment of advanced or metastatic non-squamous NSCLC. • Clarification of dosing, dose reduction, missed doses, and administration language. • Addition of instructions for bevacizumab preparation and administration for patients >110 kg. • Per standard of care, removal of 60-minute wait time following completion of paclitaxel, and clarification of carboplatin administration time. • Addition of toxicity information. • Addition of required discontinuation of bevacizumab due to severe or life threatening infusion reaction that is considered to be secondary to bevacizumab and not paclitaxel and/or carboplatin. • Table 3 clarification of congestive heart failure and infusion related reaction guidelines. • Clarification of Section 5.8 immunizations.

		• Addition of information on measurable lesions. • Removal of bone scan language. • Addition of blood sample collection time points for ADA/NAb and corresponding drug concentrations, as well as the plan to analyze the samples, according to the Scientific Advice from the EMA. • Clarification of population PK data analysis. • Update of document references. • Update of newly required sponsor template language and typographical or clerical errors.
Amendment 1 (distributed to EU Voluntary Harmonization Process participating countries **only**)	05 May 2015	• Addition of inclusion criteria to require that patients be eligible to receive study treatment of bevacizumab, paclitaxel, and carboplatin for the treatment of advanced or metastatic non-squamous NSCLC. • Clarification of mutation testing language. • Clarification of survival follow-up language. • Clarification of bevacizumab dose reductions. • Table 3 clarification of congestive heart failure and infusion related reaction guidelines.
Original protocol	04 November 2014	Not Applicable

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
AST	aspartate transaminase
ATE	arterial thromboembolic events
AUC_{72}	area under the curve (0 to 72 hours)
AUC_T	area under the curve (0 to last quantifiable time point)
AUC_{inf}	area under the curve (0 to time infinity)
CBC	complete blood count
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
C_{max}	maximum serum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CR	complete response
CRF	case report form
CSA	clinical study agreement
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DAI	dosage and administration instructions
DEHP	di-(2-ethylhexyl)phthalate
DICOM	Digital Imaging and Communications in Medicine
DNA	deoxyribonucleic acid
DOR	duration of response
DVD	digital video disc
EC	ethics committee
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EMA	European Medicines Authority
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)

Abbreviation	Term
FIGO	International Federation of Gynecology and Obstetrics
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCAb	hepatitis C antibody
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	institutional ethics committee
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	institutional review committee
IRR	infusion related reaction
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IWRS	interactive web response system
KDR	kinase insert domain receptor
LFT	liver function test
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
LSLV	last subject last visit
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance image (imaging)
MUGA	multi gated acquisition scan
N/A	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OTC	over the counter
PCD	primary completion date
PD	Progressive disease
PFS	progression-free survival

Abbreviation	Term
PK	pharmacokinetics
PMAP	population modeling analysis plan
PMAR	population modeling analysis report
PP	per-protocol
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
RECIST	Response Evaluation Criteria In Solid Tumors
RD	risk difference
RR	risk ratio (relative risk)
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SOA	schedule of activities
SOC	standard of care
SPC	summary of product characteristics
SRSD	single reference safety document
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
UPC	urine protein to creatinine ratio
US	United States
USP	United States Pharmacopeia
USPI	United States package insert
Vc	central volume
Vd	volume of distribution
VEGF	vascular endothelial growth factor
Vp	peripheral volume
WHO	World Health Organization
X ULN	times the upper limit of normal

PROTOCOL SUMMARY

Introduction

PF-06439535 (bevacizumab-Pfizer) is being developed as a potential biosimilar to bevacizumab. AVASTIN® (bevacizumab) is the commercially available bevacizumab product in the United States, European Union (bevacizumab-EU), Japan, and other regions.

Bevacizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that is composed of 2 heavy chains and 2 light chains, which are linked by disulfide bonds. It has an approximate molecular weight of 149kD and is produced in mammalian Chinese hamster ovary cells.

Bevacizumab is a mAb that binds to and inhibits the biological activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab-Pfizer has the same primary amino acid sequence as AVASTIN® and will be developed to be highly similar (biosimilar) to AVASTIN® as sourced from the European Union (bevacizumab-EU) and from the United States (bevacizumab-US).

STUDY OBJECTIVES AND ENDPOINTS

Primary Objective

- 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 non-squamous non-small cell lung cancer (NSCLC).

Secondary Objectives

- To evaluate the safety of bevacizumab-Pfizer 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 bevacizumab-Pfizer and bevacizumab-EU;
- To evaluate the immunogenicity of bevacizumab-Pfizer and bevacizumab-EU.

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) version 1.1.

Secondary Endpoints

- 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

- 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

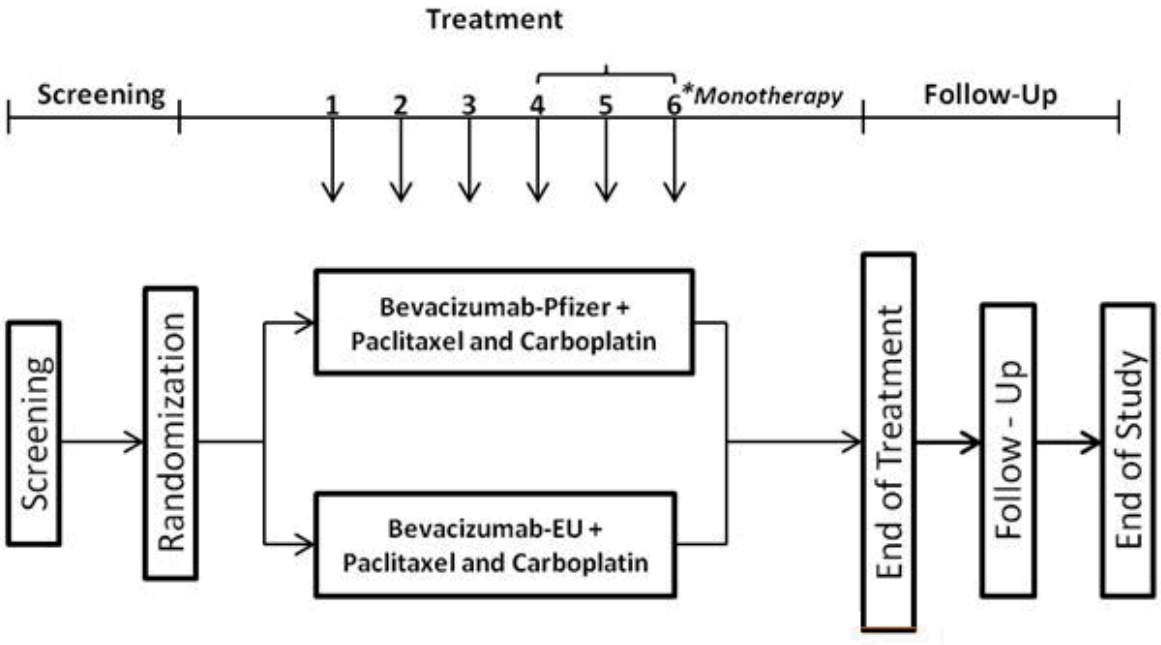
- Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing antibodies (NAb) up to 1 year from randomization

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 for at least 4 and no more than 6 cycles, followed by the assigned blinded bevacizumab monotherapy. 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). Patients will participate in the study for approximately 13 months. This includes about 1 month of screening and at least 1 year for treatment and follow-up. Actual length of participation for individual patients will depend upon the actual duration of treatment. Minimum expected participation is approximately 1 year unless shorter due to death, withdrawal of consent, or early termination of the trial. See Figure 1 for details.

Figure 1. Study Schema



* Assigned bevacizumab monotherapy: Following completion of at least 4 and no more than 6 cycles of chemotherapy

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. Schedule of Activities

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**[26]
	≤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[28]	
Study Visit Window (days)	-4	**0**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	±7
Pre-treatment Documentation										
Informed Consent[1]	X									
Demography, Medical /Cancer History, mutation status[2]	X									
Complete Physical Exam[3]	X									
Brief Physical Exam[4]		X	X	X	X	X	X	X	Per local SOC	X
Vital signs[5]	X	X	X	X	X	X	X	X	Per local SOC	X
Baseline Signs and Symptoms[6]		X							Per local SOC	
ECOG Performance Status (Appendix 1)	X	X	X	X	X	X	X	X	Per local SOC	X
Inclusion/Exclusion Criteria[7]	X									
Laboratory Studies and Tests										
Hematology[8]	X	X	X	X	X	X	X	X	Per local SOC	X
Blood Chemistry[9]	X	X	X	X	X	X	X	X	Per local SOC	X
Coagulation[10]	X								Per local SOC	X
Pregnancy Test[11]	(X)[11]	X	X	X	X	X	X	X	Per local SOC	X
Urinalysis[12]	X	X	X	X	X	X	X	X	Per local SOC	X

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**[26]
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Study Visit Window (days)	**-4**	**0**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	±7
Serological Tests [13]	(X)									
Immunogenicity (ADA/NAb)[14]		X	X	X	X		X	X		X
Pharmacokinetics[15]		X	X	X	X	X	X	X		X
Tumor Assessments										
Brain scan[16]	X	As clinically indicated and at time of confirmatory scan for PR/CR							Per local SOC	
CT or MRI of Chest, Abdomen, and other disease sites,[16]	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 SOC	X
Randomization										
Randomization[17]		X								
Drug Administration										
Paclitaxel and Carboplatin [18]		X	X	X	X	Optional	Optional			
Blinded Bevacizumab[19]		X	X	X	X	X	X	X	X	
Other Clinical Assessments										
12-lead ECG[20]	X									X
MUGA or ECHO [21]	X									X
Contraception check[22]	X	X	X	X	X	X	X	X	Per local SOC	X
Adverse Events[23]	X	Monitored continuously								
Prior Medications/Treatments[24]	X									
Concomitant Treatments[25]		Monitored continuously								
Survival Follow-up[27]		Every 2 months (±14 days) from last study drug administration								

