ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
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Aflibercept in Combination With Docetaxel in Metastatic Androgen Independent Prostate Cancer (VENICE)

This study has been completed.

Sponsor:	Sanofi
Collaborators:	Regeneron Pharmaceuticals
Information provided by (Responsible Party):	Sanofi
ClinicalTrials.gov Identifier:	NCT00519285

Purpose

Primary objective was to demonstrate overall survival improvement with aflibercept compared to placebo in patients receiving docetaxel / prednisone for metastatic androgen-independent prostate cancer (MAIPC).

The secondary objectives were:

- To assess the efficacy of aflibercept compared to placebo on other parameters such prostate-specific antigen (PSA) level, cancer related pain, progression free survival (PFS), tumor-based and skeletal events and health-related quality of life (HRQL);
- To assess the overall safety in both treatment arms;
- To determine the pharmacokinetics of intravenous (IV) aflibercept in this population;
- to determine immunogenicity of IV aflibercept.

Condition	Intervention	Phase
Prostatic Neoplasms Neoplasm Metastasis	Drug: Aflibercept Drug: Placebo (for aflibercept) Drug: Docetaxel Drug: Prednisone or Prednisolone	Phase 3

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator), Randomized, Efficacy Study
Official Title: A Multicenter, Randomized, Double Blind Study Comparing the Efficacy and Safety of Aflibercept Versus Placebo Administered Every 3 Weeks in Patients Treated With Docetaxel/ Prednisone for Metastatic Androgen-independent Prostate Cancer

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Overall Survival Time [Time Frame: From randomization up to the cut-off date (median follow-up of 35.4 months)] [Designated as safety issue: No]
  Overall survival (OS) time was measured as the time from date of randomization to the date of death due to any cause. The median OS time and its 95.6% confidence interval were estimated using the Kaplan-Meier method. In the absence of confirmation of death, the participant was censored at the last date he/she was known to be alive or the study cut-off date (when 873 deaths have occurred), whichever was earlier.

Secondary Outcome Measures:

- Prostate Specific Antigen Response Rate [Time Frame: Before randomization (baseline) then every 3 weeks up to PSA progression (≥25% increase) or the cut-off date, whichever occurred first] [Designated as safety issue: No]
  Prostate specific antigen (PSA) response was defined as ≥50% decrease from baseline in serum PSA levels, confirmed at least 3 weeks later. Increases of any magnitude during the first 12 weeks were ignored in determining PSA response.
- Time to Skeletal Related Events [Time Frame: From randomization up to the cut-off date (median follow-up of 35.4 months)] [Designated as safety issue: No]
  Skeletal Related Events (SRE) included pathological fractures and/or spinal cord compression, need for bone irradiation, including radioisotopes or bone surgery, change in antineoplastic therapy to treat bone pain. Time to SRE was defined as the time from the date of randomization to the date of occurence of the first event defining a SRE or death due to any cause, whichever occurred first. The median time to SRE and its 95% confidence interval were estimated using the Kaplan-Meier method. In the absence of SRE, the participant was censored at the last date he/she was known to be alive or the study cut-off date, whichever was earlier.
- Progression Free Survival Time [Time Frame: From randomization up to the cut-off date (median follow-up of 35.4 months)] [Designated as safety issue: No]
  Disease progression was defined as a composite of: Radiological tumor progression (≥20% increase in target lesions, or appearance of at least 2 new bone lesions); PSA progression (≥25% increase in PSA level confirmed 3 weeks later); Pain progression (increase in pain intensity or in analgesic consumption for cancer related pain confirmed 3 weeks later); Radiotherapy for cancer related symptoms; Occurence of Skeletal related events (SRE). Progression Free survival (PFS) time was measured as the time from the date of randomization up to the date of occurrence of the first event defining a disease progression or death due to any cause, whichever occurred first. The median PFS time and its 95% confidence interval were estimated using the Kaplan-Meier method. In the absence of disease progression, the participant was censored at the the date of last assessment without evidence of progression or the study cut-off date, whichever was earlier.
- Tumor Response Rate in Participants With Measurable Disease [Time Frame: Before randomization (baseline) then every 3 months up to tumor progression (≥25% increase) or the cut-off date, whichever occurred first] [Designated as safety issue: No]
  Tumor response was defined as either a Complete Response (disappearance of all target lesions) or a Partial Response (≥30% decrease from baseline in target lesions) as assessed by Response Evaluation Criteria In Solid Tumors (RECIST)version 1.0.
- Prostate Specific Antigen Progression-free Survival Time [Time Frame: From randomization up to the cut-off date (median follow-up of 35.4 months)] [Designated as safety issue: No]
  Prostate specific antigen (PSA) progression was defined as ≥25% increase in PSA level confirmed 3 weeks later, above the nadir in participants who had achieved a PSA response, or above the baseline in participants who hadn't achieved a PSA response. PSA progression-free survival (PFS) time was defined as the time from the date of randomization up to the date of the first documented PSA progression or death due to any cause, whichever occurred first. The median PSA-PFS time and its 95% confidence interval were estimated using the Kaplan-Meier method. In the absence of PSA progression or death, the participant was censored at the the date of last assessment without evidence of progression or the study cut-off date, whichever was earlier.

- Pain Progression-free Survival Time [Time Frame: From randomization up to the cut-off date (median follow-up of 35.4 months)] [Designated as safety issue: No]
  Pain progression was defined as either ≥1-point increase in Present Pain Intensity (PPI) score or ≥25% increase in Analgesics Score (AS) confirmed at least 3 weeks later, or requirement for palliative radiotherapy. PPI scale is a self-report 0-5 scale to assess pain intensity - a score 0 reflects no pain, a score 5 reflects excruciating pain. AS is a scoring method to assess analgesics consumption. Each analgesic is scored 1 or 4 depending on the analgesic type and dose. AS is the sum of the analgesic scores. Pain progression-free survival (PFS) time was measured as the time from the date of randomization up to the date of first pain progression or death due to any cause, whichever occurred first. The median pain-PFS and its 95% confidence interval were estimated using the Kaplan-Meier method. In the absence of event, the participant was censored at the the date of last assessment without evidence of pain progression or the study cut-off date, whichever was earlier.
- Pain Response Rate [Time Frame: Before randomization (baseline) then every 3 weeks up to pain progression or the cut-off date, whichever occurred first] [Designated as safety issue: No]
  Pain response was defined as either a ≥2-point decrease from baseline in Present Pain Intensity (PPI) score without increase in Analgesics Score (AS), or a ≥50% decrease from baseline in AS without increase in the PPI score confirmed at least 3 weeks later. Increases in PPI or AS during the first 12 weeks were ignored in determining pain response.
- Change From Baseline in Functional Assessment of Cancer Therapy-Prostate Total Score as a Measure of Health Related Quality of Life [Time Frame: Before randomization (baseline) then every 3 weeks until disease progression or administration of further antitumor therapy, whichever came first] [Designated as safety issue: No]
  Functional Assessment of Cancer Therapy-Prostate (FACT-P) is a 39-item participant questionnaire that measures the concerns of patients with prostate cancer. It consists of 5 subscales assessing physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate-specific concerns. FACT-P total score is the sum of the 5 subscores. It ranges from 0 to 156 with higher score indicating better quality of life.
- Number of Participants With Adverse Events as a Measure of Safety [Time Frame: From first dose of study treatment (aflibercept/placebo or docetaxel whichever came first) to last dose of study treatment (aflibercept/placebo or docetaxel whichever came last) + 30 days] [Designated as safety issue: Yes]
  Adverse Events (AE) are any unfavorable and unintended sign, symptom, syndrome or illness observed by the investigator or reported by the participant during the study. AE were collected at regular intervals throughout the study then graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.3.0).
- Number of Participants With Positive Anti-aflibercept Antibody Levels as a Measure of Immunogenicity of Aflibercept [Time Frame: Pre-dose of cycle 1 (baseline), pre-dose of each every other cycle, then 30 and 90 days after the last administration of the study drug] [Designated as safety issue: No]
  Serum for detection of anti-drug antibodies (ADA) was collected in patients treated in selected centers only. Samples were analyzed using a titer-based, bridging immunoassay developed and validated to detect ADAs in human serum. Samples with positive antibody levels were further analyzed using a validated, non-quantitative ligand binding assay to detect neutralizing antibodies Ab). A participant was considered to have positive antibody levels if antibodies were detected above the quantification limits.

