ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 11/12/2012

Grantor: CDER IND/IDE Number: BB-IND 9948 Serial Number: 0123

Study of AVE0005 (VEGF Trap) in Locally Advanced or Metastatic Platinum- and Erlotinib- Resistant Non-small-cell-lung Adenocarcinoma

This study has been completed.

Sponsor:	Sanofi
Collaborators:	Regeneron Pharmaceuticals
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00284141

Purpose

This study evaluated the efficacy and safety of aflibercept in the treatment of participants with advanced chemoresistant non-small cell lung adenocarcinoma (NSCLA).

Primary objective:

- To determine the overall objective response rate (ORR) of AVE0005 (ziv-aflibercept, aflibercept, VEGF trap, ZALTRAP®) 4.0 mg/kg intravenously (IV) every 2 weeks in participants with platinum- and erlotinib-resistant, locally advanced or metastatic NSCLA.

Secondary objective:

- To assess duration of response (DR), progression-free survival (PFS), and overall survival (OS) in this participant population
- To evaluate the safety profile of IV AVE0005 (ziv-aflibercept, aflibercept, VEGF trap, ZALTRAP®).

This study employed an Independent Review Committee (IRC) for radiological tumor assessments. For all tumor assessment-related efficacy variables, two analyses were performed: the primary analysis was based on Independent Review Committee (IRC) reviewed data and the secondary analysis was based on Investigator evaluation.

In addition, both Response Evaluation Criteria In Solid Tumors (RECIST) and Modified Response Evaluation Criteria In Solid Tumors (mRECIST) were used to assess tumors. Where as RECIST criteria only consider the longest diameter of the tumors for calculations pertaining to changes in tumor size, mRECIST

assessments also account for the differences in the cavities of lesions observed in non-small-cell lung cancer (NSCLC). Responses based on RECIST and mRECIST are reported.

Condition	Intervention	Phase
Pulmonary Diseases Neoplasms, Lung	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®)	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety/Efficacy Study
Official Title: A Multicenter, Open-label, Single-arm, Two-stage Study of the Efficacy and Safety of AVE0005 (VEGF Trap) Administered Intravenously Every 2 Weeks in Patients With Platinum- and Erlotinib-resistant Locally Advanced or Metastatic Non-small-cell Lung Adenocarcinoma

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Confirmed Objective Response (OR) Based Upon Modified Response Evaluation Criteria in Solid Tumors (RECIST) Assessed by the Independent Review Committee (IRC). [Time Frame: up to 2.5 years from initial treatment] [Designated as safety issue: No]
  OR was either complete response (CR) or partial response (PR) based on RECIST or modified RECIST. CR was the disappearance of all target/non-target lesions; and PR was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, with reference to the baseline sum LD (According to modified RECIST, to calculate LD for cavitated lesions, the longest cavitation diameters were subtracted from the LD of cavitated target lesions). Assessments were made by the IRC, and confirmed by repeat tumor imaging 4-6 weeks after documentation of the initial response.
- Confirmed Objective Response Based Upon Modified Response Evaluation Criteria in Solid Tumors (RECIST) Assessed by the Investigator. [Time Frame: up to 2.5 years from initial treatment] [Designated as safety issue: No]
  OR was either complete response (CR) or partial response (PR) based on RECIST or modified RECIST. CR was the disappearance of all target/non-target lesions; and PR was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, with reference to the baseline sum LD (According to modified RECIST, to calculate LD for cavitated lesions, the longest cavitation diameters were subtracted from the LD of cavitated target lesions). Assessments were made by the Investigator, and confirmed by repeat tumor imaging 4-6 weeks after documentation of the initial response.

Secondary Outcome Measures:

- Duration of Response (DR) [Time Frame: up to 2.5 years from initial treatment] [Designated as safety issue: No]
  DR was the time interval from the first complete response (CR) or partial response (PR) to the date of tumor progression or death from any cause, whichever was earlier. The duration of response was calculated only for those participants who achieved CR or PR.
- Progression-free Survival (PFS) Time Assessed by the Independent Review Committee (IRC) [Time Frame: up to 2.5 years from initial treatment] [Designated as safety issue: No]
  PFS time was interval from the date of registration to the date of tumor progression (by RECIST or modified RECIST), or death from any cause, whichever was earlier. Median PFS time was estimated from Kaplan-Meier Plots. Progression was at least a 20% increase in the sum of the longest diameter (LD) of tumors, compared to smallest sum LD recorded since treatment started, or the appearance of one or more new tumors. If a participant did not progress or die, the date was censored to the date of last valid tumor assessment or the date of data cut-off, whichever was earlier.
- Progression-free Survival (PFS) Time Assessed by the Investigator [Time Frame: up to 2.5 years from initial treatment] [Designated as safety issue: No]
  PFS time was interval from the date of registration to the date of tumor progression (by RECIST or modified RECIST), or death from any cause, whichever was earlier. If a participant did not progress or die, the date was censored to the date of last valid tumor assessment or the date of data cut-off, whichever was earlier. Median PFS time was estimated from Kaplan-Meier Plots. Progression was at least a 20% increase in the sum of the longest diameter (LD) of tumors, compared to smallest sum LD recorded since treatment started, or the appearance of one or more new tumors.
- Overall Survival (OS) [Time Frame: up to 2.5 years from initial treatment] [Designated as safety issue: No]