Footnotes

1. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
2. **Demographics and Medical/Cancer History:** To include 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 is not required, however patient records are to be reviewed for **known** sensitizing EGFR mutations (for example, deletion 19 or L858R) or EML4-ALK translocation positive mutations. If mutation testing is performed, samples must be tested

	by local approved laboratories, and the results must be reviewed and confirmed as negative for mutations prior to randomization.
3.	**Physical Examination:** includes head, ears, eyes, nose, mouth, skin, neck, heart and lung examinations, lymph nodes, abdomen, musculoskeletal, neurological systems, and weight. Height will be recorded at Screening only. Genitourinary examination is only required if directed by signs or symptoms.
4.	**Brief Physical Examination:** performed as directed by signs and symptoms on Day 1 (pre-dose) of each cycle after Screening.
5.	**Vital Signs:** Temperature should be taken using the same method throughout the study. Blood pressure, heart rate, and respiratory rate should be taken with the patient in the supine or sitting position after the patient has been resting quietly for at least 5 minutes and prior to dosing on dosing days. Weight should be taken at the beginning of each cycle and will be used for dose calculation in accordance with Section 5.4.1. On days of an infusion, vital signs should be taken within 30 minutes before the first infusion and within 30 minutes of the end of the last infusion.
6.	**Baseline Signs and Symptoms:** observed after Screening and before Cycle 1, Day 1 pre-dose are recorded as part of Medical History or as Brief Physical Exam findings.
7.	**Inclusion/Exclusion Criteria:** Eligibility criteria are to be reviewed to confirm eligibility prior to randomization.
8.	**Hematology:** Tests include hemoglobin, white blood cells, platelets, and absolute neutrophil count. Results of tests must be reviewed prior to each cycle of therapy.
9.	**Chemistry:** Tests include ALT, AST, alkaline phosphatase, total bilirubin, serum or plasma creatinine, sodium, potassium, total calcium, BUN or urea, magnesium, and albumin, and results must be reviewed prior to each cycle of therapy
10.	**Coagulation:** Tests include International Normalized Ratio (INR) for prothrombin time (or prothrombin time if INR is not available) and activated partial thromboplastin time. Tests may be performed more frequently if clinically indicated. Results of tests must be reviewed prior to dosing on Cycle 1 Day 1.
11.	**Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test with sensitivity of at least 25 mIU/mL will be performed by the local certified laboratory, and 2 negative tests are required before receiving the first dose of investigational product. The second negative test should be done during the first 5 days of the menstrual period, immediately preceding the first dose of any study treatment. See protocol Section 7.4 for details.
12.	**Urinalysis:** If the results of the dipstick urine protein indicate ≥2+ proteinuria, follow-up should be performed with a quantitative urine protein analysis according to local standard practices with data captured on the AE CRF if AE criteria are met. The results of the dipstick must be reviewed prior to each cycle of therapy.
13.	**Serological tests (optional):** See Exclusion criterion #21 for specifications. If testing is performed, samples must be tested by local approved laboratories, and the results must be reviewed and eligibility confirmed prior to randomization.
14.	**Immunogenicity:** Blood Sampling for ADA/NAb prior to blinded bevacizumab. If adverse events are considered possibly related to ADA formation, an additional sample may be collected at the time of the immunogenicity-related adverse events.
15.	**PKs:** Blood Sampling for Drug Concentration prior to blinded bevacizumab. Post-dose samples will also be 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 is conducted at the time of immunogenicity-related adverse events, a serum sample for drug concentration will also be collected at that sametime point .
16.	**Tumor Assessments:** Assessments must include CT with contrast or MRI of head, chest, abdomen (including adrenals) and other disease sites such as pelvis if clinically indicated. Tumor assessments are NOT to be scheduled based on cycle length or number of cycles received. Assessment delay to conform to treatment delays is not permitted. The same method of tumor assessments should be used throughout the trial. A confirmatory scan is required approximately 6 weeks (+7 days) for a CR/PR.
17.	**Randomization:** Unless clinically indicated, screening physical examination and laboratory assessments including blood chemistry, hematology, and urinalysis, are not required to be repeated for randomization if they are performed ≤7 days prior to Cycle 1, Day 1, and results meet eligibility criteria. Eligibility criteria are to be reviewed and sponsor confirmation of eligibility must be received prior to randomization. Randomization is required on day 1 of first dose (but no more than 1 day prior).
18.	**Paclitaxel and carboplatin administration:** per dosing algorithm in protocol for a total of at least 4 and no more than 6 cycles. Premedication are to be administered according to the local label or institutional guidelines. Dose delay (up to 2 weeks) and dose reduction will be permitted per local guidelines. See protocol Section 5.4.4 for details.

19.	**Blinded Bevacizumab:** 15 mg/kg by intravenous (IV) infusion on Day 1 of each of the 3-week (21-day) cycles, see See protocol Section 5.4.2 for details
20.	**ECG: 1**2-lead ECG will be obtained at Screening, as clinically indicated, and at the End-of-Treatment Visit.
21.	**MUGA or ECHO:** to assess LVEF **(**Left ventricular ejection fraction); the original methodology used for each patient must be used throughout the trial.
22.	**Contraception Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. See protocol Section 4.4.1 for details.
23.	**Adverse Events:** Patients must be followed for adverse events 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 have resolved or are determined to be "chronic" or "stable", whichever is later as assessed by the investigator. Serious adverse events should be monitored and reported from the time that the patient provides informed consent, as described in the protocol, through and including 28 calendar days after the last study treatment. Serious adverse events considered related to study treatments are to be reported whenever they occur even after 28 days after the last study treatment.
24.	**Prior Medication/ Treatments:** Medications and non-drug treatments delivered prior to initial dosing will be recorded from 28 days prior to the start of study treatment.
25.	**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 will enter the follow-up phase during which survival and new anti-cancer therapy information will be collected until the study is completed or is terminated early.
26.	**End-of-Treatment/Withdrawals:** When patients discontinue all study treatment, patients should 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.
27.	**Survival Follow-up:** After discontinuation from treatment, survival status will be collected by telephone contact every 2 months (±14 days) until death or 1 year from patient randomization,.
28.	**1 year post-randomization:** Patients who continue to receive study treatment after one year will have assessments performed according to local standard of care (SOC); reduced data collection, although tumor assessment and safety data collection are required.

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APPENDICES

1. INTRODUCTION

PF-06439535 (bevacizumab-Pfizer) is being developed as a potential biosimilar to bevacizumab. AVASTIN® (bevacizumab) is the commercially available bevacizumab product in the United States (bevacizumab-US), European Union (bevacizumab-EU), Japan, and other regions.

Bevacizumab is a recombinant humanized IgG1 monoclonal antibody (mAb) that is composed of 2 heavy chains and 2 light chains, which are linked by disulfide bonds. It has an approximate molecular weight of 149kD and is produced in mammalian Chinese hamster ovary cells.

Bevacizumab is a mAb that binds to and inhibits the biological activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab-Pfizer has the same primary amino acid sequence as AVASTIN® and will be developed to be highly similar (biosimilar) to AVASTIN® as sourced from the European Union (bevacizumab-EU) and from the United States (bevacizumab-US).

1.1. Indication

Bevacizumab-Pfizer is being evaluated as first-line treatment of patients with advanced non-squamous non-small cell lung cancer (NSCLC) and for extrapolation to other AVASTIN® (bevacizumab) indications.

In the United States bevacizumab is approved for metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment; metastatic colorectal cancer, with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line AVASTIN®-containing regimen; non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease; glioblastoma, as a single agent for adult patients with progressive disease following prior therapy; metastatic renal cell carcinoma with interferon alfa; cervical cancer in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease; and platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan.[1]

In the European Union bevacizumab is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine-based chemotherapy; first-line treatment in combination with paclitaxel of adult patients with metastatic breast cancer; first-line treatment in combination with capecitabine of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate; first-line treatment in addition to platinum-based chemotherapy of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology; first line treatment in combination with interferon alfa-2a of adult patients with advanced and/or metastatic renal cell cancer; front-line treatment in combination with

carboplatin and paclitaxel of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer; treatment of adult patients in combination with carboplatin and gemcitabine with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.[2]

In Japan bevacizumab is indicated for unresectable advanced or recurrent colorectal cancer; unresectable advanced or recurrent non-squamous non-small cell lung cancer; inoperable or recurrent breast cancer; malignant glioma including glioblastoma; and ovarian cancer.[3]

1.2. Background and Rationale

1.2.1. Background

Biological therapeutics are large complex protein molecules that require a wide variety of analytical methods to ensure consistent quality. As a result of their complexity and manufacturing methods, biologic products have inherent variability and the development of an exact replicate is not possible. Biosimilars are structurally highly similar versions of marketed biological medicines that are supported by appropriate analytical testing and clinical trials to demonstrate that they are sufficiently "similar" (both in structure and clinical function) to the marketed biological product.

Development as a biosimilar requires head-to-head comparison to an approved reference product. The European Union (EU) has a legal basis for approval of biosimilars, which defines a reference product as a product authorized in the EU (bevacizumab-EU). Similarly, the United States Biologics Price Competition and Innovation Act created an abbreviated approval pathway for biological products that are demonstrated to be biosimilar with a Food and Drug Administration (FDA)-licensed biological product (bevacizumab-US).

1.2.2. Bevacizumab

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors; Flt-1 and kinase insert domain receptor (KDR), on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis.[1,2] The blockade interaction of VEGF by bevacizumab inhibits angiogenesis and tumor growth. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

1.2.2.1. US Prescribing Information

See AVASTIN® US prescribing information.[1]

1.2.2.2. European Union Prescribing Information

See AVASTIN® EU Summary of Product Characteristics.[2]

1.2.2.3. Bevacizumab Pharmacokinetics

According to the EU Summary of Product Characteristics (quotations are italicized):

The pharmacokinetic data for bevacizumab are available from ten clinical trials in patients with solid tumours. In all clinical trials, bevacizumab was administered as an IV infusion. The rate of infusion was based on tolerability, with an initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Distribution

The typical value for central volume (Vc) was 2.73 L and 3.28 L for female and male patients respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (Vp) was 1.69 L and 2.35 L for female and male patients respectively, when bevacizumab is co-administered with anti-neoplastic agents. After correcting for body weight, male patients had a larger Vc (+20%) than female patients.

Metabolism

Assessment of bevacizumab metabolism in rabbits following a single IV dose of ^{125}I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. The metabolism and elimination of bevacizumab is similar to endogenous IgG ie, primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.

Elimination

The value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

1.2.2.4. Bevacizumab Adverse Events

The following is a summary of safety information from studies of patients receiving bevacizumab that is included in the AVASTIN® EU and US product labels. Bevacizumab is given to cancer patients who often have multiple comorbidities and it is typically administered as multiple doses in combination with cytotoxic chemotherapeutic agents. In addition, some adverse drug reactions occur after repeated doses in cancer patients.

The overall safety profile of AVASTIN® is based on data from over 4,500 patients with various malignancies, predominantly treated with AVASTIN® in combination with chemotherapy in clinical trials. The most frequently observed adverse reactions across clinical trials in patients receiving AVASTIN® were hypertension, fatigue or asthenia, diarrhea and abdominal pain. The most serious adverse reactions observed in clinical trials were gastrointestinal perforations, surgery and wound healing complications, hemorrhage, and arterial thromboembolism.