Enrollment: 1224
Study Start Date: August 2007
Primary Completion Date: February 2012
Study Completion Date: April 2012

Arms	Assigned Interventions
Placebo Comparator: Placebo Placebo added to standard chemotherapy with docetaxel plus prednisone or prednisolone	Drug: Placebo (for aflibercept) Sterile aqueous buffered solution identical to aflibercept 1-hour IV on Day 1 of each 3-Week cycle Drug: Docetaxel

Arms	Assigned Interventions
	Marketed formulation 75 mg/m², 1 hour IV on Day 1 of each 3-week cycle (immediately after Aflibercept or placebo) Other Names: Taxotere® Drug: Prednisone or Prednisolone Marketed formulation 5 mg twice daily PO from day 1 continuously
Experimental: Aflibercept Aflibercept added to standard chemotherapy with docetaxel plus prednisone or prednisolone	Drug: Aflibercept 25 mg/ml solution 6 mg/kg, 1-hour IV on Day 1 of each 3-Week cycle Other Names: AVE0005 ZALTRAP®) Drug: Docetaxel Marketed formulation 75 mg/m², 1 hour IV on Day 1 of each 3-week cycle (immediately after Aflibercept or placebo) Other Names: Taxotere® Drug: Prednisone or Prednisolone Marketed formulation 5 mg twice daily PO from day 1 continuously

Detailed Description:

The study consisted in 3-week treatment cycles until progressive disease, unacceptable toxicity, or participant's refusal of further study treatment. After disease progression, participants were to be followed every 3 months until death or the study cutoff date, whichever came first.

The study cut-off date was event-driven and was defined as the date when 873 deaths had occurred.

Eligibility

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

Criteria

Inclusion Criteria:

- Histologically- or cytologically-confirmed prostate adenocarcinoma;
- Metastatic disease;
- Progressive disease while receiving hormonal therapy or after surgical castration;
- Effective castration.

Exclusion Criteria:

- Prior cytotoxic chemotherapy for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed >3 years ago;
- Prior treatment with Vascular Endothelial Growth Factor (VEGF) inhibitors or VEGF receptor inhibitors;
- Eastern Cooperative Oncology Group (ECOG) performance status >2.

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

Contacts and Locations

Locations

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Investigators

Study Director:	Clinical Sciences & Operations	sanofi-aventis

More Information

Results Publications:

Tannock IF, Fizazi K, Ivanov S, Karlsson CT, Fléchon A, Skoneczna I, Orlandi F, Gravis G, Matveev V, Bavbek S, Gil T, Viana L, Arén O, Karyakin O, Elliott T, Birtle A, Magherini E, Hatteville L, Petrylak D, Tombal B, Rosenthal M; VENICE investigators. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. Lancet Oncol. 2013 Jul;14(8):760-8. doi: 10.1016/S1470-2045(13)70184-0. Epub 2013 Jun 4.

Responsible Party:	Sanofi
Study ID Numbers:	EFC6546 2006-004756-20 [EudraCT Number]
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	Between August 2007 and February 2010, a total of 1548 patients gave informed consent for this study.
Pre-Assignment Details	Amongst these patients, a total of 324 were screening failures (primarily due to non-compliance with exclusion criteria) and did not get randomized.

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Overall Study

	Placebo	Aflibercept
Started	612 [1]	612 [1]
TREATED	604 [2]	605 [3]
Still Treated at Cut-off Date	1 [4]	2
Completed	0 [5]	0
Not Completed	612	612
Adverse Event	127	266
Disease progression	334	186
Physician Decision	75	47
Participant's request	53	84
Consent withdrawn	4	5
Poor compliance to protocol	5	7
Reason unspecified	5	8
Not treated	8	7
Treatment ongoing	1	2

[1] Randomized
[2] Received at least part of one dose of placebo
[3] Received at least part of one dose of aflibercept
[4] The cut-off date for analysis was defined as 07 February 2012, date at which 873 deaths has occurred
[5] Participants were treated until progressive disease, unacceptable toxicity, or refusal of treatment

Baseline Characteristics

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Baseline Measures

	Placebo	Aflibercept	Total
Number of Participants	612	612	1224
Age, Continuous [units: Years] Mean (Standard Deviation)	67.6 (8.0)	67.9 (7.8)	67.8 (7.9)
Age, Customized [units: participants]			
<65 years	225	195	420
65-74 years	259	283	542
≥75 years	128	134	262
Gender, Customized Male [units: participants]	612	612	1224
Race/Ethnicity, Customized [units: participants]			
Caucasian/White	552	560	1112
Black	17	15	32
Asian/Oriental	36	32	68
Other	7	5	12

	Placebo	Aflibercept	Total
Region of Enrollment [units: Participants]			
Western Europe	219	227	446
Eastern Europe	131	132	263
North America	81	95	176
South America	88	71	159
Other region	93	87	180
Body Surface Area (BSA) [units: m^2] Mean (Standard Deviation)	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)
Eastern Co-operative Group (ECOG) performance status [1] [units: participants]			
ECOG 0	285	283	568
ECOG 1	299	303	602
ECOG 2	28	26	54

[1] ECOG performance status:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, 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

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overall Survival Time
Measure Description	Overall survival (OS) time was measured as the time from date of randomization to the date of death due to any cause. The median OS time and its 95.6% confidence interval were estimated using the Kaplan-Meier method. In the absence of confirmation of death, the participant was censored at the last date he/she was known to be alive or the study cut-off date (when 873 deaths have occurred), whichever was earlier.
Time Frame	From randomization up to the cut-off date (median follow-up of 35.4 months)

Safety Issue?	No

Analysis Population Description

The analysis was performed on the Intent-to-treat (ITT) population (i.e all randomized participants according to the treatment assigned regardless of the drug actually received).