OS was the time interval between registration to the date of death from any cause. The median time for OS was estimated from Kaplan-Meier Plots. A participant was to be censored for the OS analysis if the participant was alive by the study cut-off date. The censoring date was either the date that the participant was last known to be alive or the date of study cut-off, whichever came earlier.

- Heath-related Quality of Life (QOL) Measured Via the Lung Cancer Subscale [Time Frame: Baseline to 2.5 years] [Designated as safety issue: No]
  HRQL was assessed with the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) questionnaire, which was completed by the participants on Day 1 of Cycle 1 only (for baseline value), then on Day 14 of each even-numbered cycle to evaluate the participants symptoms. The questionnaire scored 7 symptoms: shortness of breath, weight loss, clarity in thinking, coughing, appetite, chest tightness, ease of breathing, on a 0-4 scale. The total FACT-LCS score ranged from 0-28 (where 28 was related to the worst outcome). To calculate a change, the baseline score was subtracted from the score obtained after treatment. A negative value implied an improvement in HRQL.
- Overall Safety - Number of Participants With Adverse Events [Time Frame: up to 60+/-5 days after treatment discontinuation, or or until TEAE was resolved or stabilized (Collected till 18 July 2008)] [Designated as safety issue: Yes]
  All AEs regardless of seriousness or relationship to study treatment, spanning from the first administration of study treatment until 60 days after the last administration of study treatment, were recorded, and followed until resolution or stabilization. The number of participants with all treatment emergent adverse events (TEAE), serious adverse events (SAE), TEAE leading to death, and TEAE leading to permanent treatment discontinuation are reported.
- Number of Participants With Laboratory Abnormalities [Time Frame: Up to 2.5 years] [Designated as safety issue: Yes]
  Participants with abnormal laboratory results for --Liver and renal function (Alkaline phosphatase, Alanine aminotransferase [ALT], aspartate aminotransferase [AST], Creatinine, Hyperbilirubinemia), --Electrolytes (Hypercalcemia, Hypocalcemia, Hypokalemia, Hypernatremia, Hyponatremia, Hypophosphatemia) --Metabolism (Hypoalbuminemia, Hyperglycemia, Hypoglycemia) --Hematology (Partial thromboplastin time, Anemia, Lymphopenia, Neutropenia, Thrombocytopenia, Leukopenia)
- Peak of Free Aflibercept (VEGF Trap) [Time Frame: Day 1 of the first infusion of Aflibercept (cycle 1)] [Designated as safety issue: No]
  Plasma free aflibercept levels after the first aflibercept infusion were estimated by a validated direct measured by enzyme-linked immunosorbent assay (ELISA), with a limit of quantification (LOQ) of 15.6 ng/mL.
- Free and VEGF-bound Trough Aflibercept Concentrations (VEGF Trap) [Time Frame: At the end of each treatment cycle (up to 2.5 years)] [Designated as safety issue: No]
  Median free and VEGF-bound trough concentrations were determined at the end of each cycle beyond Cycle 2 (Steady-state) for each participant. Plasma free aflibercept levels were estimated by a validated direct ELISA, with an LOQ of 15.6 ng/mL. Plasma VEGF-bound aflibercept levels were also estimated by a separate validated direct ELISA with an LOQ of 43.9 ng/mL. Mean ± SD (coefficient of variation [CV%]) values were estimated from the median values calculated for each participant.
- Number of Participants With Anti-drug Antibodies [Time Frame: up to 2.5 years after initial treatment] [Designated as safety issue: No]
  Anti-drug antibodies in a participant's serum sample were assayed with an anti-drug ELISA assay, with a lower limit of quantitation of 238.4 ng/mL for an undiluted human serum sample. Serum for anti-drug antibody analysis was collected pre-dose on every fourth cycle after Cycle 1 Day 1 (at 8 week intervals), at end of treatment (EOT), and during post-treatment follow-up 60 days after the last dose.