Depending on the patient population, the incidence of gastrointestinal perforation in AVASTIN®-treated patients, some fatal, ranges up to 3.2% depending on the patient population. Intra-abdominal inflammation may be a risk factor. The majority of cases occurred within 50 days of initiation of AVASTIN®.

AVASTIN® may adversely affect the wound healing process. Across several indications, Grade 3-5 wound healing complications were observed at a higher rate in patients receiving bevacizumab compared to the control arm.

AVASTIN® can result in 2 distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, central nervous system (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred more frequently in patients receiving AVASTIN® compared to patients receiving only chemotherapy. In clinical trials across all indications, the overall incidence of Grade 3-5 bleeding reactions ranged from 0.4% to 6.9% in AVASTIN®-treated patients, compared with up to 2.9% of patients in the chemotherapy control group.

Uncommon but serious and sometimes fatal arterial thromboembolic events (ATEs) including cerebrovascular accidents, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATEs occurred at a higher incidence in patients receiving AVASTIN® compared to those in the control arm. In clinical trials, the overall incidence of ATEs ranged up to 3.8% in the AVASTIN®-containing arms compared with up to 1.7% in the chemotherapy control arms.

In addition to the serious adverse reaction described above, special warnings and precautions are provided for gastrointestinal and non-gastrointestinal fistula formation, hypertension, posterior reversible encephalopathy syndrome, proteinuria, venous thromboembolism, congestive heart failure, neutropenia and infections, hypersensitivity/infusion reactions, osteonecrosis of the jaw, eye disorders, embryo-fetal toxicity and ovarian failure/infertility.

AVASTIN® has been associated with serious and sometimes fatal fistulae formation. In clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancers. Non-gastrointestinal perforations (eg, bronchopleural, tracheoesophageal, urogenital and biliary fistulae) were uncommon (≥0.1% to <1%) across indications.

An increased incidence of hypertension (all Grades) of up to 42% has been observed in AVASTIN®-treated patients, compared with up to 14% in those treated with comparator. Across clinical studies, the incidence of Grade 3 or 4 hypertension ranged from 5% to 18%.

The incidence and severity of proteinuria is increased in patients receiving AVASTIN® as compared to controls. In clinical trials, proteinuria has been reported with the range of 0.7% to 38% in patients receiving AVASTIN®. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria. Grade 4 proteinuria (nephrotic syndrome) occurred in up to 1.4% of patients receiving AVASTIN® in clinical trials, in some instances with fatal outcome.

Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of AVASTIN® were uncommon (<3%) and severe reactions occurred in 0.2% of patients. In some trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving AVASTIN® in combination with chemotherapy than chemotherapy alone – up to 5% in bevacizumab-treated patients.

Complete information for bevacizumab-Pfizer and bevacizumab-EU may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.

1.2.2.5. Bevacizumab Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Anti-drug antibodies (ADA) have been evaluated in studies with bevacizumab in cancer patient populations. Using an electrochemiluminescent based assay, 14 of 2,233 evaluable patients (0.63%) treated in clinical trials tested positive for anti-bevacizumab antibodies. Among these 14 patients, 3 tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay. The clinical significance of anti-product antibody formation is unknown.[1]

1.2.3. Bevacizumab-Pfizer

Pfizer has a step-wise development program including head-to-head comparison to AVASTIN® (bevacizumab) sourced from the United States (bevacizumab-US) and the European Union (bevacizumab-EU) with regard to chemistry, manufacturing, and controls (CMC)/quality, non-clinical and clinical features and performance. Head-to-head physiochemical and analytical data sufficiently demonstrated that bevacizumab-Pfizer is similar to bevacizumab-US and bevacizumab-EU to enable clinical studies.

Pfizer developed bevacizumab-Pfizer to have the same dosage form, route of administration, and dosing regimen as AVASTIN® sourced from both the US and EU. The dosing regimens will be consistent with those for which AVASTIN® is approved.

Responses to bevacizumab-Pfizer and bevacizumab-EU appeared similar when administered by intravenous (IV) injection to sexually- and skeletally-immature male cynomolgus monkeys (4/group) at a dose of 10 mg/kg/dose twice weekly for 1 month (9 total doses). Mean systemic exposures (as assessed by C_{max} and AUC_{72}) for bevacizumab-Pfizer and bevacizumab-EU appeared similar. Anti-drug antibodies (ADA) were not detected in animals dosed with bevacizumab-Pfizer vehicle, bevacizumab-EU vehicle, bevacizumab-Pfizer, or bevacizumab-EU. However, drug present in samples may have interfered with the detection of ADA. There were no bevacizumab-Pfizer- or bevacizumab-EU-related findings in clinical signs, body weight, food consumption, ophthalmology examinations, respiration rate, electrocardiograms, hematology, coagulation, clinical chemistry, or urinalysis parameters. All animals survived to their scheduled euthanasia and there were no bevacizumab-Pfizer- or bevacizumab-EU-related changes in organ weights or necropsy findings. The only bevacizumab-Pfizer- and bevacizumab-EU-related effect was the observation of physeal dysplasia in the distal femur, which was considered adverse for these growing animals. There was no biologically- or toxicologically-relevant difference in the incidence and severity of the physeal dysplasia between bevacizumab-Pfizer and bevacizumab-EU-dosed groups. Physeal dysplasia related to the inhibition of blood vessel formation is consistent with the known pharmacologic effects of bevacizumab on growing bone.

Pfizer has performed a single-dose pharmacokinetic similarity trial in healthy volunteers (B7391001). Healthy male subjects received 1 dose (5 mg/kg intravenously over 90 minutes) of bevacizumab-Pfizer (33 subjects), bevacizumab-US (33 subjects), or bevacizumab-EU (35 subjects). Of the 101 subjects dosed, 97 subjects had a sufficient number of PK samples to be included in the PK analysis population. PK similarity testing for a given test-to-reference comparison was to be considered demonstrated if 90% confidence intervals for the test-to-reference ratios of AUC_T, AUC_{inf} and C_{max} were within the 80-125% bioequivalence acceptance window.

For the PK similarity comparisons of bevacizumab-Pfizer to each of the 2 reference products (bevacizumab-EU and bevacizumab-US), the 90% confidence intervals for the test-to-reference ratios of C_{max}, AUC_T, and AUC_{inf} were all within the bioequivalence window of 80% to 125%. For the comparison of bevacizumab-EU to bevacizumab-US, the 90% confidence intervals of the ratios of C_{max}, AUC_T, and AUC_{inf} were also within 80% to 125%.

The observed safety profiles for all treatment arms did not show any clinically important imbalances in the secondary endpoints, including drug-related adverse events and serious adverse events, drug-related changes in laboratory parameters, and immunogenicity.

Immunogenicity was assessed through Day 100 of the study. One subject in the bevacizumab-EU treatment group tested positive for ADA at baseline. A total of 5 (5.0%) subjects tested positive at one or more time points post-dose through Day 100. Two (6.1%), 1 (2.9%), and 2 (6.1%) of total subjects from bevacizumab-Pfizer, bevacizumab-EU and bevacizumab-US, respectively, had at least one post-dose sample that tested positive through Day 100. Overall, the immunogenicity profiles of bevacizumab-Pfizer, bevacizumab-US, and bevacizumab-EU were shown to be similar in the study.

In conclusion, similarity among bevacizumab-Pfizer, bevacizumab-US, and bevacizumab-EU in terms of the primary endpoints (C_{max}, AUC_T, and AUC_{inf}) was demonstrated. The safety profiles of the drugs and incidence of anti-drug antibodies (ADA) were also similar. For more details, please refer to the Investigator Brochure.

1.2.4. Paclitaxel

Paclitaxel is a natural product with antitumor activity and is obtained via a semi-synthetic process from *Taxus baccata*. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.[4]

Paclitaxel is indicated for the treatment of metastatic breast cancer. While the paclitaxel prescribing information does not include combination with bevacizumab, the bevacizumab prescribing information specifies bevacizumab is indicated for treatment of NSCLC in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advance, recurrent or metastatic disease.

Common adverse events associated with the use of paclitaxel include neutropenia, leucopenia, thrombocytopenia, anemia, infections, hypersensitivity reactions, peripheral neuropathy, arthralgia, myalgia, gastrointestinal symptoms include nausea, vomiting, diarrhea, and mucositis, and alopecia.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Paclitaxel should not come in contact with plasticized polyvinylchloride (PVC) equipment or devices. Diluted paclitaxel must be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL (eg, cyclosporine) should not be treated with paclitaxel. Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension.

There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 times upper limit of normal (ULN). Extreme caution should be exercised when administering paclitaxel to such patients, with dose reduction as recommended in the prescribing information.

Injection site reactions to paclitaxel, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported with paclitaxel. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, ie, "recall," has been reported.

In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days. A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

1.2.5. Carboplatin

Carboplatin is a platinum coordination compound used as a cancer chemotherapeutic agent. It produces predominantly interstrand deoxyribonucleic acid (DNA) cross-links rather than DNA-protein cross links for a cell-cycle nonspecific effect. With the exception of carboplatin, there are no significant quantities of protein-free ultrafilterable platinum-containing species present in plasma. Platinum from carboplatin becomes bound irreversibly to plasma proteins and is slowly eliminated with a half-life of 5 days at minimum.[5]

Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents and for palliative treatment of ovarian carcinoma recurrent after prior chemotherapy. While the carboplatin prescribing information does not include combination with bevacizumab, the bevacizumab prescribing information specifies bevacizumab is indicated for treatment of NSCLC in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advance, recurrent or metastatic disease.

Common adverse events associated with the use of carboplatin include bone marrow suppression, anemia, thrombocytopenia, neutropenia, leucopenia, infections, bleedings, gastrointestinal toxicity including vomiting and nausea, peripheral neuropathies, nephrotoxicity, hepatic toxicity, electrolyte abnormalities, allergic reactions, injection site reactions, pain, and asthenia.

Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds; patients with pre-existing severe renal impairment, unless in the judgment of the physician and patient, the possible benefits of treatment outweigh the risks; patients with severe myelosuppression; and patients with bleeding tumors.

As is the case with other platinum compounds, allergic reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions, including anaphylaxis, in patients previously exposed to platinum therapy.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity and caution must be exercised when a patient receives both drugs.

Carboplatin can cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis.

Needles or intravenous sets containing aluminum parts that may come in contact with carboplatin should not be used for preparation or administration. Aluminum reacts with carboplatin causing precipitate formation and/loss of potency.

Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds. Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.[5]

1.2.6. Rationale

In order to develop a biosimilar, comparative clinical data is generally required to demonstrate there are no clinically meaningful differences between the proposed biosimilar product and the reference product in clinical pharmacology, efficacy, and safety. A healthy volunteer study comparing the PK of bevacizumab-Pfizer to bevacizumab-EU and bevacizumab-US, and bevacizumab-EU to bevacizumab-US, has been completed. This comparative clinical study is designed to show that there are no clinically meaningful differences in the safety and efficacy profile of bevacizumab-Pfizer as compared to bevacizumab-EU in a patient population for which bevacizumab is indicated.