At the cut-off date, 873 deaths had occurred, 445 in the Placebo group and 428 in the Aflibercept group.

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	612	612
Overall Survival Time [units: months] Median (95% Confidence Interval)	21.22 (19.614 to 23.754)	22.14 (20.304 to 24.082)

Statistical Analysis 1 for Overall Survival Time

Statistical Analysis Overview	Comparison Groups	Placebo, Aflibercept
	Comments	Null hypothesis: No difference between aflibercept and placebo The study was designed to provide 90% power to detect a 1.25-fold increase in median survival with aflibercept compared to placebo at a overall one-sided significance level of 0.025 with 873 deaths.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3802
	Comments	A priori threshold for statistical significance was set to 0.044 using the O'Brien-Fleming alpha spending function to account for two interim analyses.
	Method	Log Rank

	Comments	Log rank test stratified on ECOG Performance Status

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.942
	Confidence Interval	(2-Sided) 95.6% 0.822 to 1.08
	Estimation Comments	Hazard ratio (HR) aflibercept versus placebo estimated from a Cox proportional hazard model stratified on ECOG Performance Status

2. Secondary Outcome Measure:

Measure Title	Prostate Specific Antigen Response Rate
Measure Description	Prostate specific antigen (PSA) response was defined as ≥50% decrease from baseline in serum PSA levels, confirmed at least 3 weeks later. Increases of any magnitude during the first 12 weeks were ignored in determining PSA response.
Time Frame	Before randomization (baseline) then every 3 weeks up to PSA progression (≥25% increase) or the cut-off date, whichever occurred first
Safety Issue?	No

Analysis Population Description

The analysis was performed on the ITT population evaluable for PSA response (i.e. with a baseline PSA ≥10 ng/mL).

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	559	560
Prostate Specific Antigen Response Rate [units: percentage of participants] Number (95% Confidence Interval)	63.5 (59.5 to 67.5)	68.6 (64.7 to 72.4)

3. Secondary Outcome Measure:

Measure Title	Time to Skeletal Related Events
Measure Description	Skeletal Related Events (SRE) included pathological fractures and/or spinal cord compression, need for bone irradiation, including radioisotopes or bone surgery, change in antineoplastic therapy to treat bone pain. Time to SRE was defined as the time from the date of randomization to the date of occurence of the first event defining a SRE or death due to any cause, whichever occurred first. The median time to SRE and its 95% confidence interval were estimated using the Kaplan-Meier method. In the absence of SRE, the participant was censored at the last date he/she was known to be alive or the study cut-off date, whichever was earlier.
Time Frame	From randomization up to the cut-off date (median follow-up of 35.4 months)
Safety Issue?	No

Analysis Population Description

The analysis was performed on the ITT population.

At the cut-off date, SRE or death had occurred in 1013 participants, 516 in the Placebo group and 497 in the Aflibercept group.

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	612	612
Time to Skeletal Related Events [units: months] Median (95% Confidence Interval)	14.98 (13.733 to 16.427)	15.31 (14.127 to 16.657)

4. Secondary Outcome Measure:

Measure Title	Progression Free Survival Time

Measure Description	Disease progression was defined as a composite of: Radiological tumor progression (≥20% increase in target lesions, or appearance of at least 2 new bone lesions); PSA progression (≥25% increase in PSA level confirmed 3 weeks later); Pain progression (increase in pain intensity or in analgesic consumption for cancer related pain confirmed 3 weeks later); Radiotherapy for cancer related symptoms; Occurence of Skeletal related events (SRE). Progression Free survival (PFS) time was measured as the time from the date of randomization up to the date of occurrence of the first event defining a disease progression or death due to any cause, whichever occurred first. The median PFS time and its 95% confidence interval were estimated using the Kaplan-Meier method. In the absence of disease progression, the participant was censored at the the date of last assessment without evidence of progression or the study cut-off date, whichever was earlier.
Time Frame	From randomization up to the cut-off date (median follow-up of 35.4 months)
Safety Issue?	No

Analysis Population Description

The analysis was performed on the ITT population.

At the cut-off date, disease progression or death had occurred in 1184 participants, 592 in each treatment group.

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	612	612
Progression Free Survival Time [units: months] Median (95% Confidence Interval)	6.24 (5.585 to 6.899)	6.90 (6.209 to 7.359)

5. Secondary Outcome Measure:

Measure Title	Tumor Response Rate in Participants With Measurable Disease
Measure Description	Tumor response was defined as either a Complete Response (disappearance of all target lesions) or a Partial Response (≥30% decrease from baseline in target lesions) as assessed by Response Evaluation Criteria In Solid Tumors (RECIST)version 1.0.

Time Frame	Before randomization (baseline) then every 3 months up to tumor progression (≥25% increase) or the cut-off date, whichever occurred first
Safety Issue?	No

Analysis Population Description

The analysis was performed on the ITT population evaluable for tumor response (i.e. received at least one dose of study drugs (aflibercept/placebo or docetaxel), had no important deviations to protocol and was evaluable for response as per RECIST version 1.0).

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	320	323
Tumor Response Rate in Participants With Measurable Disease [units: percentage of participants] Number (95% Confidence Interval)	28.1 (23.2 to 33.1)	38.7 (33.4 to 44.0)

6. Secondary Outcome Measure:

Measure Title	Prostate Specific Antigen Progression-free Survival Time
Measure Description	Prostate specific antigen (PSA) progression was defined as ≥25% increase in PSA level confirmed 3 weeks later, above the nadir in participants who had achieved a PSA response, or above the baseline in participants who hadn't achieved a PSA response. PSA progression-free survival (PFS) time was defined as the time from the date of randomization up to the date of the first documented PSA progression or death due to any cause, whichever occurred first. The median PSA-PFS time and its 95% confidence interval were estimated using the Kaplan-Meier method. In the absence of PSA progression or death, the participant was censored at the the date of last assessment without evidence of progression or the study cut-off date, whichever was earlier.
Time Frame	From randomization up to the cut-off date (median follow-up of 35.4 months)
Safety Issue?	No

Analysis Population Description

The analysis was performed in the ITT population evaluable for PSA progression (i.e. with an evaluable baseline PSA).

At the cut-off date, PSA progression or death had occurred in 1138 participants, 571 in the Placebo group and 567 in the Aflibercept group.