Enrollment: 98
Study Start Date: January 2006
Primary Completion Date: July 2008
Study Completion Date: July 2008

Arms	Assigned Interventions
Experimental: aflibercept 4.0 mg/kg Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept every 2 weeks until a study withdrawal criterion was met.	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) Aflibercept 4.0 mg/kg administered intravenously (IV) over a period of at least 1 hour once every 2 weeks.

Arms	Assigned Interventions
	Aflibercept could be reduced by 1 dose level (to 3.0 mg/kg) or 2 dose levels (to 2.0 mg/kg) in case of uncontrolled hypertension or urinary protein >3.5 g/24 hours. Intrapatient dose escalation was not to be permitted. Participants requiring more than 2 dose level reductions would be withdrawn from study treatment.

Detailed Description:

The study included :

- A screening phase up to 21 days followed by registration
- Treatment initiation within 5 working days of registration
- A treatment phase with 14-day study treatment cycles until a study withdrawal criterion was met or up to the clinical database cut-off date (18 July 2008)
- A follow-up phase - up to 60 days after end of treatment

Withdrawal criteria that led to treatment discontinuation were:

- The participant or their legally authorized representative requested to withdraw
- In the investigator's opinion, continuation of the study would be detrimental to the participant's well being, due to reasons such as disease progression, unacceptable toxicity, noncompliance, or logistical considerations.
- A specific request by the Sponsor
- Participant had intercurrent illness that prevented further administration of study treatment
- Participant had more than 2 aflibercept dose reductions
- Participant had arterial thromboembolic events, including cerebrovascular accidents, myocardial infarctions, transient ischemic attacks, new onset or worsening of pre-existing angina
- Participant had radiographic evidence of intestinal obstruction (e.g., dilated loops of bowel accompanied by air-fluid levels) or gastrointestinal perforation (e.g., presence of extraluminal gas) requiring surgical intervention
- Participant was lost to follow-up

After discontinuing treatment, participants remained on the study until the last post-treatment visit or until recovery of drug related toxicities, whichever was later.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Participants who met the following criteria were eligible for the study.

Inclusion Criteria:

- Histologically confirmed non-small-cell lung adenocarcinoma that is locally advanced or metastatic

- Prior treatment with at least 2 cancer drug regimens in the advanced disease setting
- Platinum- and erlotinib-resistant disease defined by relapse or progression during or after treatment
- Measurable disease by RECIST criteria
- ECOG Performance status less than or equal to 2
- Resolution of any toxic effects of prior therapy
- Adequate organ and bone marrow function
- Female patients must be post-menopausal, surgically sterile or using effective contraception
- Willing and able to comply with study procedures and sign informed consent

Exclusion Criteria:

- Diagnosis of squamous-cell lung cancer or any second malignancy within the last 5 years (except for adequately treated basal cell or squamous cell skin cancer or in situ carcinoma of the cervix uteri)
- Prior treatment with a VEGF or VEGF receptor inhibitor with the exception of bevacizumab (Avastin-TM)
- Anticipation of a need for major surgical procedure
- Treatment with chemotherapy, radiotherapy, surgery, blood products, or an investigational agent within 3 weeks (6 weeks for nitrosoureas, mitomycin C, immunotherapy, or cytokine therapy) of study enrollment
- Uncontrolled hypertension
- Any severe or acute medical or psychiatric problem within the past 6 months requiring further investigation or that may cause undue risk for the patient's safety
- History of brain metastases, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease
- Active infection or on antiretroviral therapy for HIV disease
- Pregnant or breast-feeding

The above information is not intended to contain all considerations relevant to potential participation in a clinical trial.

Contacts and Locations

Locations

United States, New Jersey

sanofi-aventis administrative office

Bridgewater, New Jersey, United States, 08807

Canada

sanofi-aventis administrative office

Laval, Canada

France

sanofi-aventis administrative office

Paris, France

Investigators

Study Director:	ICD CSD	sanofi-aventis

More Information

Results Publications:

Leighl NB, Raez LE, Besse B, Rosen PJ, Barlesi F, Massarelli E, Gabrail N, Hart LL, Albain KS, Berkowitz L, Melnyk O, Shepherd FA, Sternas L, Ackerman J, Shun Z, Miller VA, Herbst RS. A multicenter, phase 2 study of vascular endothelial growth factor trap (Aflibercept) in platinum- and erlotinib-resistant adenocarcinoma of the lung. J Thorac Oncol. 2010 Jul;5(7):1054-9.

