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Study of AVE0005 (VEGF Trap) in Patients With Chemoresistant Advanced Ovarian Cancer

This study has been completed.

Sponsor:	Sanofi
Collaborators:	Regeneron Pharmaceuticals
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00327171

Purpose

This study evaluated outcomes in participants with advanced ovarian epithelial adenocarcinoma receiving aflibercept.

The primary objective was to compare the objective response rate of Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) 4.0 mg/kg and 2.0 mg/kg, administered intravenously (IV) every 2 weeks with historical control in participants with advanced ovarian epithelial (including fallopian tube and primary peritoneal) adenocarcinoma resistant to platinum and topotecan and/or liposomal doxorubicin.

The secondary objectives was to further assess efficacy, safety, pharmacokinetics, potential biological and pharmacogenomic markers of study drug activity, and health-related quality of life.

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. If an endpoint was evaluated by the IRC, the IRC reviewed data is reported for this study.

Condition	Intervention	Phase
Neoplasms Cancer of the Ovary	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®)	Phase 2

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study

Official Title: A Multicenter, Randomized, Double-blind, Parallel-arm, Two-stage Study of the Efficacy and Safety of AVE0005 (VEGF Trap) Administered Intravenously Every 2 Weeks in Patients With Platinum-resistant and topotecan-and/or Liposomal Doxorubicin-resistant Advanced Ovarian Cancer

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Number of Participants With Confirmed Objective Response (OR) as Per Response Evaluation Criteria in Solid Tumors (RECIST) Based on the Analysis by an Independent Review Committee (IRC) - Simon's Cohort [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]

  OR included Complete Response (CR) and Partial Response (PR). Per RECIST, CR was disappearance of all target or non-target lesions, or normalization of tumor marker levels (for non-target lesions) and PR was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, with baseline sum LD as reference. Tumors were assessed by an independent third-party core imaging laboratory evaluating the chest, abdomen, and pelvis by Computerized Tomography (CT) scans or Magnetic Resonance Imaging (MRI) scans; and responses were confirmed by repeat tumor imaging 4-6 weeks later.
- Number of Participants With Confirmed Objective Response (OR) as Per Response Evaluation Criteria in Solid Tumors (RECIST) Based on the Analysis by the IRC - Efficacy Evaluable Population [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]

  OR included Complete Response (CR) and Partial Response (PR). Per RECIST, CR was disappearance of all target or non-target lesions, or normalization of tumor marker levels (for non-target lesions) and PR was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, with baseline sum LD as reference. Tumors were assessed by an independent third-party core imaging laboratory evaluating the chest, abdomen, and pelvis by Computerized Tomography (CT) scans or Magnetic Resonance Imaging (MRI) scans; and responses were confirmed by repeat tumor imaging 4-6 weeks later.

Secondary Outcome Measures:

- Number of Participants With a Clinical Benefit Response (CBR) as Per RECIST Based on the Analysis by the IRC [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]

  CBR was defined as having a Stable disease (SD) for >= 6 months or a confirmed OR (PR or CR). Based on RECIST: -- SD was neither a sufficient shrinkage of the target lesions to qualify for PR nor sufficient increase to qualify for Progressive disease (PD), the persistence of non-target lesions or the maintenance of tumor marker level above the normal limits (for non-target lesions) -- CR was the disappearance of all target or 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.
- Duration of Response (DR) Based on the Analysis by an Independent Review Committee (IRC) [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]

  DR was defined as the time interval from the first documentation of CR or PR to the date of tumor progression (or disease progression) as determined by RECIST, or death from any cause, whichever was earlier. Based on RECIST, progressive disease was at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, the appearance of one or more new target or non-target lesions, or the unequivocal progression of existing non-target lesions.
- Tumor Marker Response Rate (TMRR) Based on the Gynecologic Cancer Intergroup (GCIG) Definition [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]

  TMRR was the proportion of evaluable participants achieving a cancer antigen -125 (CA-125) response based on GCIG definition. A response to CA-125 occurred if after two elevated levels before therapy there was at least a 50% decrease in a post-treatment serum sample, which was confirmed by an independent sample collected 21 days or later that was =< 110% of the post-treatment serum sample.
- Time to Tumor Progression (TTP) as Per RECIST Based on the Analysis by the IRC [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]

  TTP was defined as the time interval measured from the date of randomization to the date of tumor progression as determined by RECIST. TTP was estimated from Kaplan-Meier curves. For a participant who did not reach tumor progression during study, the censoring date was the date of

the last valid tumor burden assessment or the date of study cut-off, whichever was earlier. If the participant had no valid post-baseline tumor burden assessment due to early termination, the censoring date was the date of randomization.