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	606	608
Prostate Specific Antigen Progression-free Survival Time [units: months] Median (95% Confidence Interval)	8.11 (7.622 to 8.575)	8.25 (7.819 to 8.772)

7. Secondary Outcome Measure:

Measure Title	Pain Progression-free Survival Time
Measure Description	Pain progression was defined as either ≥1-point increase in Present Pain Intensity (PPI) score or ≥25% increase in Analgesics Score (AS) confirmed at least 3 weeks later, or requirement for palliative radiotherapy. PPI scale is a self-report 0-5 scale to assess pain intensity - a score 0 reflects no pain, a score 5 reflects excruciating pain. AS is a scoring method to assess analgesics consumption. Each analgesic is scored 1 or 4 depending on the analgesic type and dose. AS is the sum of the analgesic scores. Pain progression-free survival (PFS) time was measured as the time from the date of randomization up to the date of first pain progression or death due to any cause, whichever occurred first. The median pain-PFS and its 95% confidence interval were estimated using the Kaplan-Meier method. In the absence of event, the participant was censored at the the date of last assessment without evidence of pain progression or the study cut-off date, whichever was earlier.
Time Frame	From randomization up to the cut-off date (median follow-up of 35.4 months)
Safety Issue?	No

Analysis Population Description

The analysis was performed on the ITT population evaluable for pain progression (i.e. with no pain or with stable pain at baseline).

At the cut-off date, pain progression or death had occurred in 507 participants, 263 in the Placebo group and 244 in the Aflibercept group.

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	301	287
Pain Progression-free Survival Time [units: months] Median (95% Confidence Interval)	9.72 (8.509 to 11.499)	9.20 (8.181 to 10.448)

8. Secondary Outcome Measure:

Measure Title	Pain Response Rate
Measure Description	Pain response was defined as either a ≥2-point decrease from baseline in Present Pain Intensity (PPI) score without increase in Analgesics Score (AS), or a ≥50% decrease from baseline in AS without increase in the PPI score confirmed at least 3 weeks later. Increases in PPI or AS during the first 12 weeks were ignored in determining pain response.
Time Frame	Before randomization (baseline) then every 3 weeks up to pain progression or the cut-off date, whichever occurred first
Safety Issue?	No

Analysis Population Description

The analysis was performed in the ITT population evaluable for pain response (i.e. stable analgesia at baseline and, baseline PPI ≥2 and/or baseline AS ≥10 points).

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

	Description
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	67	67
Pain Response Rate [units: percentage of participants] Number (95% Confidence Interval)	46.3 (34.3 to 58.2)	35.8 (24.3 to 47.3)

9. Secondary Outcome Measure:

Measure Title	Change From Baseline in Functional Assessment of Cancer Therapy-Prostate Total Score as a Measure of Health Related Quality of Life
Measure Description	Functional Assessment of Cancer Therapy-Prostate (FACT-P) is a 39-item participant questionnaire that measures the concerns of patients with prostate cancer. It consists of 5 subscales assessing physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate-specific concerns. FACT-P total score is the sum of the 5 subscores. It ranges from 0 to 156 with higher score indicating better quality of life.
Time Frame	Before randomization (baseline) then every 3 weeks until disease progression or administration of further antitumor therapy, whichever came first
Safety Issue?	No

Analysis Population Description

The analysis was performed on the ITT population evaluable for Health related quality of life (i.e. with baseline and at least one post-baseline evaluable FACT-P questionnaire).

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	574	568
Change From Baseline in Functional Assessment of Cancer Therapy-Prostate Total Score as a Measure of Health Related Quality of Life [units: units on a scale] Mean (Standard Deviation)		
Change from baseline at cycle 1 (n =493, 461)	5.08 (12.73)	1.30 (15.70)
Change from baseline at cycle 2 (n =467, 437)	6.22 (14.50)	-0.03 (17.99)
Change from baseline at cycle 6 (n =293, 224)	5.50 (16.38)	-1.00 (16.85)
Change from baseline at cycle 10 (n =158, 117)	6.61 (16.35)	-1.60 (15.41)

10. Secondary Outcome Measure:

Measure Title	Number of Participants With Adverse Events as a Measure of Safety
Measure Description	Adverse Events (AE) are any unfavorable and unintended sign, symptom, syndrome or illness observed by the investigator or reported by the participant during the study. AE were collected at regular intervals throughout the study then graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.3.0).
Time Frame	From first dose of study treatment (aflibercept/placebo or docetaxel whichever came first) to last dose of study treatment (aflibercept/placebo or docetaxel whichever came last) + 30 days
Safety Issue?	Yes

Analysis Population Description

The analysis was performed on the safety population (i.e. all randomized and treated participants according to the treatment actually received). Six participants in the Placebo group who received at least one dose of aflibercept in error were considered in the Aflibercept group.

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	598	611
Number of Participants With Adverse Events as a Measure of Safety [units: participants]		
Any Adverse Event	585	607
- Grade 3-4 AE	290	470
- Serious AE	184	331
- AE leading to death	23	46
--- Related AE leading to death	8	19
- AE leading to permanent discontinuation	125	268
- AE leading to premature discontinuation	73	116

11. Secondary Outcome Measure:

Measure Title	Number of Participants With Positive Anti-aflibercept Antibody Levels as a Measure of Immunogenicity of Aflibercept
Measure Description	Serum for detection of anti-drug antibodies (ADA) was collected in patients treated in selected centers only. Samples were analyzed using a titer-based, bridging immunoassay developed and validated to detect ADAs in human serum. Samples with positive antibody levels were further analyzed using a validated, non-quantitative ligand binding assay to detect neutralizing antibodies Ab). A participant was considered to have positive antibody levels if antibodies were detected above the quantification limits.
Time Frame	Pre-dose of cycle 1 (baseline), pre-dose of each every other cycle, then 30 and 90 days after the last administration of the study drug
Safety Issue?	No

Analysis Population Description

The analysis was performed on the safety population evaluable for immunogenicity (i.e. exposed to aflibercept with serum samples evaluable for immunogenicity).

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Measured Values

	Placebo	Aflibercept
Number of Participants Analyzed	149	179
Number of Participants With Positive Anti-aflibercept Antibody Levels as a Measure of Immunogenicity of Aflibercept [units: participants]		
At baseline	0	2
At any time post-baseline	4	9
- Neutralizing Ab	0	2
- Not neutralizing Ab	2	5
- Neutralizing potential not evaluated	2	2

Reported Adverse Events

Time Frame	Adverse Events (AE) were collected from signature of the informed consent form up to the last visit in the study.
Additional Description	The analysis was performed on the safety population as described for Outcome measure 10 (i.e. according to the treatment actually received) and included all AE that developed or worsened from first dose of aflibercept/ placebo or docetaxel whichever came first, to 30 days after last dose of aflibercept/placebo or docetaxel whichever came last.