Responsible Party: Sanofi
Study ID Numbers: ARD6123
AVE0005B/2001
Health Authority: United States: Food and Drug Administration
Canada: Health Canada

Study Results

Participant Flow

Recruitment Details	98 participants were registered into the study, of whom, 96 were exposed to study treatment.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Overall Study

	Aflibercept 4.0 mg/kg
Started	98
TREATED	96 [1]
ONGOING TREATMENT	2 [2]
Completed	0 [3]
Not Completed	98
Disease Progression / Lack of efficacy	51
Adverse Event	19
Participant's request	9
Symptomatic / Clinical Progression	11
Clinical deterioration / death	2

	Aflibercept 4.0 mg/kg
General decline	1
Pneumonia	1
Did not take study medication	2
Ongoing treatment	2

[1] Participants received at least part of one dose of Aflibercept.
[2] Participants were still on study treatment at the clinical database cut-off date.
[3] Participants met treatment discontinuation criteria or were still ongoing treatment.

Baseline Characteristics

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Baseline Measures

	Aflibercept 4.0 mg/kg
Number of Participants	98
Age, Continuous [units: years] Mean (Standard Deviation)	60.2 (11.0)
Gender, Male/Female [units: participants]	
Female	58
Male	40
Race/Ethnicity, Customized [units: participants]	
Caucasian	79
Black	3
Asian, Oriental	5
Unknown or Not Reported	11

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Confirmed Objective Response (OR) Based Upon Modified Response Evaluation Criteria in Solid Tumors (RECIST) Assessed by the Independent Review Committee (IRC).
Measure Description	OR was either complete response (CR) or partial response (PR) based on RECIST or modified RECIST. CR was the disappearance of all target/nor-target lesions; and PR was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, with reference to the baseline sum LD (According to modified RECIST, to calculate LD for cavitated lesions, the longest cavitation diameters were subtracted from the LD of cavitated target lesions). Assessments were made by the IRC, and confirmed by repeat tumor imaging 4-6 weeks after documentation of the initial response.
Time Frame	up to 2.5 years from initial treatment
Safety Issue?	No

Analysis Population Description

Simon's cohort: The first 84 evaluable participants, based on Simon's two-stage study design that required 84 evaluable participants to maintain a targeted 90% power.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg Arm Assessed by Modified RECIST	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks assessed by RECIST criteria.
Aflibercept 4.0 mg/kg Arm Assessed by RECIST	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks assessed by modified RECIST criteria.

Measured Values

	Aflibercept 4.0 mg/kg Arm Assessed by Modified RECIST	Aflibercept 4.0 mg/kg Arm Assessed by RECIST
Number of Participants Analyzed	84	84
Confirmed Objective Response (OR) Based Upon Modified Response Evaluation Criteria in Solid Tumors (RECIST) Assessed by the Independent Review Committee (IRC). [units: Participants]	0	0

2. Primary Outcome Measure:

Measure Title	Confirmed Objective Response Based Upon Modified Response Evaluation Criteria in Solid Tumors (RECIST) Assessed by the Investigator.
Measure Description	OR was either complete response (CR) or partial response (PR) based on RECIST or modified RECIST. CR was the disappearance of all target/nor-target lesions; and PR was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, with reference to the baseline sum LD (According to modified RECIST, to calculate LD for cavitated lesions, the longest cavitation diameters were subtracted from the LD of cavitated target lesions). Assessments were made by the Investigator, and confirmed by repeat tumor imaging 4-6 weeks after documentation of the initial response.
Time Frame	up to 2.5 years from initial treatment
Safety Issue?	No

Analysis Population Description

Simon's cohort: The first 84 evaluable participants, based on Simon's two-stage study design that required 84 evaluable participants to maintain a targeted 90% power.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg Arm Assessed by Modified RECIST	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks assessed by RECIST criteria.
Aflibercept 4.0 mg/kg Arm Assessed by RECIST	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks assessed by modified RECIST criteria.

Measured Values

	Aflibercept 4.0 mg/kg Arm Assessed by Modified RECIST	Aflibercept 4.0 mg/kg Arm Assessed by RECIST
Number of Participants Analyzed	84	84
Confirmed Objective Response Based Upon Modified Response Evaluation Criteria in Solid Tumors (RECIST) Assessed by the Investigator. [units: participants]		
Objective response (OR)	2	2
Complete response (CR)	0	0
Partial response (PR)	2	2

3. Secondary Outcome Measure:

Measure Title	Duration of Response (DR)
Measure Description	DR was the time interval from the first complete response (CR) or partial response (PR) to the date of tumor progression or death from any cause, whichever was earlier. The duration of response was calculated only for those participants who achieved CR or PR.
Time Frame	up to 2.5 years from initial treatment
Safety Issue?	No

Analysis Population Description

No modified RECIST responses, as confirmed by the IRC review, were observed. Only 2 responders were reported by the Investigators. Therefore, the analyses for duration of response was not performed.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Measured Values

	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	0

No data displayed because Outcome Measure has zero total participants analyzed.

4. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) Time Assessed by the Independent Review Committee (IRC)
Measure Description	PFS time was interval from the date of registration to the date of tumor progression (by RECIST or modified RECIST), or death from any cause, whichever was earlier. Median PFS time was estimated from Kaplan-Meier Plots. Progression was at least a 20% increase in the sum of the longest diameter (LD) of tumors, compared to smallest sum LD recorded since treatment started, or the appearance of one or more new tumors. If a participant did not progress or die, the date was censored to the date of last valid tumor assessment or the date of data cut-off, whichever was earlier.
Time Frame	up to 2.5 years from initial treatment
Safety Issue?	No

Analysis Population Description
All registered participants. 18 participants were censored.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg Arm Assessed by Modified RECIST	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks assessed by RECIST criteria.
Aflibercept 4.0 mg/kg Arm Assessed by RECIST	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks assessed by modified RECIST criteria.

Measured Values

	Aflibercept 4.0 mg/kg Arm Assessed by Modified RECIST	Aflibercept 4.0 mg/kg Arm Assessed by RECIST
Number of Participants Analyzed	98	98
Number of Participants with PFS Events Analyzed	80	80
Progression-free Survival (PFS) Time Assessed by the Independent Review Committee (IRC) [units: weeks] Median (95% Confidence Interval)	11.3 (9.3 to 16.1)	11.3 (9.3 to 16.1)

5. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) Time Assessed by the Investigator
Measure Description	PFS time was interval from the date of registration to the date of tumor progression (by RECIST or modified RECIST), or death from any cause, whichever was earlier. If a participant did not progress or die, the date was censored to the date of last valid tumor assessment or the date of data cut-off, whichever was earlier. Median PFS time was estimated from Kaplan-Meier Plots. Progression was at least a 20% increase in the sum of the longest diameter (LD) of tumors, compared to smallest sum LD recorded since treatment started, or the appearance of one or more new tumors.
Time Frame	up to 2.5 years from initial treatment
Safety Issue?	No

Analysis Population Description
All registered participants. 17 participants were censored.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg Arm Assessed by Modified RECIST	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks assessed by RECIST criteria.
Aflibercept 4.0 mg/kg Arm Assessed by RECIST	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks assessed by modified RECIST criteria.

Measured Values

	Aflibercept 4.0 mg/kg Arm Assessed by Modified RECIST	Aflibercept 4.0 mg/kg Arm Assessed by RECIST
Number of Participants Analyzed	98	98
Number of Participants with PFS Events Analyzed	81	81
Progression-free Survival (PFS) Time Assessed by the Investigator [units: weeks] Median (95% Confidence Interval)	12.0 (10.0 to 16.0)	11.9 (9.7 to 14.7)

6. Secondary Outcome Measure:

Measure Title	Overall Survival (OS)
Measure Description	OS was the time interval between registration to the date of death from any cause. The median time for OS was estimated from Kaplan-Meier Plots. A participant was to be censored for the OS analysis if the participant was alive by the study cut-off date. The censoring date was either the date that the participant was last known to be alive or the date of study cut-off, whichever came earlier.
Time Frame	up to 2.5 years from initial treatment
Safety Issue?	No

Analysis Population Description

All registered participants. 38 participants were censored for OS.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Measured Values

	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	98
Number of Participant with OS Event (death) Analyzed	60
Overall Survival (OS) [units: months] Median (95% Confidence Interval)	26.9 (21.0 to 49.3)

7. Secondary Outcome Measure:

Measure Title	Heath-related Quality of Life (QOL) Measured Via the Lung Cancer Subscale
Measure Description	HRQL was assessed with the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) questionnaire, which was completed by the participants on Day 1 of Cycle 1 only (for baseline value), then on Day 14 of each even-numbered cycle to evaluate the participants symptoms. The questionnaire scored 7 symptoms: shortness of breath, weight loss, clarity in thinking, coughing, appetite, chest tightness, ease of breathing, on a 0-4 scale. The total FACT-LCS score ranged from 0-28 (where 28 was related to the worst outcome). To calculate a change, the baseline score was subtracted from the score obtained after treatment. A negative value implied an improvement in HRQL.
Time Frame	Baseline to 2.5 years
Safety Issue?	No

Analysis Population Description

All registered participants with available questionnaires at the timepoint assessed.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Measured Values

	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	83
Heath-related Quality of Life (QOL) Measured Via the Lung Cancer Subscale [units: score on a scale]	