- Time to Tumor Marker (CA-125) Progression (TTMP) [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]
  TTMP was the time interval from the date of randomization to the date of tumor marker progression as was defined by GCIG for the evaluable participants. TTMP was estimated using Kaplan-Meier curves. For a participant who did not reach tumor marker progression (TMP) during study, the censoring date was the date of the last valid tumor burden assessment or the date of study cut-off, whichever was earlier. If the participant had no valid post-baseline tumor burden assessment due to early termination, the censoring date was the date of randomization.
- Number of Participants With Disease Progression Events for Progression-free Survival (PFS) Analysis by the IRC. [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]
  PFS was as the time interval measured from the date of randomization to the date of tumor progression as determined by RECIST or death from any cause, whichever was earlier. The number of participants with tumor/disease progression are reported. Participants who did not reach tumor progression during study, or had no valid post-baseline tumor burden assessment due to early termination, were censored in the PFS analysis.
- Progression-free Survival (PFS) Time Based on Analysis by the IRC [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]
  PFS was as the time interval measured from the date of randomization to the date of tumor progression as determined by RECIST or death from any cause, whichever was earlier. PFS was estimated using Kaplan-Meier curves. For a participant who did not reach tumor progression during study, the censoring date was the date of the last valid tumor burden assessment or the date of study cut-off, whichever was earlier. If the participant had no valid post-baseline tumor burden assessment due to early termination, the censoring date was the date of randomization.
- Overall Survival (OS) Time [Time Frame: From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)] [Designated as safety issue: No]
  OS was the time interval between randomization and the date of death from any cause. OS was estimated using Kaplan-Meier curves A participant was censored for the OS analysis if the participant were alive during the study. The censoring date was either at the date that the participant was last known to be alive or the date of study cut-off, whichever was earlier.
- Overall Safety - Number of Participants With Adverse Events (AE) [Time Frame: up to 30+/-5 days after treatment discontinuation, or up to recovery or stabilization of a followed-up adverse event] [Designated as safety issue: Yes]
  All AEs regardless of seriousness or relationship to study treatment, spanning from the first administration of study treatment until 30 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.
- Participant's Assessment of Health Related Quality of Life (HRQL) Using a by Using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Questionnaire [Time Frame: On Day 1 of Cycle 1 (baseline) , and after Day 14 of Cycle 2] [Designated as safety issue: No]
  The FACT-O questionnaire consists of 38 scored questions (scored from 0-4) that address physical well-being, social/family well-being, emotional well-being, functional well-being and some additional concerns which relate specifically to ovarian cancer symptoms. For each question, higher scores reflect a better quality of life. The total FACT-O score ranges from 0-152, with 152 indicating the best outcome.

Enrollment: 218
Study Start Date: May 2006
Primary Completion Date: April 2008
Study Completion Date: March 2010

Arms	Assigned Interventions
Experimental: Aflibercept 2.0 mg/kg	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®)

Arms	Assigned Interventions
Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept.	Aflibercept 2.0 mg/kg administered intravenously (IV) over 1 hour once every 2 weeks. Aflibercept could be reduced by 1 dose level (to 1.0 mg/kg) or 2 dose levels (to 0.5 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.
Experimental: Aflibercept 4.0 mg/kg Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept.	Drug: Aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) Aflibercept 4.0 mg/kg administered intravenously (IV) over 1 hour once every 2 weeks. Aflibercept could be reduced by 1 dose level (to 2.0 mg/kg) or 2 dose levels (to 1.0 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 period for 21 days
- Randomization at baseline (Treatment was initiated with 5 days of randomization)
- A treatment period with 14-day study treatment cycles until a study withdrawal criterion was met
- A follow-up period up to 60 days after the 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: Female
Accepts Healthy Volunteers: No

Criteria

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

Inclusion Criteria:

- Histologically-confirmed ovarian epithelial (including fallopian tube and primary peritoneal) adenocarcinoma.
- Prior treatment with at least 2 treatment regimens in the advanced disease treatment setting
- Platinum-resistant disease defined by relapse or progression of disease during or after treatment, or drug intolerance
- Topotecan- and/or liposomal doxorubicin-resistant disease defined by relapse or progression of disease during or after treatment, or drug intolerance
- Evidence of at least one unidimensional measurable tumor lesion by computed tomography (CT) or magnetic resonance imaging (MRI) scan according to Response Evaluation Criteria in Solid Tumors (RECIST) that has not been treated with surgery or radiation therapy

Exclusion Criteria:

- Diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or for in situ carcinoma of the cervix uteri
- Prior treatment with a vascular endothelial growth factor (VEGF) or VEGF receptor inhibitor
- More than 3 chemotherapy regimens in the advanced disease treatment setting
- Uncontrolled hypertension

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
Australia
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Macquarie Park, Australia
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Gouda, Netherlands
Portugal
sanofi-aventis administrative office
Porto Salvo, Portugal
Spain
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Barcelona, Spain
Sweden
sanofi-aventis administrative office
Bromma, Sweden
Switzerland
sanofi-aventis administrative office
Geneva, Switzerland

Investigators

Study Director:	ICD CSD	sanofi-aventis

More Information

Responsible Party:	Sanofi
Study ID Numbers:	ARD6122 AVE0005
Health Authority:	United States: Food and Drug Administration Spain: Ministry of Health Sweden: Medical Products Agency

Study Results

Participant Flow

Recruitment Details	218 participants were randomized in this study. Three participants in the 2 mg/kg treatment group did not receive any study medication.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Overall Study

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Started	109	109
Completed	1 [1]	0 [1]
Not Completed	108	109
Did not receive study medication	3	0
Adverse Event	23	23
Disease progression/lack of efficacy	68	69
Investigator/participant request	1	8
Clinical progression	12	8
Undisclosed history of ischemia	0	1
Unspecified	1	0

[1] Participants received treatment until they met treatment discontinuation criteria

Baseline Characteristics

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Baseline Measures

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg	Total
Number of Participants	109	109	218
Age, Customized [units: participants]			
<35 years	3	3	6
>=35 to <45 years	10	6	16
>=45 to <55 years	21	25	46
>=55 to <65 years	37	43	80
>=65 to <75 years	32	25	57
>=75 years	6	7	13
Gender, Male/Female [units: participants]			
Female	109	109	218
Male	0	0	0
Race/Ethnicity, Customized [units: participants]			
Caucasian	104	107	211
Black	3	1	4
Asian, Oriental	1	1	2
Unknown or Not Reported	1	0	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Confirmed Objective Response (OR) as Per Response Evaluation Criteria in Solid Tumors (RECIST) Based on the Analysis by an Independent Review Committee (IRC) - Simon's Cohort
Measure Description	OR included Complete Response (CR) and Partial Response (PR). Per RECIST, CR was disappearance of all target or non-target lesions, or normalization of tumor marker levels (for non-target lesions) and PR was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, with baseline sum LD as reference. Tumors were assessed by an independent third-party core imaging laboratory evaluating the chest, abdomen, and pelvis by Computerized Tomography (CT) scans or Magnetic Resonance Imaging (MRI) scans; and responses were confirmed by repeat tumor imaging 4-6 weeks later.

Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Simon's cohort: The first 67 evaluable participants, based on Simon's two-stage design that required 67 evaluable participants per group to maintain a targeted 80% power for Objective response rate versus historical controls.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	67	67
Number of Participants With Confirmed Objective Response (OR) as Per Response Evaluation Criteria in Solid Tumors (RECIST) Based on the Analysis by an Independent Review Committee (IRC) - Simon's Cohort [units: participants]	0	3

2. Primary Outcome Measure:

Measure Title	Number of Participants With Confirmed Objective Response (OR) as Per Response Evaluation Criteria in Solid Tumors (RECIST) Based on the Analysis by the IRC - Efficacy Evaluable Population
Measure Description	OR included Complete Response (CR) and Partial Response (PR). Per RECIST, CR was disappearance of all target or non-target lesions, or normalization of tumor marker levels (for non-target lesions) and PR was at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, with baseline sum LD as reference. Tumors were assessed by an independent third-party core imaging laboratory evaluating the chest, abdomen, and pelvis by Computerized Tomography (CT) scans or Magnetic Resonance Imaging (MRI) scans; and responses were confirmed by repeat tumor imaging 4-6 weeks later.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Efficacy evaluable population: All participants with advanced ovarian epithelial carcinoma who were randomized, underwent baseline tumor assessment, and received at least part of one dose of aflibercept.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	106	109
Number of Participants With Confirmed Objective Response (OR) as Per Response Evaluation Criteria in Solid Tumors (RECIST) Based on the Analysis by the IRC - Efficacy Evaluable Population [units: participants]	1	5