Reporting Groups

	Description
Placebo	Placebo, 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

	Description
Aflibercept	Aflibercept, 6 mg/kg 1 hour IV, immediately followed by docetaxel, 75 mg/m² 1 hour IV, every 3 weeks in combination with oral prednisone or prednisolone, 5 mg PO twice daily

Serious Adverse Events

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Total	184/598 (30.77%)	331/611 (54.17%)
Blood and lymphatic system disorders		
Anaemia [A] *	3/598 (0.5%)	2/611 (0.33%)
Febrile neutropenia [A] *	21/598 (3.51%)	48/611 (7.86%)
Leukopenia [A] *	1/598 (0.17%)	1/611 (0.16%)
Neutropenia [A] *	8/598 (1.34%)	30/611 (4.91%)
Normochromic normocytic anaemia [A] *	1/598 (0.17%)	0/611 (0%)
Pancytopenia [A] *	0/598 (0%)	1/611 (0.16%)
Thrombocytopenia [A] *	0/598 (0%)	1/611 (0.16%)
Thrombotic microangiopathy [A] *	0/598 (0%)	2/611 (0.33%)
Cardiac disorders		
Acute myocardial infarction [A] *	5/598 (0.84%)	0/611 (0%)
Angina pectoris [A] *	0/598 (0%)	1/611 (0.16%)
Angina unstable [A] *	0/598 (0%)	1/611 (0.16%)
Atrial fibrillation [A] *	3/598 (0.5%)	7/611 (1.15%)
Atrioventricular block complete [A] *	1/598 (0.17%)	0/611 (0%)
Cardiac arrest [A] *	1/598 (0.17%)	0/611 (0%)
Coronary artery stenosis [A] *	1/598 (0.17%)	0/611 (0%)
Left ventricular dysfunction [A] *	1/598 (0.17%)	0/611 (0%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Left ventricular failure [A] *	0/598 (0%)	1/611 (0.16%)
Mitral valve incompetence [A] *	0/598 (0%)	1/611 (0.16%)
Myocardial infarction [A] *	2/598 (0.33%)	1/611 (0.16%)
Myocardial ischaemia [A] *	2/598 (0.33%)	0/611 (0%)
Palpitations [A] *	0/598 (0%)	1/611 (0.16%)
Restrictive cardiomyopathy [A] *	0/598 (0%)	1/611 (0.16%)
Sinus tachycardia [A] *	0/598 (0%)	1/611 (0.16%)
Supraventricular tachycardia [A] *	0/598 (0%)	1/611 (0.16%)
Tachycardia paroxysmal [A] *	1/598 (0.17%)	0/611 (0%)
Ventricular extrasystoles [A] *	0/598 (0%)	1/611 (0.16%)
Ventricular fibrillation [A] *	0/598 (0%)	1/611 (0.16%)
Endocrine disorders		
Hyperthyroidism [A] *	0/598 (0%)	1/611 (0.16%)
Eye disorders		
Corneal erosion [A] *	0/598 (0%)	1/611 (0.16%)
Pigmentary glaucoma [A] *	0/598 (0%)	1/611 (0.16%)
Gastrointestinal disorders		
Abdominal pain [A] *	1/598 (0.17%)	2/611 (0.33%)
Abdominal pain upper [A] *	0/598 (0%)	1/611 (0.16%)
Anal fissure [A] *	0/598 (0%)	3/611 (0.49%)
Anal fistula [A] *	0/598 (0%)	5/611 (0.82%)
Anal inflammation [A] *	1/598 (0.17%)	0/611 (0%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Colitis [A] *	0/598 (0%)	1/611 (0.16%)
Colitis ischaemic [A] *	0/598 (0%)	2/611 (0.33%)
Constipation [A] *	3/598 (0.5%)	3/611 (0.49%)
Diarrhoea [A] *	11/598 (1.84%)	17/611 (2.78%)
Diverticular perforation [A] *	0/598 (0%)	5/611 (0.82%)
Diverticulum intestinal [A] *	0/598 (0%)	1/611 (0.16%)
Duodenal ulcer [A] *	0/598 (0%)	2/611 (0.33%)
Duodenal ulcer haemorrhage [A] *	0/598 (0%)	1/611 (0.16%)
Duodenal ulcer perforation [A] *	1/598 (0.17%)	1/611 (0.16%)
Dysphagia [A] *	0/598 (0%)	1/611 (0.16%)
Enteritis [A] *	0/598 (0%)	1/611 (0.16%)
Enterovesical fistula [A] *	0/598 (0%)	2/611 (0.33%)
Faecalith [A] *	0/598 (0%)	1/611 (0.16%)
Gastric haemorrhage [A] *	0/598 (0%)	1/611 (0.16%)
Gastric ulcer [A] *	0/598 (0%)	2/611 (0.33%)
Gastric ulcer haemorrhage [A] *	0/598 (0%)	1/611 (0.16%)
Gastritis [A] *	0/598 (0%)	1/611 (0.16%)
Gastritis erosive [A] *	0/598 (0%)	1/611 (0.16%)
Gastrointestinal haemorrhage [A] *	3/598 (0.5%)	3/611 (0.49%)
Gastrointestinal inflammation [A] *	0/598 (0%)	2/611 (0.33%)
Gastrointestinal tract mucosal discolouration [A] *	0/598 (0%)	1/611 (0.16%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Haematochezia [A] *	1/598 (0.17%)	0/611 (0%)
Ileus [A] *	0/598 (0%)	2/611 (0.33%)
Ileus paralytic [A] *	1/598 (0.17%)	0/611 (0%)
Intestinal obstruction [A] *	0/598 (0%)	1/611 (0.16%)
Intestinal perforation [A] *	0/598 (0%)	7/611 (1.15%)
Intestinal prolapse [A] *	0/598 (0%)	1/611 (0.16%)
Large intestine perforation [A] *	0/598 (0%)	1/611 (0.16%)
Lower gastrointestinal haemorrhage [A] *	1/598 (0.17%)	3/611 (0.49%)
Mallory-weiss syndrome [A] *	0/598 (0%)	1/611 (0.16%)
Nausea [A] *	1/598 (0.17%)	1/611 (0.16%)
Necrotising colitis [A] *	0/598 (0%)	1/611 (0.16%)
Neutropenic colitis [A] *	0/598 (0%)	1/611 (0.16%)
Oesophageal ulcer [A] *	0/598 (0%)	3/611 (0.49%)
Oesophagitis [A] *	0/598 (0%)	1/611 (0.16%)
Omental infarction [A] *	0/598 (0%)	1/611 (0.16%)
Peptic ulcer [A] *	0/598 (0%)	2/611 (0.33%)
Peptic ulcer perforation [A] *	0/598 (0%)	1/611 (0.16%)
Periproctitis [A] *	1/598 (0.17%)	0/611 (0%)
Pharyngoesophageal diverticulum [A] *	0/598 (0%)	1/611 (0.16%)
Pneumoperitoneum [A] *	0/598 (0%)	1/611 (0.16%)
Rectal haemorrhage [A] *	0/598 (0%)	4/611 (0.65%)
Rectal ulcer [A] *	1/598 (0.17%)	3/611 (0.49%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Rectal ulcer haemorrhage [A] *	0/598 (0%)	1/611 (0.16%)
Small intestinal haemorrhage [A] *	0/598 (0%)	1/611 (0.16%)
Stomatitis [A] *	1/598 (0.17%)	14/611 (2.29%)
Upper gastrointestinal haemorrhage [A] *	1/598 (0.17%)	2/611 (0.33%)
Vomiting [A] *	3/598 (0.5%)	5/611 (0.82%)
General disorders		
Asthenia [A] *	3/598 (0.5%)	6/611 (0.98%)
Death [A] *	1/598 (0.17%)	2/611 (0.33%)
Disease progression [A] *	3/598 (0.5%)	10/611 (1.64%)
Fatigue [A] *	0/598 (0%)	5/611 (0.82%)