	Aflibercept 4.0 mg/kg
Mean (Standard Deviation)	
Baseline FACT-LCS Score (N=83)	19.9 (3.9)
Change from baseline at Cycle 2 (N=58)	-1.5 (3.6)
Change from baseline at Cycle 4 (N=41)	-1.9 (4.7)
Change from baseline at Cycle 6 (N=25)	-1.0 (5.0)
Change from baseline at Cycle 8 (N=13)	-1.4 (4.7)
Change from baseline at Cycle 10 (N=10)	-1.7 (6.9)
Change from baseline to last assessment (N=70)	-3.3 (5.2)

8. Secondary Outcome Measure:

Measure Title	Overall Safety - Number of Participants With Adverse Events
Measure Description	All AEs regardless of seriousness or relationship to study treatment, spanning from the first administration of study treatment until 60 days after the last administration of study treatment, were recorded, and followed until resolution or stabilization. The number of participants with all treatment emergent adverse events (TEAE), serious adverse events (SAE), TEAE leading to death, and TEAE leading to permanent treatment discontinuation are reported.
Time Frame	up to 60+/-5 days after treatment discontinuation, or or until TEAE was resolved or stabilized (Collected till 18 July 2008)
Safety Issue?	Yes

Analysis Population Description

All participants who received at least part of 1 dose of study treatment.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Measured Values

	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	96
Overall Safety - Number of Participants With Adverse Events	

	Aflibercept 4.0 mg/kg
[units: participants]	
With any TEAE	96
With any Serious TEAE	47
With any TEAE leading to Death	16
with any TEAE leading to Treatment discontinuation	19

9. Secondary Outcome Measure:

Measure Title	Number of Participants With Laboratory Abnormalities
Measure Description	Participants with abnormal laboratory results for • Liver and renal function (Alkaline phosphatase, Alanine aminotransferase [ALT], aspartate aminotransferase [AST], Creatinine, Hyperbilirubinemia), • Electrolytes (Hypercalcemia, Hypocalcemia, Hypokalemia, Hypernatremia, Hyponatremia, Hypophosphatemia) • Metabolism (Hypoalbuminemia, Hyperglycemia, Hypoglycemia) • Hematology (Partial thromboplastin time, Anemia, Lymphopenia, Neutropenia, Thrombocytopenia, Leukopenia)
Time Frame	Up to 2.5 years
Safety Issue?	Yes

Analysis Population Description

All participants who received at least part of 1 dose of study treatment.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Measured Values

	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	96
Number of Participants With Laboratory Abnormalities [units: Participants]	
LIVER AND RENAL FUNCTION- Alkaline Phosphatase	39

	Aflibercept 4.0 mg/kg
LIVER AND RENAL FUNCTION - ALT	35
LIVER AND RENAL FUNCTION - AST	37
LIVER AND RENAL FUNCTION - Creatinine	15
LIVER AND RENAL FUNCTION - Hyperbilirubinemia	4
ELECTROLYTES - Hypercalcemia	6
ELECTROLYTES - Hypocalcemia	15
ELECTROLYTES - Hyperkalemia	24
ELECTROLYTES - Hypokalemia	10
ELECTROLYTES - Hypernatremia	5
ELECTROLYTES - Hyponatremia	41
ELECTROLYTES - Hypophosphatemia (N=91)	14
METABOLISM - Hypoalbuminemia (N=91)	44
METABOLISM - Hyperglycemia	81
METABOLISM - Hypoglycemia	10
HEMATOLOGY - Partial thromboplastin time (N=81)	30
HEMATOLOGY - Anemia	34
HEMATOLOGY - Lymphopenia (N=84)	60
HEMATOLOGY - Neutropenia (N=78)	4
HEMATOLOGY - Thrombocytopenia	11
HEMATOLOGY - Leukopenia	11

10. Secondary Outcome Measure:

Measure Title	Peak of Free Aflibercept (VEGF Trap)
Measure Description	Plasma free aflibercept levels after the first aflibercept infusion were estimated by a validated direct measured by enzyme-linked immunosorbent assay (ELISA), with a limit of quantification (LOQ) of 15.6 ng/mL.

Time Frame	Day 1 of the first infusion of Aflibercept (cycle 1)
Safety Issue?	No

Analysis Population Description

All participants who received at least part of 1 dose of study treatment and had evaluable blood samples.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Measured Values

	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	47
Peak of Free Aflibercept (VEGF Trap) [units: micrograms/mL] Mean (Standard Deviation)	71.4 (31.8)