3. Secondary Outcome Measure:

Measure Title	Number of Participants With a Clinical Benefit Response (CBR) as Per RECIST Based on the Analysis by the IRC
Measure Description	CBR was defined as having a Stable disease (SD) for >= 6 months or a confirmed OR (PR or CR). Based on RECIST: • SD was neither a sufficient shrinkage of the target lesions to qualify for PR nor sufficient increase to qualify for Progressive disease (PD), the persistence of non-target lesions or the maintenance of tumor marker level above the normal limits (for non-target lesions) • CR was the disappearance of all target or 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.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Simon's cohort: The first 67 evaluable participants, based on Simon’s two-stage design that required 67 evaluable participants per group to maintain a targeted 80% power for Objective response rate versus historical controls.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	67	67
Number of Participants With a Clinical Benefit Response (CBR) as Per RECIST Based on the Analysis by the IRC [units: participants]	12	7

4. Secondary Outcome Measure:

Measure Title	Duration of Response (DR) Based on the Analysis by an Independent Review Committee (IRC)
Measure Description	DR was defined as the time interval from the first documentation of CR or PR to the date of tumor progression (or disease progression) as determined by RECIST, or death from any cause, whichever was earlier. Based on RECIST, progressive disease was at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, the appearance of one or more new target or non-target lesions, or the unequivocal progression of existing non-target lesions.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Efficacy evaluable population: All participants with advanced ovarian epithelial carcinoma who were randomized, underwent baseline tumor assessment, and received at least part of one dose of aflibercept.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks

	Description
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	1	5
Duration of Response (DR) Based on the Analysis by an Independent Review Committee (IRC) [units: days] Mean (Standard Deviation)	164 (NA) [1]	149.8 (70.4)

[1] NA: Not calculable since only one participant achieved CR or PR

5. Secondary Outcome Measure:

Measure Title	Tumor Marker Response Rate (TMRR) Based on the Gynecologic Cancer Intergroup (GCIG) Definition
Measure Description	TMRR was the proportion of evaluable participants achieving a cancer antigen -125 (CA-125) response based on GCIG definition. A response to CA-125 occurred if after two elevated levels before therapy there was at least a 50% decrease in a post-treatment serum sample, which was confirmed by an independent sample collected 21 days or later that was =< 110% of the post-treatment serum sample.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Randomized participants who received at least part of one dose of aflibercept, had a baseline tumor assessment, had a valid CA-125 assessment (requiring at least two pretreatment sample and 2 post-treatment samples), did not receive mouse antibodies and had no medical or surgical interference with their peritoneum or pleura in the previous 28 days.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	61	69
Tumor Marker Response Rate (TMRR) Based on the Gynecologic Cancer Intergroup (GCIG) Definition [units: percentage of participants] Mean (95% Confidence Interval)	11.5 (4.7 to 22.2)	11.6 (5.1 to 21.6)

6. Secondary Outcome Measure:

Measure Title	Time to Tumor Progression (TTP) as Per RECIST Based on the Analysis by the IRC
Measure Description	TTP was defined as the time interval measured from the date of randomization to the date of tumor progression as determined by RECIST. TTP was estimated from Kaplan-Meier curves. For a participant who did not reach tumor progression during study, the censoring date was the date of the last valid tumor burden assessment or the date of study cut-off, whichever was earlier. If the participant had no valid post-baseline tumor burden assessment due to early termination, the censoring date was the date of randomization.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Efficacy evaluable population: All participants with advanced ovarian epithelial carcinoma who were randomized, underwent baseline tumor assessment, and received at least part of one dose of aflibercept.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	106	109
Number of Tumor Progression Events Analyzed	66	66

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Time to Tumor Progression (TTP) as Per RECIST Based on the Analysis by the IRC [units: weeks] Median (95% Confidence Interval)	13.1 (12.1 to 16.7)	12.7 (12 to 18.9)

Statistical Analysis 1 for Time to Tumor Progression (TTP) as Per RECIST Based on the Analysis by the IRC

Statistical Analysis Overview	Comparison Groups	Aflibercept 2.0 mg/kg, Aflibercept 4.0 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5043
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.123
	Confidence Interval	(2-Sided) 95% 0.80 to 1.58
	Estimation Comments	Estimated using Cox proportional Hazard model using treatment as the factor

7. Secondary Outcome Measure:

Measure Title	Time to Tumor Marker (CA-125) Progression (TTMP)
Measure Description	TTMP was the time interval from the date of randomization to the date of tumor marker progression as was defined by GCIG for the evaluable participants. TTMP was estimated using Kaplan-Meier curves. For a participant who did not reach tumor marker progression (TMP) during study, the censoring date was the date of the last valid tumor burden assessment or the date of study cut-off, whichever was earlier. If the participant had no valid post-baseline tumor burden assessment due to early termination, the censoring date was the date of randomization.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Participants with a valid assessment of CA-125 (requiring at least one pretreatment sample and 2 post-treatment samples).