General physical health deterioration [A] *	0/598 (0%)	1/611 (0.16%)
Impaired healing [A] *	0/598 (0%)	1/611 (0.16%)
Infusion site extravasation [A] *	0/598 (0%)	1/611 (0.16%)
Injection site reaction [A] *	1/598 (0.17%)	0/611 (0%)
Multi-organ failure [A] *	1/598 (0.17%)	1/611 (0.16%)
Non-cardiac chest pain [A] *	1/598 (0.17%)	1/611 (0.16%)
Oedema peripheral [A] *	1/598 (0.17%)	1/611 (0.16%)
Pain [A] *	0/598 (0%)	1/611 (0.16%)
Performance status decreased [A] *	0/598 (0%)	1/611 (0.16%)
Pyrexia [A] *	6/598 (1%)	8/611 (1.31%)
Sudden cardiac death [A] *	0/598 (0%)	1/611 (0.16%)
Sudden death [A] *	0/598 (0%)	2/611 (0.33%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Hepatobiliary disorders		
Bile duct obstruction [A] *	0/598 (0%)	1/611 (0.16%)
Hepatitis [A] *	1/598 (0.17%)	0/611 (0%)
Immune system disorders		
Anaphylactic reaction [A] *	1/598 (0.17%)	0/611 (0%)
Drug hypersensitivity [A] *	1/598 (0.17%)	3/611 (0.49%)
Hypersensitivity [A] *	1/598 (0.17%)	3/611 (0.49%)
Infections and infestations		
Abdominal abscess [A] *	1/598 (0.17%)	1/611 (0.16%)
Abdominal infection [A] *	0/598 (0%)	1/611 (0.16%)
Abscess intestinal [A] *	0/598 (0%)	2/611 (0.33%)
Abscess limb [A] *	1/598 (0.17%)	0/611 (0%)
Anal abscess [A] *	0/598 (0%)	13/611 (2.13%)
Anal infection [A] *	0/598 (0%)	1/611 (0.16%)
Appendicitis [A] *	1/598 (0.17%)	0/611 (0%)
Aspergillosis [A] *	0/598 (0%)	1/611 (0.16%)
Bacteraemia [A] *	1/598 (0.17%)	0/611 (0%)
Bronchiolitis [A] *	0/598 (0%)	1/611 (0.16%)
Bronchitis [A] *	1/598 (0.17%)	2/611 (0.33%)
Bronchopneumonia [A] *	1/598 (0.17%)	3/611 (0.49%)
Catheter site cellulitis [A] *	1/598 (0.17%)	0/611 (0%)
Cellulitis [A] *	1/598 (0.17%)	1/611 (0.16%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Cystitis [A] *	1/598 (0.17%)	0/611 (0%)
Cystitis bacterial [A] *	1/598 (0.17%)	0/611 (0%)
Cytomegalovirus hepatitis [A] *	1/598 (0.17%)	0/611 (0%)
Device related infection [A] *	0/598 (0%)	1/611 (0.16%)
Diverticulitis [A] *	0/598 (0%)	4/611 (0.65%)
Erysipelas [A] *	0/598 (0%)	2/611 (0.33%)
Escherichia sepsis [A] *	1/598 (0.17%)	1/611 (0.16%)
Escherichia urinary tract infection [A] *	1/598 (0.17%)	0/611 (0%)
Gastroenteritis [A] *	0/598 (0%)	1/611 (0.16%)
Gastroenteritis viral [A] *	0/598 (0%)	1/611 (0.16%)
Gastrointestinal infection [A] *	1/598 (0.17%)	0/611 (0%)
Herpes oesophagitis [A] *	0/598 (0%)	1/611 (0.16%)
Herpes zoster [A] *	0/598 (0%)	1/611 (0.16%)
Infected bites [A] *	0/598 (0%)	1/611 (0.16%)
Infection [A] *	1/598 (0.17%)	2/611 (0.33%)
Infectious peritonitis [A] *	0/598 (0%)	1/611 (0.16%)
Listeria sepsis [A] *	1/598 (0.17%)	0/611 (0%)
Lobar pneumonia [A] *	1/598 (0.17%)	1/611 (0.16%)
Localised infection [A] *	0/598 (0%)	1/611 (0.16%)
Lower respiratory tract infection [A] *	2/598 (0.33%)	0/611 (0%)
Lung abscess [A] *	1/598 (0.17%)	0/611 (0%)
Lung infection [A] *	1/598 (0.17%)	0/611 (0%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Nasal abscess [A] *	1/598 (0.17%)	0/611 (0%)
Necrotising fasciitis [A] *	0/598 (0%)	2/611 (0.33%)
Neutropenic infection [A] *	12/598 (2.01%)	22/611 (3.6%)
Neutropenic sepsis [A] *	3/598 (0.5%)	7/611 (1.15%)
Oral candidiasis [A] *	0/598 (0%)	1/611 (0.16%)
Osteomyelitis [A] *	1/598 (0.17%)	0/611 (0%)
Peridiverticular abscess [A] *	0/598 (0%)	3/611 (0.49%)
Perineal abscess [A] *	1/598 (0.17%)	0/611 (0%)
Perirectal abscess [A] *	1/598 (0.17%)	0/611 (0%)
Pharyngitis [A] *	0/598 (0%)	1/611 (0.16%)
Pneumonia [A] *	11/598 (1.84%)	21/611 (3.44%)
Pneumonia bacterial [A] *	0/598 (0%)	1/611 (0.16%)
Pneumonia necrotising [A] *	0/598 (0%)	1/611 (0.16%)
Pneumonia staphylococcal [A] *	1/598 (0.17%)	1/611 (0.16%)
Post procedural infection [A] *	0/598 (0%)	1/611 (0.16%)
Pulmonary sepsis [A] *	1/598 (0.17%)	0/611 (0%)
Pulmonary tuberculosis [A] *	0/598 (0%)	1/611 (0.16%)
Pyelonephritis acute [A] *	0/598 (0%)	1/611 (0.16%)
Pyonephrosis [A] *	1/598 (0.17%)	1/611 (0.16%)
Rectal abscess [A] *	0/598 (0%)	3/611 (0.49%)
Respiratory tract infection [A] *	1/598 (0.17%)	1/611 (0.16%)
Sepsis [A] *	2/598 (0.33%)	4/611 (0.65%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Septic shock [A] *	1/598 (0.17%)	2/611 (0.33%)
Skin infection [A] *	1/598 (0.17%)	1/611 (0.16%)
Staphylococcal bacteraemia [A] *	0/598 (0%)	1/611 (0.16%)
Staphylococcal infection [A] *	1/598 (0.17%)	0/611 (0%)
Tracheobronchitis [A] *	0/598 (0%)	1/611 (0.16%)
Upper respiratory tract infection [A] *	2/598 (0.33%)	1/611 (0.16%)
Urinary tract infection [A] *	4/598 (0.67%)	10/611 (1.64%)
Urosepsis [A] *	1/598 (0.17%)	0/611 (0%)
West nile viral infection [A] *	1/598 (0.17%)	0/611 (0%)
Injury, poisoning and procedural complications		
Abdominal wound dehiscence [A] *	0/598 (0%)	2/611 (0.33%)
Fall [A] *	0/598 (0%)	1/611 (0.16%)
Gastroenteritis radiation [A] *	0/598 (0%)	1/611 (0.16%)
Joint dislocation [A] *	0/598 (0%)	1/611 (0.16%)
Pelvic fracture [A] *	1/598 (0.17%)	0/611 (0%)
Pneumothorax traumatic [A] *	0/598 (0%)	1/611 (0.16%)
Post procedural haemorrhage [A] *	1/598 (0.17%)	0/611 (0%)
Procedural complication [A] *	1/598 (0.17%)	0/611 (0%)
Skull fracture [A] *	1/598 (0.17%)	0/611 (0%)
Traumatic fracture [A] *	1/598 (0.17%)	2/611 (0.33%)
Upper limb fracture [A] *	1/598 (0.17%)	0/611 (0%)
Urinary bladder rupture [A] *	0/598 (0%)	1/611 (0.16%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Investigations		