11. Secondary Outcome Measure:

Measure Title	Free and VEGF-bound Trough Aflibercept Concentrations (VEGF Trap)
Measure Description	Median free and VEGF-bound trough concentrations were determined at the end of each cycle beyond Cycle 2 (Steady-state) for each participant. Plasma free aflibercept levels were estimated by a validated direct ELISA, with an LOQ of 15.6 ng/mL. Plasma VEGF-bound aflibercept levels were also estimated by a separate validated direct ELISA with an LOQ of 43.9 ng/mL. Mean ± SD (coefficient of variation [CV%]) values were estimated from the median values calculated for each participant.
Time Frame	At the end of each treatment cycle (up to 2.5 years)
Safety Issue?	No

Analysis Population Description

All participants who received at least part of 1 dose of study treatment and had evaluable blood samples on Day 1 of Cycle 3 for measurement of VEGF-bound aflibercept.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Measured Values

	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	61
Free and VEGF-bound Trough Aflibercept Concentrations (VEGF Trap) [units: micrograms/mL] Mean (Standard Deviation)	
Trough free aflibercept concentration	9.53 (6.28)
Trough VEGF-bound aflibercept concentration	3.48 (1.04)

12. Secondary Outcome Measure:

Measure Title	Number of Participants With Anti-drug Antibodies
Measure Description	Anti-drug antibodies in a participant's serum sample were assayed with an anti-drug ELISA assay, with a lower limit of quantitation of 238.4 ng/mL for an undiluted human serum sample. Serum for anti-drug antibody analysis was collected pre-dose on every fourth cycle after Cycle 1 Day 1 (at 8 week intervals), at end of treatment (EOT), and during post-treatment follow-up 60 days after the last dose.
Time Frame	up to 2.5 years after initial treatment
Safety Issue?	No

Analysis Population Description

All participants who received at least part of 1 dose of study treatment and had evaluable blood samples.

Reporting Groups

	Description
Aflibercept 4.0 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Measured Values

	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	80
Number of Participants With Anti-drug Antibodies [units: participants]	0

Reported Adverse Events

Time Frame	From treatment initiation to February 24, 2009.
Additional Description	[Not specified]

Reporting Groups

	Description
4 mg/kg	Participants with metastatic non-small-cell lung adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every 2 weeks until a study withdrawal criterion was met.

Serious Adverse Events

	4 mg/kg
	Affected/At Risk (%)
Total	48/96 (50%)
Blood and lymphatic system disorders	
Febrile neutropenia [A] *	1/96 (1.04%)
Cardiac disorders	
Atrial flutter [A] *	1/96 (1.04%)
Cardiac failure congestive [A] *	2/96 (2.08%)
Cardio-respiratory arrest [A] *	1/96 (1.04%)
Cardiomyopathy [A] *	1/96 (1.04%)
Gastrointestinal disorders	

	4 mg/kg
	Affected/At Risk (%)
Abdominal discomfort [A] *	1/96 (1.04%)
Abdominal pain [A] *	1/96 (1.04%)
Dysphagia [A] *	1/96 (1.04%)
Nausea [A] *	1/96 (1.04%)
Obstruction gastric [A] *	1/96 (1.04%)
Pancreatitis acute [A] *	1/96 (1.04%)
General disorders	
Asthenia [A] *	1/96 (1.04%)
Disease progression [A] *	7/96 (7.29%)
Fatigue [A] *	2/96 (2.08%)
Non-cardiac chest pain [A] *	2/96 (2.08%)
Infections and infestations	
Cellulitis [A] *	1/96 (1.04%)
Pneumonia [A] *	6/96 (6.25%)
Sepsis [A] *	2/96 (2.08%)
Injury, poisoning and procedural complications	
Facial bones fracture [A] *	1/96 (1.04%)
Fall [A] *	1/96 (1.04%)
Radiation injury [A] *	1/96 (1.04%)
Investigations	
Blood creatinine increased [A] *	1/96 (1.04%)
Metabolism and nutrition disorders	
Dehydration [A] *	2/96 (2.08%)

	4 mg/kg
	Affected/At Risk (%)
Diabetic ketoacidosis [A] *	1/96 (1.04%)
Failure to thrive [A] *	1/96 (1.04%)
Hyponatraemia [A] *	1/96 (1.04%)
Musculoskeletal and connective tissue disorders	
Bone pain [A] *	1/96 (1.04%)
Musculoskeletal pain [A] *	1/96 (1.04%)
Pathological fracture [A] *	1/96 (1.04%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Leukaemia [A] *	1/96 (1.04%)
Metastatic pain [A] *	1/96 (1.04%)
Nervous system disorders	
Cerebral ischaemia [A] *	1/96 (1.04%)
Cerebrovascular accident [A] *	1/96 (1.04%)
Reversible posterior leukoencephalopathy syndrome [A] *	1/96 (1.04%)
Psychiatric disorders	
Anxiety [A] *	1/96 (1.04%)
Mental status changes [A] *	1/96 (1.04%)
Renal and urinary disorders	
Bladder stenosis [A] *	1/96 (1.04%)
Hydronephrosis [A] *	1/96 (1.04%)
Urinary retention [A] *	1/96 (1.04%)
Respiratory, thoracic and mediastinal disorders	