In order to support global development of bevacizumab-Pfizer as a potential biosimilar, one comparator arm is included in this study. The comparator to be used in this clinical trial is bevacizumab sourced from the EU (bevacizumab-EU).

The totality of data, including the 3-way analytical similarity assessment and the 3-way PK similarity data from Study B7391001, have established a scientific bridge between bevacizumab-EU and bevacizumab-US, and therefore adequately justify the use of bevacizumab-EU as the sole comparator in the proposed comparative efficacy and safety trial.

Patients with previously untreated advanced NSCLC represent a population with well categorized safety and efficacy profile for treatment with bevacizumab and paclitaxel and carboplatin. As such, this population is considered to be a sensitive population to demonstrate that there are no clinically meaningful differences between bevacizumab-Pfizer and bevacizumab-EU.

The dose and regimen for bevacizumab-Pfizer and bevacizumab-EU in this comparative trial was chosen to be consistent with product labeling of bevacizumab-EU. The chemotherapy given with the investigational products and the regimens used are considered standard of care.[12]

Demonstration of similar safety and efficacy profiles of bevacizumab-Pfizer with the innovator product will, in part, provide evidence that bevacizumab-Pfizer is biosimilar.

In order to determine the sample size of a biosimilarity trial, a point estimate of the primary endpoint has to be made. In this study, the primary endpoint is based on best response by a second tumor assessment after 6 weeks by Week 19, which corresponds to the end of six 3-week cycles. If the investigator identifies a complete or a partial response based on RECIST 1.1 criteria, those responses should be confirmed after 6 weeks with the same imaging sequence (whenever possible). For assessment of the long term safety profile and the number of patients with anti-drug antibodies (ADA) at 1 year, the study will continue up to last subject last visit (LSLV) (see Section 13).

In order to keep this study in historical context, 3 randomized studies of bevacizumab plus paclitaxel and carboplatin were reviewed and key features were incorporated.[6,7,8] For example, the patient population is similar to that of the Phase 3 study conducted by the

Eastern Cooperative Oncology Group (ECOG).[6] Patients in that trial had recurrent or advanced non–small-cell lung cancer (Stage IIIB or IV). Eligible patients were required to have histologically or cytologically confirmed, newly diagnosed stage IIIB (malignant pleural effusion) or Stage IV cancer or recurrent non–small-cell lung cancer for which they had not received chemotherapy. Other inclusion criteria were measurable or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), an ECOG performance status of 0 or 1, and adequate hematologic, hepatic, and renal function (including urinary excretion of ≤500 mg of protein per day). Exclusion criteria included but were not limited to histologic evidence of predominantly squamous-cell cancer; central nervous system (CNS) metastases (to reduce concern about possible CNS hemorrhage); pregnancy or lactation; a history of documented hemorrhagic diathesis or coagulopathy; therapeutic anticoagulation; regular use of aspirin (>325 mg per day), nonsteroidal anti-inflammatory agents, or other agents known to inhibit platelet function; radiation therapy within 21 days before enrollment or major surgery within 28 days before enrollment; clinically significant cardiovascular disease; and medically uncontrolled hypertension.[6]

Though the eligibility criteria for this protocol are similar to those of the ECOG Phase 3 trial, there are differences with potential study population implications. First, the new staging system for lung cancer introduced in 2010[10] now includes Stage IIIB with malignant effusion into Stage IV. RECIST[11] which required measurements of lesions in 2 perpendicular directions has been replaced with RECIST 1.1,[12] which requires only the longest diameter of cancer lesions and the shortest diameter of lymph nodes to be measured. The second and perhaps biggest difference is the exclusion of patient with known tumors that have epidermal growth factor rector (EGFR) sensitizing mutations and anaplastic lymphoma kinase (ALK) rearrangements. These tumors have a high response rate to approved tyrosine kinase inhibitors (TKI) targeting these tissues such as gefitinib, erlotinib, and crizotinib.[13,14,15] Patients with these mutations are not eligible for this protocol. While obtaining tissue for these mutations is now a standard of care for patients with NSCLC, it was not at the time of the ECOG Phase 3 trial. It is not known whether patients with these mutations respond differently to chemotherapy and bevacizumab than those without the mutations, so this protocol assumes that response rates will not be different. However, patients with these mutations may live longer than those without, so PFS and survival may be different from the Phase 3 ECOG trial.

Treatment assignments in the Phase 3 ECOG trial were stratified according to measurable versus nonmeasurable disease, prior radiation, therapy versus no prior radiation therapy, prior weight loss of less than 5% versus 5% or more, and non–small-cell lung cancer, stage IIIB, with pleural effusion versus Stage IV or recurrent disease. The primary end point was overall survival. The 95% confidence intervals for death overlapped for each of these parameters in the Phase 3 ECOG trial. How response rates behaved by these stratification parameters is not known. Because response rate is the primary efficacy endpoint, only patients with measureable disease are eligible. The vast majority of patients in the Phase 3 ECOG study had no prior radiation therapy. Most patients did not have ≥5% weight loss, and this degree of weight loss did not seem to effect survival. Most patients had Stage IV disease (using the old staging system). It seems that the stratification in the Phase 3 ECOG trial provided limited benefit. In consultation with respected leaders in the

area of NSCLC, it was felt that the current study should be stratified for randomization balance by other factors. The factors chosen are region (according to drug depot supplying the site), sex (male/female), and smoking history (never/ever). It is recognized that sex and smoking history may be less important in terms of response because patients with tissue where the majority of cells are squamous cells are excluded.

Based on the data gathered thus far, bevacizumab-Pfizer appears to be similar to the innovator product; although confirmation is required in this Phase 3 study. The benefit/risk data available for bevacizumab-Pfizer, including the Phase 1 data, support the product's progression to the Phase 3 program.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary

- 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.

2.1.2. Secondary

- To evaluate the safety of bevacizumab-Pfizer 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 bevacizumab-Pfizer and bevacizumab-EU;
- To evaluate the immunogenicity of bevacizumab-Pfizer and bevacizumab-EU.

2.2. Endpoints

2.2.1. 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) version 1.1.

2.2.2. Secondary Endpoints

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

3. STUDY DESIGN

3.1. Study Overview

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; up to approximately 10% more patients may be enrolled due to operational/logistical considerations. Patients will be randomized (1:1) to receive at least 4 and no more than 6 cycles of either bevacizumab-Pfizer plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin, followed by the assigned blinded bevacizumab monotherapy. 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). Patients will participate in the study on average for approximately 13 months. This includes about 1 month of screening and at least 1 year of treatment and follow-up. Actual length of participation for individual patients will depend upon the actual duration of treatment. Minimum expected participation is approximately 1 year unless shorter due to death, progression on therapy, withdrawal of consent, or early termination of the trial. 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. See study schema (Figure 1) in Study Design section for details.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male and female patients age ≥18 years of age, or ≥ age of consent in the region.

2. Newly diagnosed Stage IIIB or IV non-small cell lung cancer (according to Revised International System for Staging Lung Cancer criteria of 2010) or recurrent non-small cell lung cancer (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 v1.1).

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% is acceptable for any single value if in the investigator's opinion the patient does not have an increased safety risk):

   Bone Marrow Function

   a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ cells/L ($1500/mm^3$);

   b. Platelet count $\geq 100 \times 10^9$ cells/L ($100{,}000/mm^3$);

   c. Hemoglobin ≥9.0 g/dL (90 g/L);

   Renal Function

   d. Serum or plasma creatinine ≤1.5 x upper limit of normal (ULN);

   e. Urine dipstick proteinuria <2+ (ie, either 0, trace, or 1+). If urine dipstick is >1+ then a 24 hour urine for protein must have demonstrated urinary excretion of ≤500 mg of protein per day or urine protein to creatinine ratio (UPC) ratio <1;

   Liver Function

   f. Total bilirubin ≤1.5 x ULN (<3 ULN if Gilbert's disease);

   g. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤3 x ULN (≤5 x ULN if liver metastases are 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 has been informed of all pertinent aspects of the study.

11. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

12. Be 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 must agree to use 2 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 are not of childbearing potential (ie, meet at least 1 of the following criteria):

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or
    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

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

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Small cell lung cancer (SCLC) or combination SCLC and NSCLC. Squamous-cell tumors and mixed adenosquamous carcinomas of predominantly squamous nature.

2. Evidence of a tumor that compresses or invades major blood vessels or tumor cavitation that is likely to bleed.

3. Known sensitizing EGFR mutations (for example, deletion 19 or L858R) or EML4-ALK translocation positive mutations. If mutation testing is performed, the results must be reviewed and confirmed as negative for mutations prior to randomization.

4. History of other cancer within 5 years prior to 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 is 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 are eligible, however those with symptomatic or painful bone metastases should not have received palliative local radiation for at least 2 weeks prior to 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 (eg, INR >1.5 and aPTT greater than ULN unless on prophylactic anticoagulation).

8. Medically uncontrolled hypertension or systolic blood pressure >150 mmHg or diastolic blood pressure >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 must be off of anti-infective agents.

13. Comorbities that would increase the risk of toxicity.

14. Concurrent administration of other anticancer therapies. Bisphosphonate or Rank-Ligand inhibitor therapy for pre-existing bone metastases or osteoporosis is 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 is not confirmed by pathology). Treated and stable (asymptomatic; off steroids) brain metastases are 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 is required only in countries where regulations mandate testing. In all other countries, testing should be considered if a patient is at risk for having undiagnosed infection (for example due to history of injection drug use or due to geographic location).

    a. Hepatitis B infection as detected by positive testing for hepatitis B surface antigen (HBsAg), and detectable viral load.

    b. 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 was completed ≥4 weeks before randomization are 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 increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

24. Patients who are 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 are Pfizer employees directly involved in the conduct of the trial.

25. Prior treatment with immunotherapy or bevacizumab.

4.3. Randomization Criteria

Eligibility criteria are to be reviewed and sponsor confirmation of eligibility must be received and confirmed prior to randomization.

- Randomization of eligible patients is required as close as possible to Day 1 dosing and no more than 1 day prior to administration of first dose of investigational product.
- The investigators or their pre-specified designee will randomize eligible patients by web-based interactive response system (IWRS) as described in the Impala Quick Reference Guide.
- At the time of randomization, information about patient demographics and stratification factors will be requested.
- The central computerized system will provide the randomization number and treatment assignment.