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	76	84
Number of Tumor Marker Progression events Analyzed	15	20
Time to Tumor Marker (CA-125) Progression (TTMP) [units: weeks] Median (95% Confidence Interval)	NA (24.1 to NA) [1]	NA (22.7 to NA) [1]

[1] The value was not calculable due to the limited number of events.

8. Secondary Outcome Measure:

Measure Title	Number of Participants With Disease Progression Events for Progression-free Survival (PFS) Analysis by the IRC.
Measure Description	PFS was as the time interval measured from the date of randomization to the date of tumor progression as determined by RECIST or death from any cause, whichever was earlier. The number of participants with tumor/disease progression are reported. Participants who did not reach tumor progression during study, or had no valid post-baseline tumor burden assessment due to early termination, were censored in the PFS analysis.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Efficacy evaluable population: All participants with advanced ovarian epithelial carcinoma who were randomized, underwent baseline tumor assessment, and received at least part of one dose of aflibercept.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	106	109
Number of Participants With Disease Progression Events for Progression-free Survival (PFS) Analysis by the IRC. [units: participants]		
With disease progression as the first event	66	66
Death without disease progression	16	23
Censored due to drop-out	18	14
Censored at study cut-off	6	6

9. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) Time Based on Analysis by the IRC
Measure Description	PFS was as the time interval measured from the date of randomization to the date of tumor progression as determined by RECIST or death from any cause, whichever was earlier. PFS was estimated using Kaplan-Meier curves. For a participant who did not reach tumor progression during study, the censoring date was the date of the last valid tumor burden assessment or the date of study cut-off, whichever was earlier. If the participant had no valid post-baseline tumor burden assessment due to early termination, the censoring date was the date of randomization.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Efficacy evaluable population: All participants with advanced ovarian epithelial carcinoma who were randomized, underwent baseline tumor assessment, and received at least part of one dose of aflibercept.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	106	109
Number of PFS Events Analyzed	82	89
Progression-free Survival (PFS) Time Based on Analysis by the IRC [units: weeks] Median (95% Confidence Interval)	13.0 (11.7 to 16.7)	13.3 (11.2 to 18.9)

Statistical Analysis 1 for Progression-free Survival (PFS) Time Based on Analysis by the IRC

Statistical Analysis Overview	Comparison Groups	Aflibercept 2.0 mg/kg, Aflibercept 4.0 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5592
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.093
	Confidence Interval	(2-Sided) 95% 0.81 to 1.48
	Estimation Comments	Estimated using Cox proportional Hazard model using treatment as the factor (4mg/kg vs. 2mg/kg)

10. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) Time
Measure Description	OS was the time interval between randomization and the date of death from any cause. OS was estimated using Kaplan-Meier curves A participant was censored for the OS analysis if the participant were alive during the study. The censoring date was either at the date that the participant was last known to be alive or the date of study cut-off, whichever was earlier.
Time Frame	From enrollment to efficacy cut-off date, 18 January 2008 (approximately 20 months)
Safety Issue?	No

Analysis Population Description

Efficacy evaluable population: All participants with advanced ovarian epithelial carcinoma who were randomized, underwent baseline tumor assessment, and received at least part of one dose of aflibercept.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	106	109
Number of Events (Death) Analyzed	50	58
Overall Survival (OS) Time [units: weeks] Median (95% Confidence Interval)	59.0 (41.6 to 84.1)	49.3 (37.4 to 62.7)

Statistical Analysis 1 for Overall Survival (OS) Time

Statistical Analysis Overview	Comparison Groups	Aflibercept 2.0 mg/kg, Aflibercept 4.0 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5457
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.124
	Confidence Interval	(2-Sided) 95% 0.77 to 1.64
	Estimation Comments	Estimated using Cox proportional Hazard model using treatment as the factor (4 mg/kg vs. 2mg/kg)

11. Secondary Outcome Measure:

Measure Title	Overall Safety - Number of Participants With Adverse Events (AE)
Measure Description	All AEs regardless of seriousness or relationship to study treatment, spanning from the first administration of study treatment until 30 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 30+/-5 days after treatment discontinuation, or up to recovery or stabilization of a followed-up adverse event
Safety Issue?	Yes

Analysis Population Description

Safety population: All randomized participants who received at least part of one dose of study treatment.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	106	109
Overall Safety - Number of Participants With Adverse Events (AE) [units: participants]		
With any TEAE	106	108
With any serious TEAE	50	55
With any TEAE leading to death	14	14
With TEAE leading to treatment discontinuation	23	24