	4 mg/kg
	Affected/At Risk (%)
Chronic obstructive pulmonary disease [A] *	2/96 (2.08%)
Dyspnoea [A] *	8/96 (8.33%)
Epistaxis [A] *	2/96 (2.08%)
Haemoptysis [A] *	2/96 (2.08%)
Pleural effusion [A] *	2/96 (2.08%)
Pneumothorax [A] *	1/96 (1.04%)
Pulmonary embolism [A] *	4/96 (4.17%)
Respiratory failure [A] *	2/96 (2.08%)
Vascular disorders	
Axillary vein thrombosis [A] *	1/96 (1.04%)
Deep vein thrombosis [A] *	2/96 (2.08%)
Hypertension [A] *	2/96 (2.08%)
Superior vena caval occlusion [A] *	1/96 (1.04%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 11.1

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	4 mg/kg
	Affected/At Risk (%)
Total	93/96 (96.88%)
Gastrointestinal disorders	
Abdominal pain [A] *	6/96 (6.25%)
Constipation [A] *	27/96 (28.12%)
Diarrhoea [A] *	12/96 (12.5%)

	4 mg/kg
	Affected/At Risk (%)
Dry mouth [A] *	6/96 (6.25%)
Dysphagia [A] *	6/96 (6.25%)
Nausea [A] *	23/96 (23.96%)
Oral pain [A] *	5/96 (5.21%)
Vomiting [A] *	16/96 (16.67%)
General disorders	
Asthenia [A] *	16/96 (16.67%)
Chest pain [A] *	5/96 (5.21%)
Disease progression [A] *	6/96 (6.25%)
Fatigue [A] *	39/96 (40.62%)
Mucosal inflammation [A] *	5/96 (5.21%)
Oedema peripheral [A] *	20/96 (20.83%)
Pain [A] *	6/96 (6.25%)
Pyrexia [A] *	11/96 (11.46%)
Infections and infestations	
Pneumonia [A] *	5/96 (5.21%)
Upper respiratory tract infection [A] *	6/96 (6.25%)
Urinary tract infection [A] *	11/96 (11.46%)
Investigations	
Weight decreased [A] *	9/96 (9.38%)
Metabolism and nutrition disorders	
Anorexia [A] *	24/96 (25%)
Decreased appetite [A] *	9/96 (9.38%)

	4 mg/kg
	Affected/At Risk (%)
Dehydration [A] *	5/96 (5.21%)
Hyponatraemia [A] *	7/96 (7.29%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	14/96 (14.58%)
Back pain [A] *	8/96 (8.33%)
Bone pain [A] *	7/96 (7.29%)
Flank pain [A] *	5/96 (5.21%)
Musculoskeletal chest pain [A] *	7/96 (7.29%)
Musculoskeletal pain [A] *	10/96 (10.42%)
Myalgia [A] *	8/96 (8.33%)
Pain in extremity [A] *	7/96 (7.29%)
Nervous system disorders	
Dizziness [A] *	8/96 (8.33%)
Headache [A] *	38/96 (39.58%)
Psychiatric disorders	
Anxiety [A] *	7/96 (7.29%)
Depression [A] *	8/96 (8.33%)
Insomnia [A] *	10/96 (10.42%)
Renal and urinary disorders	
Proteinuria [A] *	15/96 (15.62%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	22/96 (22.92%)
Dysphonia [A] *	27/96 (28.12%)

	4 mg/kg
	Affected/At Risk (%)
Dyspnoea [A] *	37/96 (38.54%)
Epistaxis [A] *	19/96 (19.79%)
Haemoptysis [A] *	11/96 (11.46%)
Oropharyngeal pain [A] *	6/96 (6.25%)
Pleural effusion [A] *	5/96 (5.21%)
Productive cough [A] *	6/96 (6.25%)
Skin and subcutaneous tissue disorders	
Rash [A] *	8/96 (8.33%)
Vascular disorders	
Hypertension [A] *	38/96 (39.58%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 11.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The investigator shall have the right to independently publish study results from his site after a multicenter publication, or 12 months after the completion of the study by all sites. He must provide the sponsor a copy of any such publication derived from the study for review and comment at least 45 days (20 days for abstracts) in advance of any submission, and delay publication till the approval of the publication is given in writing by the Sponsor (not to exceed ninety days).

Results Point of Contact:

Name/Official Title: Trial Transparency Team

Organization: Sanofi
Phone:
Email: Contact-Us@Sanofi.com