4.4. Lifestyle Guidelines

4.4.1. Contraception

In this study, patients of childbearing potential will receive bevacizumab-EU as well as paclitaxel and carboplatin, which have been associated with teratogenic risk. Patients should be advised to avoid becoming pregnant and not to father a child while receiving treatment in this study. While the teratogenicity of bevacizumab-Pfizer has not been studied, it is expected to be the same as that of bevacizumab-EU. Those who, in the opinion of the investigator, are sexually active and at risk for pregnancy must agree to use 2 methods of highly effective contraception throughout the study and continue to do so for at least 6 months after the last dose of study treatment. The investigator or his/her designee, in consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient and his female partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his/her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the Schedule of Activities (Table 1) and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same

treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD) or intrauterine system (IUS).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study coordinator's manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, **contact information for the investigational site**, and **contact details for a contact center** in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact center number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

After a patient has provided written informed consent and completed the necessary Screening assessments, the clinical site must complete an Eligibility Review Form and send it to the sponsor for approval of patient randomization. Upon receipt of the sponsor's approval, the site may randomize the patient by contacting the online Interactive Web Response System (IWRS) to register the patient by indicating minimal information sufficient to distinguish one patient from another, and will then receive a unique patient identification number that will be retained throughout the study.

Following site initiation, the system will automatically trigger initial drug shipment to the site when the first patient is screened. The system will also automatically trigger additional shipments to replace investigational product (IP) that is used at the site.

Randomization will be according to a randomization schedule generated by the Sponsor, and to which the Sponsor's personnel directly involved in the study conduct are blinded. The only exception will be in the event of an emerging safety issue which may require blind breaking (Section 5.2).

5.2. Breaking the Blind

Treatment assignments for this study will be blinded to the patients, investigator/study staff and Sponsor's study team conducting the trial. The study pharmacists (or qualified designee) preparing treatment infusions will be unblinded, and pharmacy records will be monitored by a Sponsor appointed unblinded monitor.

At the initiation of the study, the study site will be instructed on using IWRS for breaking the blind. Blinding should only be broken in an emergency situation for reasons of individual patient safety when knowledge of the investigation product (IP) assignment is required for medical management. The Investigator should contact the Sponsor's study representative, whenever possible, before breaking the blind. At all other times, the treatment and randomization information will be kept confidential and will not be released to the investigational/study staff until the conclusion of the study.

If the blind for a patient has been broken, the reason must be fully documented in source documents and entered on the electronic case report form (eCRF) and the patient must be discontinued from all study treatment. Any adverse event (AE) or serious adverse event (SAE) associated with breaking the blind must be recorded in source documents and eCRF and reported as an SAE, if appropriate.

5.3. Patient Compliance

All study medications for this protocol are intravenous drugs administered by trained and qualified personnel. Records of each dose will be maintained and variations in doses will be managed as per Section 5.4.1. Patients who miss dosing or scheduled visits, tests or procedures for reasons other than adverse events or unavoidable administrative reasons will be reminded of the importance of maintaining the dosing schedule. Repeat non-compliance may result in withdrawal from the study in accordance with Section 6.4.1.

5.4. Drug Supplies

5.4.1. Administration and dosing

The dosing algorithm for paclitaxel, carboplatin, and blinded bevacizumab are shown below.

On treatment days when both bevacizumab and paclitaxel-carboplatin are administered, the order of administration should be: 1) paclitaxel, 2) carboplatin, 3) bevacizumab.

Dose recalculations at the beginning of each cycle is recommended but not required if the weight is within 10% of baseline (Cycle 1 Day 1 dosing). The dose should be recalculated if the patient's weight changes more than 10% from baseline or if the dose has been modified and be used as the new baseline going forward for future dose calculations.

Regional standards for derivation of dose calculations such as rounding conventions or BSA/dose capping for safety concerns are acceptable. Excluding these expected variations, administered doses of carboplatin, paclitaxel, or bevacizumab within a range of +/-10% from the intended dose would not be considered a deviation.

Table 2. Dosing Algorithm

Dose Level	Paclitaxel	Carboplatin	Bevacizumab-Pfizer or bevacizumab-EU (blinded bevacizumab)
Starting dose	200 mg/m^2	AUC 6 (max=900mg)	15 mg/kg
Dose level -1 (first episode of AE*)	175 mg/m^2	AUC 5 (max=750mg)	7.5mg/kg after discussion with sponsor
Dose level -2 (second episode of AE*)	150 mg/m^2	AUC 4 (max=600mg)	Discontinue
Dose level -3 (third episode of AE*)	Discontinue Therapy		--

*for carboplatin/paclitaxel: Grade 3 or 4 febrile neutropenia, nausea, vomiting, stomatitis

5.4.2. Bevacizumab

5.4.2.1. Dosage Form(s) and Packaging

Bevacizumab (bevacizumab-Pfizer or bevacizumab-EU) will be provided by the Sponsor as blinded supplies in which the external packaging for each vial will appear identical and will be identified with a unique container number. Each container will be packaged with a tamper-resistant seal. Only the unblinded pharmacist or appropriately qualified unblinded staff member preparing the study medication is allowed to break the tamper-resistant seal. The Sponsor must be notified of any study medication in which the tamper-resistant seal has been broken and this medication should not be used.

Bevacizumab-Pfizer and bevacizumab-EU are clear, colorless to pale brown liquid in a glass vial with a rubber stopper. Each 20 mL glass vial contains 400 mg of bevacizumab in 16 ml of solution.

5.4.2.2. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Bevacizumab-Pfizer will be prepared and dispensed in accordance with the European Medicines Authority (EMA) approved labeling for AVASTIN® (bevacizumab-EU). See the Dosage and Administration Instructions (DAI), for instructions in how to prepare the investigational product for administration.

Study drug should be prepared and dispensed by an appropriately qualified and experienced unblinded member of the study staff (eg, unblinded physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. No information concerning patient treatment assignments will be communicated from the unblinded pharmacist to blinded investigators, site study staff, Sponsor study staff, or study patients.

Vials of investigational product (bevacizumab) should be stored refrigerated (2-8°C; 36-46°F) in original packaging until ready for use. Prior to dose preparation, the vial should be gently inverted or swirled to mix thoroughly. To avoid foaming, pharmacists should not shake vials. Bevacizumab should not be mixed or diluted with Dextrose solutions.

Parenteral investigational products should be inspected visually for particulate matter and discoloration (ie, change in color) prior to administration, whenever the solution and container permit. If particulates or discoloration are observed, do not use the vial(s) and notify the Study Monitor.

The study drug product should not be mixed or diluted with other drugs. Any unused portion left in the vial or bag should be discarded in accordance with local requirements.

5.4.2.2.1. Bevacizumab Regimen

Blinded bevacizumab will be administered once at the start of every 21-day cycle. The initial dose is 15 mg/kg delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. If during the shortened infusions, infusion related reactions occur, the length of the infusion can be lengthened at the discretion of the clinician. For the infusion of bevacizumab in patients over 110 kg, the dilution volume and infusion time should be increased per the Dosage and Administration Instructions (DAI) document and institutional standards. The concentration of bevacizumab solution should be kept within the range of 1.4 mg/ml to 16.50 mg/ml.[2]

Infusions should not be administered as an intravenous push or bolus injection. Infusions should not be administered or mixed with dextrose solutions.

Assigned blinded bevacizumab may continue to be administered after the chemotherapy has been discontinued until RECIST 1.1 defined disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurs, or end of treatment in accordance with Section 13 whichever comes first.

5.4.2.2.2. Bevacizumab Regimen Adjustments

The infusion of the investigational product should be interrupted if the patient develops dyspnea or hypotension that is deemed clinically significant by the investigator. If a patient experiences an allergic reaction, hypersensitivity, adult respiratory distress syndrome, of Grade 3 or Grade 4 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03), they will be discontinued from treatment with the investigational product. Additionally, if a patient experiences a drug-related bronchospasm of any grade according to NCI-CTCAE, they too will be discontinued from treatment with the investigational product. For patients who experience infusion-associated symptoms not previously specified, infusions should be slowed to ≤50% or interrupted.

No dose reductions from 15mg/kg are planned for bevacizumab-Pfizer or bevacizumab-EU. However, in rare cases where dose reduction is deemed necessary, the investigator can decrease the dose of blinded bevacizumab to 7.5 mg/kg with the concurrence of the Sponsor. In the event of toxicity attributed to bevacizumab, treatment should be either temporarily (up to 2 weeks) or permanently discontinued as described in Table 3. Following a temporary discontinuation, treatment may resume in accordance with local standard of care.

Table 3. Bevacizumab Dose Adjustment Guidelines

ADVERSE EVENT	ACTION
Infusion Reaction	• Mild or moderate: decrease rate of infusion • Dyspnea or clinically significant hypotension: interrupt infusion, administer appropriate medical therapy, which may include intravenous fluids, epinephrine, corticosteroids, diphenhydramine, bronchodilators, or oxygen; monitor until complete resolution • Severe or life-threatening: permanently discontinue therapy
Gastrointestinal Perforations	• Therapy should be permanently discontinued in patients who develop gastrointestinal perforation
Fistulae	• Permanently discontinue bevacizumab in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula (NCI-CTCAE v.4.03). Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of bevacizumab should be considered.

ADVERSE EVENT	ACTION
Wound Healing Complications	• Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery. • Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
Hypertension	• Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.
Posterior Reversible Encephalopathy Syndrome (PRES)	• In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.
Proteinuria/nephrotic syndrome	• Bevacizumab should be permanently discontinued in patients who develop nephrotic syndrome .
Arterial thromboembolism	• Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions.
Venous thromboembolism	• Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.
Haemorrhage	• Bevacizumab should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy. • Bevacizumab treatment should be discontinued in cases of intracranial bleeding.
Pulmonary haemorrhage/haemoptysis	• Patients with recent pulmonary haemorrhage/ haemoptysis (>2.5 ml of red blood) should not be treated with bevacizumab.
Congestive heart failure (CHF)	• When treating patients with cardiovascular disease that has developed or worsened after the initiation of the study treatments, the investigator should determine the benefits and risks of continuing bevacizumab and/or paclitaxel/carboplatin.

ADVERSE EVENT	ACTION
Osteonecrosis of the jaw (ONJ)	• Caution should be exercised when bevacizumab and intravenous or oral bisphosphonates are administered simultaneously or sequentially. • In patients who have previously received or are receiving intravenous or oral bisphosphonates invasive dental procedures should be avoided, if possible.

5.4.3. Paclitaxel and Carboplatin

5.4.3.1. Paclitaxel and Carboplatin Provision

Paclitaxel and carboplatin to be administered during this study will be branded or generic product available in the local region. Note that nanoparticle protein-bound paclitaxel (nab-paclitaxel, Abraxane®) may NOT be substituted for the cremophor formulation of paclitaxel. Paclitaxel and carboplatin will be procured by study sites and reimbursed by the Sponsor through the contractual agreement with the study institution unless local regulations or other limitations require direct provision of background therapies by the Sponsor. Paclitaxel and carboplatin are to be stored, prepared and administered according to locally approved product labeling.