12. Secondary Outcome Measure:

Measure Title	Participant's Assessment of Health Related Quality of Life (HRQL) Using a by Using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Questionnaire
Measure Description	The FACT-O questionnaire consists of 38 scored questions (scored from 0-4) that address physical well-being, social/ family well-being, emotional well-being, functional well-being and some additional concerns which relate specifically to ovarian cancer symptoms. For each question, higher scores reflect a better quality of life. The total FACT-O score ranges from 0-152, with 152 indicating the best outcome.
Time Frame	On Day 1 of Cycle 1 (baseline) , and after Day 14 of Cycle 2
Safety Issue?	No

Analysis Population Description

All randomized participants who had evaluable FACT-O questionnaires.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Measured Values

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
Number of Participants Analyzed	97	104
Participant's Assessment of Health Related Quality of Life (HRQL) Using a by Using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Questionnaire [units: score on a scale] Mean (Standard Deviation)		
Baseline (N=97, N=104)	105.3 (20.0)	101.1 (22)
Change (baseline to Cycle 2-Day 14) (N=79, N=77)	-1.1 (12.7)	-2.8 (13.9)

Reported Adverse Events

Time Frame	From treatment initiation to June 9, 2010
Additional Description	Safety population: All randomized participants who received at least part of one dose of study treatment.

Reporting Groups

	Description
Aflibercept 2.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 2.0 mg/kg Aflibercept intravenously every two weeks
Aflibercept 4.0 mg/kg	Participants with advanced ovarian epithelial adenocarcinoma administered 4.0 mg/kg Aflibercept intravenously every two weeks

Serious Adverse Events

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Total	51/106 (48.11%)	56/109 (51.38%)
Blood and lymphatic system disorders		
Anaemia [A] *	2/106 (1.89%)	1/109 (0.92%)
Thrombocytopenia [A] *	1/106 (0.94%)	0/109 (0%)

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Thrombotic thrombocytopenic purpura [A] *	0/106 (0%)	1/109 (0.92%)
Cardiac disorders		
Angina pectoris [A] *	1/106 (0.94%)	0/109 (0%)
Cardio-respiratory arrest [A] *	1/106 (0.94%)	0/109 (0%)
Congestive cardiomyopathy [A] *	1/106 (0.94%)	0/109 (0%)
Left ventricular dysfunction [A] *	0/106 (0%)	1/109 (0.92%)
Ear and labyrinth disorders		
Vertigo [A] *	0/106 (0%)	1/109 (0.92%)
Eye disorders		
Blindness transient [A] *	0/106 (0%)	1/109 (0.92%)
Gastrointestinal disorders		
Abdominal pain [A] *	4/106 (3.77%)	6/109 (5.5%)
Ascites [A] *	1/106 (0.94%)	0/109 (0%)
Colonic obstruction [A] *	1/106 (0.94%)	0/109 (0%)
Crohn's disease [A] *	1/106 (0.94%)	0/109 (0%)
Diarrhoea [A] *	1/106 (0.94%)	1/109 (0.92%)
Gastrointestinal haemorrhage [A] *	0/106 (0%)	1/109 (0.92%)
Gastrointestinal necrosis [A] *	1/106 (0.94%)	0/109 (0%)
Gastrointestinal obstruction [A] *	2/106 (1.89%)	1/109 (0.92%)
Intestinal obstruction [A] *	10/106 (9.43%)	6/109 (5.5%)
Intestinal perforation [A] *	1/106 (0.94%)	2/109 (1.83%)
Melaena [A] *	1/106 (0.94%)	0/109 (0%)
Nausea [A] *	3/106 (2.83%)	0/109 (0%)

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Small intestinal obstruction [A] *	0/106 (0%)	2/109 (1.83%)
Subileus [A] *	0/106 (0%)	2/109 (1.83%)
Vomiting [A] *	2/106 (1.89%)	2/109 (1.83%)
General disorders		
Asthenia [A] *	1/106 (0.94%)	2/109 (1.83%)
Disease progression [A] *	3/106 (2.83%)	7/109 (6.42%)
Fatigue [A] *	0/106 (0%)	1/109 (0.92%)
General physical health deterioration [A] *	0/106 (0%)	2/109 (1.83%)
Pyrexia [A] *	2/106 (1.89%)	2/109 (1.83%)
Sudden death [A] *	0/106 (0%)	1/109 (0.92%)
Hepatobiliary disorders		
Jaundice cholestatic [A] *	1/106 (0.94%)	0/109 (0%)
Infections and infestations		
Abscess intestinal [A] *	0/106 (0%)	1/109 (0.92%)
Appendicitis [A] *	0/106 (0%)	1/109 (0.92%)
Catheter site infection [A] *	0/106 (0%)	1/109 (0.92%)
Clostridial infection [A] *	0/106 (0%)	1/109 (0.92%)
Clostridium difficile colitis [A] *	0/106 (0%)	1/109 (0.92%)
Device related infection [A] *	1/106 (0.94%)	0/109 (0%)
Febrile infection [A] *	1/106 (0.94%)	1/109 (0.92%)
Gastroenteritis salmonella [A] *	1/106 (0.94%)	0/109 (0%)
Hepatitis a [A] *	0/106 (0%)	1/109 (0.92%)