Electrocardiogram st-t segment abnormal [A] *	0/598 (0%)	1/611 (0.16%)
Electrocardiogram t wave inversion [A] *	0/598 (0%)	1/611 (0.16%)
Haemoglobin decreased [A] *	0/598 (0%)	2/611 (0.33%)
International normalised ratio increased [A] *	0/598 (0%)	1/611 (0.16%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	0/598 (0%)	1/611 (0.16%)
Dehydration [A] *	2/598 (0.33%)	19/611 (3.11%)
Diabetes mellitus inadequate control [A] *	1/598 (0.17%)	0/611 (0%)
Failure to thrive [A] *	0/598 (0%)	2/611 (0.33%)
Hyperglycaemia [A] *	2/598 (0.33%)	1/611 (0.16%)
Hypernatraemia [A] *	0/598 (0%)	1/611 (0.16%)
Hypocalcaemia [A] *	0/598 (0%)	2/611 (0.33%)
Hypoglycaemia [A] *	1/598 (0.17%)	2/611 (0.33%)
Hyponatraemia [A] *	0/598 (0%)	2/611 (0.33%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	1/598 (0.17%)	1/611 (0.16%)
Back pain [A] *	6/598 (1%)	0/611 (0%)
Bone pain [A] *	1/598 (0.17%)	0/611 (0%)
Intervertebral disc protrusion [A] *	1/598 (0.17%)	0/611 (0%)
Muscular weakness [A] *	2/598 (0.33%)	0/611 (0%)
Neck pain [A] *	1/598 (0.17%)	0/611 (0%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Osteonecrosis of jaw [A] *	1/598 (0.17%)	1/611 (0.16%)
Osteoporotic fracture [A] *	0/598 (0%)	1/611 (0.16%)
Pathological fracture [A] *	3/598 (0.5%)	2/611 (0.33%)
Spinal osteoarthritis [A] *	0/598 (0%)	1/611 (0.16%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Cardiac myxoma [A] *	1/598 (0.17%)	0/611 (0%)
Colon cancer [A] *	1/598 (0.17%)	2/611 (0.33%)
Colorectal cancer [A] *	0/598 (0%)	1/611 (0.16%)
Lung neoplasm malignant [A] *	1/598 (0.17%)	0/611 (0%)
Meningioma [A] *	0/598 (0%)	1/611 (0.16%)
Metastases to bone [A] *	1/598 (0.17%)	0/611 (0%)
Metastatic pain [A] *	3/598 (0.5%)	0/611 (0%)
Pituitary tumour benign [A] *	1/598 (0.17%)	0/611 (0%)
Tumour pain [A] *	1/598 (0.17%)	0/611 (0%)
Nervous system disorders		
Ataxia [A] *	1/598 (0.17%)	0/611 (0%)
Cerebral infarction [A] *	0/598 (0%)	1/611 (0.16%)
Cerebral ischaemia [A] *	2/598 (0.33%)	0/611 (0%)
Convulsion [A] *	1/598 (0.17%)	1/611 (0.16%)
Grand mal convulsion [A] *	0/598 (0%)	1/611 (0.16%)
Haemorrhagic stroke [A] *	1/598 (0.17%)	0/611 (0%)
Hypoaesthesia [A] *	0/598 (0%)	1/611 (0.16%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Hypotonia [A] *	0/598 (0%)	1/611 (0.16%)
Ischaemic stroke [A] *	2/598 (0.33%)	0/611 (0%)
Leukoencephalopathy [A] *	0/598 (0%)	1/611 (0.16%)
Loss of consciousness [A] *	0/598 (0%)	1/611 (0.16%)
Peripheral motor neuropathy [A] *	1/598 (0.17%)	2/611 (0.33%)
Peripheral sensory neuropathy [A] *	0/598 (0%)	1/611 (0.16%)
Posterior reversible encephalopathy syndrome [A] *	0/598 (0%)	1/611 (0.16%)
Presyncope [A] *	0/598 (0%)	3/611 (0.49%)
Spinal cord compression [A] *	8/598 (1.34%)	2/611 (0.33%)
Syncope [A] *	4/598 (0.67%)	8/611 (1.31%)
Transient ischaemic attack [A] *	1/598 (0.17%)	1/611 (0.16%)
Vocal cord paralysis [A] *	0/598 (0%)	1/611 (0.16%)
Psychiatric disorders		
Anxiety [A] *	0/598 (0%)	1/611 (0.16%)
Confusional state [A] *	0/598 (0%)	1/611 (0.16%)
Depression [A] *	1/598 (0.17%)	0/611 (0%)
Mental status changes [A] *	1/598 (0.17%)	0/611 (0%)
Renal and urinary disorders		
Bladder neck obstruction [A] *	1/598 (0.17%)	0/611 (0%)
Haematuria [A] *	4/598 (0.67%)	5/611 (0.82%)
Hydronephrosis [A] *	1/598 (0.17%)	1/611 (0.16%)
Nephrotic syndrome [A] *	0/598 (0%)	1/611 (0.16%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Proteinuria [A] *	0/598 (0%)	1/611 (0.16%)
Renal colic [A] *	1/598 (0.17%)	0/611 (0%)
Renal failure [A] *	1/598 (0.17%)	1/611 (0.16%)
Renal failure acute [A] *	0/598 (0%)	1/611 (0.16%)
Ureteric haemorrhage [A] *	0/598 (0%)	1/611 (0.16%)
Urethral meatus stenosis [A] *	1/598 (0.17%)	0/611 (0%)
Urethral stenosis [A] *	1/598 (0.17%)	1/611 (0.16%)
Urinary retention [A] *	3/598 (0.5%)	2/611 (0.33%)
Urinary tract obstruction [A] *	1/598 (0.17%)	0/611 (0%)
Reproductive system and breast disorders		
Genital ulceration [A] *	0/598 (0%)	1/611 (0.16%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome [A] *	0/598 (0%)	1/611 (0.16%)
Acute respiratory failure [A] *	0/598 (0%)	2/611 (0.33%)
Bronchospasm [A] *	0/598 (0%)	1/611 (0.16%)
Dyspnoea [A] *	3/598 (0.5%)	2/611 (0.33%)
Dyspnoea exertional [A] *	0/598 (0%)	1/611 (0.16%)
Epistaxis [A] *	1/598 (0.17%)	20/611 (3.27%)
Haemoptysis [A] *	1/598 (0.17%)	1/611 (0.16%)
Hypoxia [A] *	0/598 (0%)	2/611 (0.33%)
Interstitial lung disease [A] *	1/598 (0.17%)	1/611 (0.16%)
Oropharyngeal pain [A] *	0/598 (0%)	2/611 (0.33%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Pleural effusion [A] *	0/598 (0%)	1/611 (0.16%)
Pneumonitis [A] *	0/598 (0%)	1/611 (0.16%)
Pneumothorax [A] *	0/598 (0%)	1/611 (0.16%)
Pulmonary embolism [A] *	17/598 (2.84%)	13/611 (2.13%)
Respiratory failure [A] *	0/598 (0%)	2/611 (0.33%)
Vascular disorders		
Deep vein thrombosis [A] *	6/598 (1%)	4/611 (0.65%)
Hypertension [A] *	1/598 (0.17%)	5/611 (0.82%)
Hypertensive crisis [A] *	0/598 (0%)	1/611 (0.16%)
Hypotension [A] *	3/598 (0.5%)	4/611 (0.65%)
Orthostatic hypotension [A] *	1/598 (0.17%)	2/611 (0.33%)
Phlebitis superficial [A] *	1/598 (0.17%)	0/611 (0%)
Subclavian artery stenosis [A] *	1/598 (0.17%)	0/611 (0%)
Venous thrombosis limb [A] *	0/598 (0%)	1/611 (0.16%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 14.0