5.4.3.2. Premedication for Administration

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

5.4.3.2.1. Paclitaxel

All patients should be pre-medicated prior to paclitaxel administration in order to prevent severe hypersensitivity reaction. Such premedication may consist of dexamethasone 20 mg orally administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel. Premedication regimens that are standard for the institution or region may be used instead. Premedication will be supplied by the site.

5.4.3.2.2. Carboplatin

Carboplatin is administered as the second drug of the chemotherapy doublet combination.

Carboplatin can induce emesis, which can be more severe in patients with prior emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics which should be given per local standard of care. Because anti-emetics may be given prior to the paclitaxel, extra doses as premedication may not be necessary, although additional doses may be required if the patient develops emesis. Premedication according to institutional guidelines should be used if paclitaxel has been discontinued.

5.4.3.3. Regimen and Starting Dose(s)

5.4.3.3.1. Paclitaxel

Following pre-medication, paclitaxel is administered as the first drug when chemotherapy is administered. Paclitaxel at a dose of 200 mg/m^2 will be administered by IV infusion over 3 hours on Day 1 in 21-day cycles. In the absence of progressive disease, patients will receive paclitaxel treatment for at least 4 but no more than 6 cycles. Dose reduction for toxicity is allowed.

5.4.3.3.2. Carboplatin

Carboplatin is administered over a minimum of 15 minutes, and can be administered immediately after the paclitaxel infusion has completed. Patients will be administered carboplatin for at least 4 and no more than 6 cycles. Dose reduction for toxicity is allowed.

The initial dose of carboplatin is based on the use of mathematical formulae, which are based on a patient's pre-existing renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. The use of dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either under dosing (in patients with above average renal function) or over dosing (in patients with impaired renal function).

A simple formula for calculating dosage, based upon a patient's glomerular filtration rate (GFR in mL/min) and carboplatin target area under the concentration versus time curve (AUC in mg/mL.min), has been proposed by Calvert.[5,18]

$$\text{Total Dose (mg)} = (\text{target AUC is } 6.0) \times (\text{GFR (ml/min)} + 25).$$

Glomerular filtration rate (GFR) is estimated for males as:

$$\text{GFR} = \frac{[(140 - \text{age}) \times (\text{weight in kg})]}{(72 * \text{creatinine in mg/dL})}$$

For females, a correction factor of 0.85 is used.

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m^2.

Alternate formulas per local standard of care may be utilized to derive the dose of carboplatin.

5.4.3.3.3. Dose Adjustments for Paclitaxel and Carboplatin

All study drug treatment associated or possibly associated toxicities should be managed by standard medical practice. Patient toxicity should be clinically assessed before, during, and after each infusion. If the investigational product causes unmanageable levels of toxicity at any time in the study, the investigational product should be discontinued. Instruction for treatment delays and dosing modifications for paclitaxel and carboplatin are as follows:

- Reduced doses may not be increased.
- Dose modifications should be based on the AE that requires the largest change.
- Severity of AEs will be graded based on CTCAE version 4.03.
- Study therapy will be delayed until the AE is graded ≤1, except in the case of anemia, neuropathy, alopecia, proteinuria, and laboratory abnormalities that are deemed unrelated to treatment and clinically insignificant per investigator.
- If study treatments must be withheld due to hematologic toxicity, complete blood count (CBC) and platelet counts should be obtained weekly until the counts reach the lower acceptance limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

Once a dose of paclitaxel has been reduced for a patient, all subsequent cycles should be administered at that dose, unless further dose reduction is required. Treatment with paclitaxel will be stopped in case of RECIST defined disease progression, unacceptable toxicity, death, or withdrawal of consent occurs.

Dose delay (up to 2 weeks) and dose reduction of paclitaxel and/or carboplatin will be permitted per local guidelines. The dose adjustments for paclitaxel and carboplatin presented in Table 2 in the Administration and Dosing (Section 5.4.1) are to be used as a guideline for investigators. Additional measures may be taken as necessary per investigator's medical judgment and per locally approved labels as well as local standard of care. Two dose reductions are allowed per patient, and all reductions should be considered permanent with no re-escalation permitted. All dose adjustments should be documented in the patient source notes. Missed dose(s) of paclitaxel will not be made up. If paclitaxel dosing is held at any point, study procedures should proceed on schedule without any delay; this includes tumor assessments.

Dose reduction of carboplatin for hematologic toxicity should be made based on institutional or regional standard of care guidelines. All dose reductions should be considered permanent with no re-escalation permitted. All dose adjustments should be documented in the patient source notes. Missed dose(s) of carboplatin will not be made up. If carboplatin dosing is held at any point, study procedures should proceed on schedule without any delay; this includes tumor assessments.

In cases where a delay in dosing is required for one or more of the drugs, the date of Day 1 of the next cycle should be delayed and all drugs required for that cycle be given on the new scheduled Day 1. Note that tumor assessments are calendar based and are not modified to fit a change in dosing schedule.

5.4.4. Missed/ Delayed Dose(s) of Study Treatment

Missed dose(s) of study treatment will not be made up. If one of the chemotherapeutic agents is delayed, the other agent and bevacizumab treatment should be delayed and Day 1 of the cycle should be shifted. If the both chemotherapeutic agents cannot be administered within 2 weeks, they should be discontinued. If only one of the chemotherapeutic agents is discontinued, the other can be continued. Similarly if blinded bevacizumab cannot be administered for 2 weeks from scheduled time due to intolerable adverse events,

bevacizumab should be discontinued. The interval between treatment cycles should be no less than 3 weeks and no more than 5 weeks in order to maintain 3 weeks per cycle with a maximum 2 week delay.) Tumor assessments should not be shifted as they are calendar based. If bevacizumab-Pfizer or bevacizumab-EU is held or discontinued, paclitaxel and/or carboplatin should be continued for at least 4 and no more than 6 cycles. For those patients who discontinue chemotherapy and investigational products, every effort should be made to remain on study for follow-up, at least through Week 19 and if there is a response through Week 25.

5.5. Drug Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all study treatments, including any investigational products, comparative agents and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Bevacizumab should be stored refrigerated at 2 to 8°Celsius in its original container to protect it from light and in accordance with the label. See the Dosage and Administration Instructions (DAI) and Investigational Product Manual for complete details on storage conditions of the investigational product.

Paclitaxel and carboplatin should be stored per the locally approved product labeling. Refer to product labeling for complete details on handling and preparation requirements.

Paclitaxel is to be stored in original packaging between 20 to 25°Celsius (68 to 77°Fahrenheit). Retain in original packaging to protect from light. Contact of the undiluted paclitaxel concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer, (di-(2-ethylhexyl)phthalate (DEHP)], which may be leached from PVC infusion bags or sets, diluted paclitaxel should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene administration sets.

Carboplatin is to be stored in original packaging at 25°Celsius with excursions between 15 to 30°Celsius (59 to 86°Fahrenheit) permitted. Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin should not be used for preparation and administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

All parenteral products should be inspected for particulate matter and discoloration prior to use. If any particulate matter or discoloration is observed, the products should not be used and the study monitor should be notified.

Storage conditions stated in the single reference safety document (SRSD) (ie, investigator's brochure) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approved the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions. Specific details regarding information the site should report for each excursion will be provided to the site.

The Investigational Product Manual should be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range.

5.6. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

Medications used to prevent possible adverse events or treat adverse events are allowed at the discretion of the investigator. Use of concomitant treatments should follow the standard of care for the treating institution.

Pretreatment for bevacizumab hypersensitivity reactions should not be given unless hypersensitivity reactions have occurred with prior administration in an individual patient. The treatment regimen can produce clinically significant myelosuppression. Transfusions

and growth factors are allowed and should be used according to institutional guidelines. Bisphosphonate or Rank-Ligand inhibitor therapy for pre-existing bone metastases or osteoporosis is allowed.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs.

Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics.

Patients receiving paclitaxel should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists as per the regional prescribing information or institutional guidelines.

Medications and non-drug treatments will be 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 will enter the follow-up phase during which survival and new anti-cancer therapy information will be collected until the study is completed or is terminated early.

5.8. Additional Anticancer and Prohibited Treatments Including Radiotherapy

Additional anticancer treatments including radiotherapy are prohibited, even for palliative treatment of bone or brain metastatic lesions. The need for such additional treatments constitutes progressive disease and the patient should be discontinued from study medications under this study.

Patients participating in this study should discuss with their doctors the risks and benefits of immunizations (particularly live vaccine based immunizations) during this study.

No other investigational drug or treatment for benign indications may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

6. STUDY PROCEDURES

The Schedule of Activities (Table 1) provides an overview of the protocol visits and procedures. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

6.1. Screening

Voluntary, written, dated, and signed institutional review committee (IRC) or institutional ethics committee (IEC) approved informed consent must be obtained before any study specific procedures are performed.

For details on screening procedures, see the Schedule of Activities (Table 1).

6.1.1. Screen Failure

Patients who completed the informed consent process but do **not** meet all eligibility criteria and therefore are **not** randomized to any treatment arm will be considered as screen failures. If the conditions that led to screen failure are resolved, the patient may be rescreened and if eligible, enrolled.

6.2. Study Period

For details on procedures during the study period, see the Schedule of Activities (Table 1).

6.3. End-of-Treatment/Withdrawal

See Schedule of Activities for details.

6.4. Long Term Follow-up

For details on follow-up procedures, see the Schedule of Activities (Table 1).

6.4.1. Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information. Patients should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Criteria that may be used to discontinue patient from receipt of study medication will include, but will not be limited to:

- Objective disease progression according to RECIST 1.1 as determined by the investigator;
- Global deterioration of health status requiring discontinuation;
- Adverse events;
- Significant protocol violation;

- Lost to follow-up;
- Refusal for further treatment;
- Study terminated by Sponsor;
- Death.

Reasons for discontinuation from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Refusal for further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved Adverse Events (AEs).

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.4.2. Lost to Follow-Up

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, faxes, or emails as well as lack of response by patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Efficacy Assessments

Disease assessments are to be performed as scheduled according to calendar days, regardless of treatment delays resulting from toxicity. Care must be taken in scheduling disease assessments to prevent the introduction of bias based on treatment delays.

Failure to perform any of the required disease assessments will result in the inability to determine disease status for the impacted time point. A series of incomplete disease assessments will result in inability to determine disease response status and censoring of PFS back to the time of the last full assessment that did not show progression. Frequently off-schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

CT and MRI are the best currently available and most reproducible methods of measuring target lesions selected for response assessment. MRI should only be used when considered more appropriate than CT or when there is a contraindication for CT with contrast. Assessment delay to conform to treatment delays is not permitted. The same method of tumor assessments should be used throughout the trial.