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Peritonitis bacterial [A] *	0/106 (0%)	1/109 (0.92%)
Pneumonia [A] *	2/106 (1.89%)	2/109 (1.83%)
Pneumonia streptococcal [A] *	1/106 (0.94%)	0/109 (0%)
Pyelonephritis [A] *	0/106 (0%)	1/109 (0.92%)
Sepsis [A] *	1/106 (0.94%)	0/109 (0%)
Septic shock [A] *	1/106 (0.94%)	0/109 (0%)
Urinary tract infection [A] *	1/106 (0.94%)	0/109 (0%)
Injury, poisoning and procedural complications		
Ankle fracture [A] *	0/106 (0%)	1/109 (0.92%)
Narcotic intoxication [A] *	0/106 (0%)	1/109 (0.92%)
Wound dehiscence [A] *	0/106 (0%)	1/109 (0.92%)
Investigations		
Blood alkaline phosphatase increased [A] *	1/106 (0.94%)	0/109 (0%)
Blood creatinine increased [A] *	1/106 (0.94%)	0/109 (0%)
Gamma-glutamyltransferase increased [A] *	1/106 (0.94%)	0/109 (0%)
Hepatic enzyme increased [A] *	1/106 (0.94%)	0/109 (0%)
International normalised ratio increased [A] *	0/106 (0%)	1/109 (0.92%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	2/106 (1.89%)	0/109 (0%)
Dehydration [A] *	4/106 (3.77%)	2/109 (1.83%)
Hypoalbuminaemia [A] *	1/106 (0.94%)	0/109 (0%)
Hyponatraemia [A] *	1/106 (0.94%)	1/109 (0.92%)

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Type 1 diabetes mellitus [A] *	0/106 (0%)	1/109 (0.92%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	0/106 (0%)	1/109 (0.92%)
Musculoskeletal chest pain [A] *	0/106 (0%)	1/109 (0.92%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Cardiac myxoma [A] *	1/106 (0.94%)	0/109 (0%)
Malignant pleural effusion [A] *	1/106 (0.94%)	0/109 (0%)
Metastases to central nervous system [A] *	0/106 (0%)	2/109 (1.83%)
Metastases to lymph nodes [A] *	1/106 (0.94%)	0/109 (0%)
Metastases to small intestine [A] *	0/106 (0%)	1/109 (0.92%)
Nervous system disorders		
Grand mal convulsion [A] *	0/106 (0%)	1/109 (0.92%)
Headache [A] *	1/106 (0.94%)	2/109 (1.83%)
Hypertensive encephalopathy [A] *	0/106 (0%)	1/109 (0.92%)
Polyneuropathy [A] *	0/106 (0%)	1/109 (0.92%)
Syncope [A] *	1/106 (0.94%)	0/109 (0%)
Transient ischaemic attack [A] *	1/106 (0.94%)	0/109 (0%)
Renal and urinary disorders		
Hydronephrosis [A] *	1/106 (0.94%)	0/109 (0%)
Nephrotic syndrome [A] *	1/106 (0.94%)	0/109 (0%)
Proteinuria [A] *	1/106 (0.94%)	1/109 (0.92%)
Renal failure [A] *	3/106 (2.83%)	3/109 (2.75%)
Renal failure acute [A] *	0/106 (0%)	1/109 (0.92%)

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Urinary retention [A] *	1/106 (0.94%)	0/109 (0%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome [A] *	1/106 (0.94%)	0/109 (0%)
Chronic obstructive pulmonary disease [A] *	0/106 (0%)	1/109 (0.92%)
Dyspnoea [A] *	2/106 (1.89%)	4/109 (3.67%)
Hypoxia [A] *	1/106 (0.94%)	0/109 (0%)
Pleural effusion [A] *	3/106 (2.83%)	1/109 (0.92%)
Pneumonia aspiration [A] *	0/106 (0%)	1/109 (0.92%)
Pulmonary embolism [A] *	1/106 (0.94%)	2/109 (1.83%)
Pulmonary oedema [A] *	0/106 (0%)	1/109 (0.92%)
Respiratory failure [A] *	1/106 (0.94%)	0/109 (0%)
Skin and subcutaneous tissue disorders		
Erythema [A] *	0/106 (0%)	1/109 (0.92%)
Vascular disorders		
Deep vein thrombosis [A] *	0/106 (0%)	1/109 (0.92%)
Hypertension [A] *	4/106 (3.77%)	6/109 (5.5%)
Phlebitis [A] *	0/106 (0%)	1/109 (0.92%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.0