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

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Total	551/598 (92.14%)	573/611 (93.78%)
Eye disorders		
Lacrimation increased [A] *	71/598 (11.87%)	119/611 (19.48%)
Gastrointestinal disorders		

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Abdominal pain [A] *	45/598 (7.53%)	47/611 (7.69%)
Constipation [A] *	131/598 (21.91%)	133/611 (21.77%)
Diarrhoea [A] *	209/598 (34.95%)	268/611 (43.86%)
Dyspepsia [A] *	29/598 (4.85%)	31/611 (5.07%)
Dysphagia [A] *	1/598 (0.17%)	31/611 (5.07%)
Haemorrhoids [A] *	14/598 (2.34%)	31/611 (5.07%)
Nausea [A] *	166/598 (27.76%)	165/611 (27%)
Stomatitis [A] *	123/598 (20.57%)	340/611 (55.65%)
Vomiting [A] *	84/598 (14.05%)	90/611 (14.73%)
General disorders		
Asthenia [A] *	123/598 (20.57%)	144/611 (23.57%)
Fatigue [A] *	241/598 (40.3%)	243/611 (39.77%)
Oedema peripheral [A] *	157/598 (26.25%)	57/611 (9.33%)
Pyrexia [A] *	54/598 (9.03%)	61/611 (9.98%)
Infections and infestations		
Nasopharyngitis [A] *	36/598 (6.02%)	23/611 (3.76%)
Urinary tract infection [A] *	38/598 (6.35%)	39/611 (6.38%)
Investigations		
Weight decreased [A] *	51/598 (8.53%)	201/611 (32.9%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	110/598 (18.39%)	190/611 (31.1%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	66/598 (11.04%)	42/611 (6.87%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Back pain [A] *	83/598 (13.88%)	55/611 (9%)
Bone pain [A] *	44/598 (7.36%)	35/611 (5.73%)
Muscle spasms [A] *	31/598 (5.18%)	17/611 (2.78%)
Musculoskeletal pain [A] *	33/598 (5.52%)	21/611 (3.44%)
Myalgia [A] *	58/598 (9.7%)	41/611 (6.71%)
Pain in extremity [A] *	62/598 (10.37%)	42/611 (6.87%)
Nervous system disorders		
Dizziness [A] *	50/598 (8.36%)	29/611 (4.75%)
Dysgeusia [A] *	107/598 (17.89%)	108/611 (17.68%)
Headache [A] *	45/598 (7.53%)	95/611 (15.55%)
Neuropathy peripheral [A] *	76/598 (12.71%)	56/611 (9.17%)
Paraesthesia [A] *	49/598 (8.19%)	38/611 (6.22%)
Peripheral sensory neuropathy [A] *	75/598 (12.54%)	51/611 (8.35%)
Psychiatric disorders		
Insomnia [A] *	44/598 (7.36%)	45/611 (7.36%)
Renal and urinary disorders		
Proteinuria [A] *	6/598 (1%)	31/611 (5.07%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	77/598 (12.88%)	111/611 (18.17%)
Dysphonia [A] *	36/598 (6.02%)	230/611 (37.64%)
Dyspnoea [A] *	62/598 (10.37%)	89/611 (14.57%)
Epistaxis [A] *	55/598 (9.2%)	199/611 (32.57%)
Oropharyngeal pain [A] *	23/598 (3.85%)	69/611 (11.29%)

	Placebo	Aflibercept
	Affected/At Risk (%)	Affected/At Risk (%)
Rhinorrhoea [A] *	17/598 (2.84%)	38/611 (6.22%)
Skin and subcutaneous tissue disorders		
Alopecia [A] *	268/598 (44.82%)	224/611 (36.66%)
Nail disorder [A] *	97/598 (16.22%)	94/611 (15.38%)
Palmar-plantar erythrodysaesthesia syndrome [A] *	5/598 (0.84%)	51/611 (8.35%)
Rash [A] *	33/598 (5.52%)	49/611 (8.02%)
Vascular disorders		
Hypertension [A] *	66/598 (11.04%)	207/611 (33.88%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 14.0

Limitations and Caveats

Pain response initially defined as a key secondary endpoint together with PSA response, time to occurence of SRE and PFS was finally considered as an exploratory endpoint in final statistical analysis plan.

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 to a journal, and delay publication till the approval of the publication is given in writing by the Sponsor (not to exceed ninety days).

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