The CT scans should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. Depending on the adequacy for evaluation of disease, a combination of CT without contrast and MRI should most often be used. CT without contrast is preferred for evaluation of lesions in lung parenchyma. MRI is not adequate for evaluation of lung parenchyma but should also be performed to evaluate all other aspects of the chest. MRI of the abdomen and pelvis should substitute for CT with contrast unless the method does not adequately depict the individual's disease, in which case CT without contrast is preferred.

Other methods of evaluation should be used as appropriate. For patients having effusions or ascites, cases having cytological proof of malignancy should be considered non-target legions. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be considered to be lung cancer legions.

For the purpose of study endpoint analyses, the determination of best disease response (PR or CR) and progression will be made in accordance with RECIST v1.1 at the opinion of the investigator. Responses must be confirmed by a second set of scans including brain scan obtained 6 weeks (±7 days) later.

For the purposes of quality control, central review of tumor assessments may be performed at the discretion of the Sponsor. Materials to be forwarded for independent review upon request by the Sponsor are all imaging studies performed on study, preferably in digital format sent through the vendor's internet link or on compact disc or digital video disc (DVD) disc. All digital media must be in Digital Imaging and Communications in Medicine (DICOM) format. Films may be forwarded for review if necessary; all films must be original (second original film acceptable) rather than copies of films. Further information on materials to be forwarded for independent review will be provided in the core imaging laboratory Study Manual.

7.2. Safety Assessments

7.2.1. Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03), timing, seriousness, and relatedness.

Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

7.2.2. Laboratory Safety Assessments

Hematology and Blood Chemistry: Hematology and blood chemistry tests will include the parameters presented in Table 4. Blood tests will be drawn at the time points described in Schedule of Activities table and analyzed at local laboratories. Additional blood tests may be performed per standard of care, at the investigator's discretion for the purpose of planning treatment administration, dose modification, following adverse events, or as clinically indicated.

Table 4. Hematology and Chemistry Panels

Hematology Panel	Blood Chemistry Panel
Hemoglobin	ALT
White Blood Cells	AST
Platelets	Alkaline Phosphatase
Absolute Neutrophil Count	Total Bilirubin
	Serum or Plasma Creatinine
Coagulation Panel	Sodium
International Normalized Ratio for prothrombin time	Potassium
Activated Partial Thromboplastin Time	Total Calcium
	Magnesium
	BUN or Urea
	Albumin

7.2.3. Other Safety Assessments

See Schedule of Activities for details.

7.3. Pharmacokinetic Evaluations

The drug concentrations of bevacizumab-Pfizer and bevacizumab-EU will be determined using serum samples collected at the time points specified in the Schedule of Activities (Table 1). Every effort will be made to collect these PK samples within the time window provided, as specified in the Schedule of Activities (Table 1). The actual time of each sample collection will be recorded on the source document and eCRF.

Details on sample collection, processing and shipment will be provided in the central laboratory manual.

The drug concentration sample analysis will be analyzed by the designated analytical laboratory using a validated analytical method in compliance with Pfizer standard operating procedures. All samples, unless otherwise specified below, will be analyzed.

For the pre-dose samples collected during the single-agent bevacizumab-Pfizer or bevacizumab-EU treatment period, analysis will be conducted for samples collected every other cycle, starting from the initiation of the single agent bevacizumab-Pfizer or bevacizumab-EU therapy (eg, Cycles 7, 9, 11, 13, and so on, for a patient who initiates the single agent therapy from Cycle 7). The other pre-dose samples collected during the single-agent bevacizumab-Pfizer or bevacizumab-EU treatment period (eg, Cycles 8, 10, 12, and so on, for a patient who initiates the single agent therapy from Cycle 7) will not be analyzed unless corresponding immunogenicity samples are to be analyzed.

7.4. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed by the local certified laboratory, and 2 negative tests are required before receiving the first dose of investigational product. The second negative test should be done during the first 5 days of the menstrual period, immediately preceding the first dose of any study treatment. In the absence of regular menstrual bleeding, the patient should have used 2 different methods of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), per the schedule of activities and at the end of treatment visit to confirm the patient has not become pregnant during the study. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication and remain on the study for follow up. Pregnancy tests may also be repeated as per request of IRBs or IECs or if required by local regulations. Patients who have missed a menstrual period or who show an indeterminate or positive result may not further progress in the study until pregnancy is ruled out.

7.5. Biomarkers

No biomarkers will be collected for the purposes of research in this trial.

7.6. Immunogenicity Assessments

Blood samples for assessment of ADA and neutralizing antibodies will be collected at time points specified on the Schedule of Assessments. Details on the sample collection, processing, and shipment are provided in the central laboratory manual.

The sample analysis will be conducted by the designated analytical laboratory using a validated analytical method in compliance with Pfizer standard operating procedures. All samples, unless otherwise specified, will be analyzed.

For the pre-dose samples collected during the single-agent bevacizumab-Pfizer or bevacizumab-EU treatment period, analysis will be conducted for samples collected every other cycle, starting from the initiation of the single agent bevacizumab-Pfizer or bevacizumab-EU therapy (eg, Cycles 7, 9, 11, 13, and so on, for a patient who initiates the single agent therapy from Cycle 7). The other pre-dose samples collected during the single-agent bevacizumab-Pfizer or bevacizumab-EU treatment period (eg, Cycles 8, 10, 12, and so on, for a patient who initiates the single agent therapy from Cycle 7) will not be analyzed unless the immunogenicity results suggest that there is a need to analyze these samples.

A sensitive and specific immunoassay for detecting anti-drug antibodies in human serum will be used to analyze the ADA samples. The ADA assay uses biotinylated- and ruthenium-labeled bevacizumab-Pfizer as reagents and has been validated in compliance with Good Laboratory Practice. Analysis of ADA samples will follow a tiered approach. Samples will first be screened for ADA; any samples that are positive in the screening assay will be further analyzed to confirm the positive result and determine the antibody titers. Samples determined to be positive for ADA may be further characterized for neutralizing antibodies .

7.7. Testing Lung Tissue for Mutations

See Schedule of Activity for details.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with Common Terminology Criteria for Adverse Events CTCAE Grade 5 (see the section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize patient safety or require intervention to prevent one of the other AE outcomes, then the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between the investigational product or study drug and an efficacy endpoint specified below, the events highlighted below should not be reported by the investigator as SAEs as described in the Serious Adverse Event Reporting Requirements section of this protocol. These events are anticipated to occur in a population with non-squamous non-small cell lung cancer. However, these events should still be captured as adverse events in the case report form.

Efficacy endpoints that will not be reported in an expedited manner:

1. Progression of the malignancy under study (including signs and symptoms of progression) will not be reported as SAEs unless the outcome is fatal within the safety reporting period.

2. Disease progression-related events that are fatal will not be reported individually in an expedited manner because they are anticipated to occur in the study population.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected based on the expectation of frequency of the event(s) in question in the population for comparison, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analysis of safety data will be performed on a regular basis per internal standard operating procedures.

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (x ULN) concurrent with a total bilirubin value ≥2 x ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 x ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

- For patients with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 x ULN, or ≥8 x ULN (whichever is smaller).

Concurrent with

- For patients with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 x ULN **or** if the value reaches ≥3 x ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);

- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment: NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or within 6 months of having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant within 6 months after discontinuing and/or being exposed to the study treatments;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment or within 6 months of having been exposed to the study treatments, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Patient Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an

expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL

Detailed methodology for summary and statistical analyses of the data collected in the study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Patients will be randomized to a 1:1 ratio into 2 treatment groups. Randomization will be stratified by region, gender, and smoking status. The primary endpoint is best response by Week 19. Response determination will be made at the site by the Investigator. In order to consider a patient to be a responder, the response will need to be confirmed by a set of tumor assessments 6 weeks (±7 days) later. The primary efficacy analysis for equivalence will be performed when all patients has completed Week 19 tumor assessment and had the opportunity to subsequently confirm response at Week 25. Once all patients have been followed until death, withdrawal of consent, or 1 year from randomization, whichever is shortest, analysis of secondary endpoints such as overall survival, PFS, PK/immunogenicity, and 1-year safety results can be conducted..

9.1. Sample Size Determination

Based on the results of a meta-analysis combining Sandler (2006),[6] Johnson (2004),[7] and Niho (2012),[8] the objective response rate (ORR) to bevacizumab + chemotherapy combination therapy was estimated to be approximately 40% based on fixed effect model, and the response rate to chemotherapy alone was estimated to be 21% based on the fixed model. For sample size calculation the ORR is assumed to be 38%. The relative risk (RR) for ((bevacizumab + chemotherapy)/ chemotherapy alone) was estimated to be 2.17 with

95% confidence interval (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 for the 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 for the 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.

A sample size of 656 patients (328 per treatment arm) will also provide approximately 74% power for achieving equivalence for the 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%.

9.2. Analysis Population

9.2.1. 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.

9.2.2. 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 with major protocol deviation will be determined based on blinded data review prior to database release.

9.2.3. Pharmacokinetics Population

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

9.2.4. 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.

9.3. Efficacy Analysis

9.3.1. Analysis of Primary Endpoint

The primary efficacy endpoint of the study is ORR defined as the percent of patients within each treatment group who achieved Complete Response (CR) or Partial Response (PR) by the time of the Week 19 efficacy analysis in accordance with the RECIST 1.1. Confirmation of response is required by tumor assessments done approximately 6 weeks after the response. Responses that are not confirmed will not be counted in the primary analysis but may be included in a sensitivity analysis.

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 RR, with following hypothesis:

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

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

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 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).

For the EU, equivalence will be tested based on RD, with following hypothesis:

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

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

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.

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 the US scenario unless otherwise requested by local regulators and outlined in the SAP.

Descriptive statistics (frequency and percentage) for CR, PR, and ORR in each treatment group will be presented. Depending on the region the 90% or 95% confidence interval of these response rates will be constructed.

Miettinen and Nurminen (1985)[9] method will be used as the primary analysis method for the binomial distributed efficacy endpoint ORR. Detailed analysis will be described in the SAP.

9.3.2. Analysis of Secondary Endpoints

9.3.2.1. Duration of Response

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.

DOR will only be calculated for the subgroup of patients with an objective response.

The Kaplan-Meier method will be used to assess DOR.

9.3.2.2. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from date of randomization to first progression of disease (PD) or death due to any cause in the absence of documented PD. Censoring for the PFS 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 the study. Patients lacking an evaluation of disease after randomization will have their PFS time censored on the date of randomization with duration of 1 day. Patients who start a new anti-cancer therapy prior to documented PD will have the endpoint censored at the date of the last tumor assessment prior to the start of the new therapy.