Other Adverse Events

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

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Total	105/106 (99.06%)	106/109 (97.25%)

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Blood and lymphatic system disorders		
Anaemia [A] *	6/106 (5.66%)	2/109 (1.83%)
Gastrointestinal disorders		
Abdominal pain [A] *	36/106 (33.96%)	40/109 (36.7%)
Abdominal pain upper [A] *	14/106 (13.21%)	17/109 (15.6%)
Constipation [A] *	37/106 (34.91%)	27/109 (24.77%)
Diarrhoea [A] *	31/106 (29.25%)	39/109 (35.78%)
Dry mouth [A] *	6/106 (5.66%)	4/109 (3.67%)
Intestinal obstruction [A] *	8/106 (7.55%)	4/109 (3.67%)
Nausea [A] *	44/106 (41.51%)	43/109 (39.45%)
Stomatitis [A] *	10/106 (9.43%)	8/109 (7.34%)
Toothache [A] *	9/106 (8.49%)	7/109 (6.42%)
Vomiting [A] *	38/106 (35.85%)	30/109 (27.52%)
General disorders		
Asthenia [A] *	30/106 (28.3%)	27/109 (24.77%)
Fatigue [A] *	42/106 (39.62%)	44/109 (40.37%)
Mucosal inflammation [A] *	13/106 (12.26%)	19/109 (17.43%)
Oedema peripheral [A] *	12/106 (11.32%)	12/109 (11.01%)
Pyrexia [A] *	18/106 (16.98%)	21/109 (19.27%)
Infections and infestations		
Nasopharyngitis [A] *	7/106 (6.6%)	9/109 (8.26%)
Urinary tract infection [A] *	13/106 (12.26%)	5/109 (4.59%)
Investigations		

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Weight decreased [A] *	8/106 (7.55%)	11/109 (10.09%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	42/106 (39.62%)	30/109 (27.52%)
Dehydration [A] *	3/106 (2.83%)	9/109 (8.26%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	25/106 (23.58%)	28/109 (25.69%)
Back pain [A] *	15/106 (14.15%)	10/109 (9.17%)
Muscle spasms [A] *	2/106 (1.89%)	7/109 (6.42%)
Musculoskeletal pain [A] *	15/106 (14.15%)	13/109 (11.93%)
Myalgia [A] *	8/106 (7.55%)	17/109 (15.6%)
Neck pain [A] *	8/106 (7.55%)	6/109 (5.5%)
Pain in extremity [A] *	9/106 (8.49%)	8/109 (7.34%)
Nervous system disorders		
Dizziness [A] *	9/106 (8.49%)	12/109 (11.01%)
Headache [A] *	54/106 (50.94%)	54/109 (49.54%)
Neuropathy peripheral [A] *	8/106 (7.55%)	4/109 (3.67%)
Paraesthesia [A] *	6/106 (5.66%)	8/109 (7.34%)
Psychiatric disorders		
Anxiety [A] *	4/106 (3.77%)	7/109 (6.42%)
Depression [A] *	3/106 (2.83%)	7/109 (6.42%)
Insomnia [A] *	8/106 (7.55%)	11/109 (10.09%)
Renal and urinary disorders		
Proteinuria [A] *	21/106 (19.81%)	23/109 (21.1%)

	Aflibercept 2.0 mg/kg	Aflibercept 4.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	10/106 (9.43%)	21/109 (19.27%)
Dysphonia [A] *	39/106 (36.79%)	46/109 (42.2%)
Dyspnoea [A] *	15/106 (14.15%)	20/109 (18.35%)
Epistaxis [A] *	8/106 (7.55%)	21/109 (19.27%)
Oropharyngeal pain [A] *	7/106 (6.6%)	11/109 (10.09%)
Rhinorrhoea [A] *	4/106 (3.77%)	7/109 (6.42%)
Skin and subcutaneous tissue disorders		
Nail disorder [A] *	4/106 (3.77%)	6/109 (5.5%)
Rash [A] *	10/106 (9.43%)	9/109 (8.26%)
Vascular disorders		
Hypertension [A] *	60/106 (56.6%)	57/109 (52.29%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.0

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 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:

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