The Kaplan-Meier method will be used to assess the 1-year PFS, to estimate the 1-year PFS rate, and the confidence intervals of the 1-year PFS rate. A two-sided log-rank test will be used to compare the 1-year PFS between the two treatments.

9.3.2.3. 1-Year Survival

Time to death is defined as the time from date of randomization to death due to any cause while the patient is on the study. Patients will be censored for this endpoint on the date of the last tumor assessment if they do not die at that time.

The Kaplan-Meier method will be used to assess the 1-year survival, to estimate the 1-year survival rate, and the confidence intervals of the 1-year survival rate. A two-sided log-rank test will be used to compare the 1-year survival between the two treatments.

9.3.2.4. Pharmacokinetics, Biomarkers and Immunogenicity

PK/Immunogenicity analyses will be performed at 1 year. See Section 9.4.4.

9.4. Safety Analysis

All patients treated with at least one dose of study treatment (bevacizumab, paclitaxel or carboplatin) will be included in all safety analyses. Listings of all patient data at 1 year from randomization will be prepared. Data summaries will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Details of planned analyses will be described in the SAP.

9.4.1. Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of adverse events will be graded according to the NCI CTCAE version 4.03[16] whenever possible.

Adverse events (treatment emergent adverse events; treatment-related adverse events; adverse events classified as NCI CTCAE Grade 3 or higher; and serious adverse events) will be summarized by body system and preferred term according to MedDRA terminology. Treatment emergent adverse event (TEAE) is defined as any adverse event that occurs after the beginning of the study treatment or any pre-existing adverse event that worsens after the beginning of the study treatment.

Additionally, the Pfizer standard 3-tier adverse events reporting approach will be utilized in this study, details of this approach will be described in the SAP.

Adverse events leading to death or discontinuation of trial treatment will be presented by treatment group.

Adverse events recorded on the CRF as infusion related reactions (IRRs) will be summarized both as individual events and as a group for the purpose of comparing the overall incidence of IRRs in the 2 treatment arms.

Selected adverse events and syndromes will be summarized using grouped Medical Dictionary for Regulatory Activities (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.*[17]
- Clinically significant decrease in LVEF.

9.4.2. Laboratory Abnormalities

Hematology and chemistry laboratory data will be summarized by treatment and visit. The laboratory results will be graded according to NCI CTCAE severity grade. The frequencies

of the worst severity grade observed will be displayed by study treatment. Shift tables of baseline against each post-baseline visit will be provided for selected laboratory tests to examine the distribution of laboratory toxicities. For parameters for which an NCI CTCAE scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment and visit.

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

9.4.3. Prior Concomitant Medications

Collected prior and concomitant medications will be coded by the World Health Organization (WHO) medical dictionary; patients who received these medications will be listed and summarized by treatment group separately.

9.4.4. Pharmacokinetics, Biomarkers and Immunogenicity

9.4.4.1. Pharmacokinetics

The drug concentration-time data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum) according to treatment.

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.

The detailed procedures for the population PK analysis, including the model implementation and evaluation, will be described in the Population Modeling Analysis Plan (PMAP). The results of the analysis will be summarized in a Population Modeling and Analysis Report (PMAR).

9.4.4.2. Biomarker Analysis

There are no biomarker assessments required for this trial.

9.4.4.3. Immunogenicity

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.

9.4.5. Other Endpoints

Demographic and baseline characteristics such as patient age, sex, height, weight, ethnicity, prior therapy, medical history, ECOG performance status, and tumor mutations will be tabulated and summarized using descriptive statistics. Relationships between baseline patient characteristics and study outcome variables will be explored with appropriate techniques.

Study drug administration for each study drug will be described in terms of the total number of cycles administered, the medium (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy.

9.5. Interim Analysis

There will be no interim analysis in this study. The primary analysis for efficacy conducted after all patients have undergone Week 25 tumor assessments unless discontinued earlier is considered the final analysis. Secondary analyses done after all patients have been followed for at least 1 year, unless discontinued earlier, are also considered final analyses. Data collected on patients after 1 year from randomization are considered supplemental to the final analyses.

9.6. Early Unblinding For PK

The main purpose of this early unblinding is to prepare for the population PK analysis. The selected study data will become unblinded prior to dataset release to allow early evaluation of PK models. This evaluation will enable timely and seamless analysis/reporting of population PK after the database release. This early unblinding will occur when at least 50% of the patients complete the week 25 assessments. The data comprising of PK, ADA, NAb and patient level demographic and baseline data will be unblinded.

Individuals serving on the early unblinding team will not be members of the study's blinded operations team from the time that they have access to the unblinded data until the completion of unblinding.

9.7. Data Monitoring Committee

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. The recommendations made by the EDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

9.8. Central Radiology Review

As this is a randomized trial, central radiology review will not be performed. However, for purposes of quality control, the Sponsor may elect to have all or some tumor assessments reviewed by an independent imaging vendor.

The central radiology review will be done by a vendor contracted with the Sponsor. Instructions for forwarding images for review will be provided in study documentation.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be patient to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. Use of initials should be avoided in compliance with Pfizer guidelines. The study site will maintain a confidential list of patients who participated in the study linking their numerical code to the patient's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures. All advertisements must be approved by the study Sponsor prior to use.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State. 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.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as the time at which the last patient has completed the LSLV, at which time study objectives have been met and the study is considered completed. LSLV is defined as up to 1 year from randomization of the last patient (End of Treatment) plus 28 day follow-up.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of bevacizumab-Pfizer at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within one week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, , and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated. For this protocol the primary completion date is when all patients have been followed for 1 year after randomization not including patients who died or withdrew consent prior to 1 year.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials,gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by the principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, patient to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. ECOG Performance Status

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

Appendix 2. Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 Guidelines

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

CATEGORIZING LESIONS AT BASELINE

Measureable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter at least 10 mm or greater when assessed by CT or MRI, measured in the axial plane. If the slice thickness is greater than 5 mm (including any inter-slice gap), the longest diameter must be at least twice the slice thickness.
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray, only if the tumor is clearly outlined by well-aerated lung.
- Malignant lymph nodes with a short axis (defined as the largest measurement perpendicular to the longest diameter of the lesion) 15 mm or greater when assessed by CT or MRI.

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

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

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

Normal Sites

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

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

Tumor Assessments

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

The determination of whether lesions are measurable is performed only at baseline. "Measurable" at baseline means eligible for selection as target lesions, and thus for quantitative assessment throughout the trial. Once selected as a target lesion, a lesion remains target throughout the trial.

Target Lesions

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

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

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

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

Non-Target Disease

All non-target disease is non-target. All measureable lesions not identified as target lesions are also included as non-target disease. Measurements are not require but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same techniques as baseline, including consistent administration of contract and timing of scanning. If not, subsequent objective statuses may be indeterminate.

Target Disease

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

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

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

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

- Indeterminate. Progression has not been assessed,

    - one or more target lesions have not been assessed,

    - or assessment methods used were inconsistent with those used at baseline and impaired assessment,

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

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

Non-Target Disease

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

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

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

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

New Lesions

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

Supplemental Investigations

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

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

Subjective Progression

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

Table 5 demonstrates how the objective response status is determined from the assessment of target, non-target, and new lesions at each evaluation.

Table 5. Objective Response Status at Each Evaluation

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

Response (partial or complete) must be confirmed by tumor assessments conducted 6 weeks (±7 days) after the response was noted.

Appendix 3. Tumor Staging

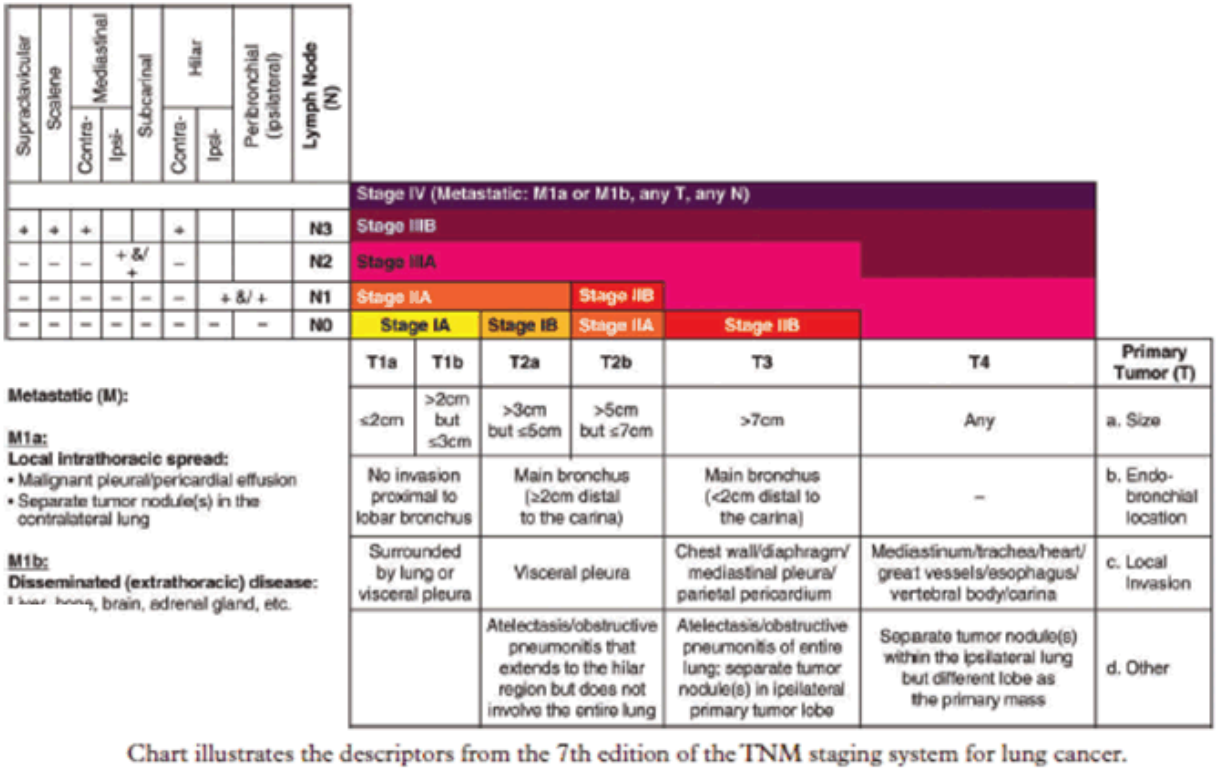

Chart illustrates the descriptors from the 7th edition of the TNM staging system for lung cancer.