Clinical trial results:
Randomized, Open Label Multi-Center Study Comparing Cabazitaxel at 20 mg/m² and at 25 mg/m² Every 3 Weeks in Combination with Prednisone for the Treatment of Metastatic Castration-Resistant Prostate Cancer Previously Treated With a Docetaxel-Containing Regimen

Summary

EudraCT number	2010-022163-35
Trial protocol	NL HU BE ES GB FR DE PL
Global end of trial date	19 August 2015

Results information

Result version number	v1 (current)
This version publication date	03 September 2016
First version publication date	03 September 2016

Trial information

Trial identification

Sponsor protocol code	EFC11785

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01308580
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non inferiority in terms of overall survival (OS) of cabazitaxel 20 mg/m² (Arm A) versus cabazitaxel 25 mg/m² (Arm B) in combination with prednisone in subjects with metastatic castration resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 20
Country: Number of subjects enrolled	Australia: 121
Country: Number of subjects enrolled	Brazil: 67
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	Chile: 23
Country: Number of subjects enrolled	Korea, Republic of: 57
Country: Number of subjects enrolled	Peru: 28
Country: Number of subjects enrolled	Russian Federation: 75
Country: Number of subjects enrolled	South Africa: 34
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Tunisia: 16
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	United States: 51
Country: Number of subjects enrolled	Netherlands: 47
Country: Number of subjects enrolled	Poland: 30

Country: Number of subjects enrolled	Romania: 86
Country: Number of subjects enrolled	Spain: 86
Country: Number of subjects enrolled	United Kingdom: 96
Country: Number of subjects enrolled	Belgium: 81
Country: Number of subjects enrolled	France: 127
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Hungary: 50
Worldwide total number of subjects	1200
EEA total number of subjects	644

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	362
From 65 to 84 years	830
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 172 centers in 22 countries.

Pre-assignment

Screening details:

A total of 1463 subjects were screened between 19 April 2011 and 18 November 2013. Out of 1463 subjects, 1200 were enrolled in study and 263 were not eligible to join study. Subjects were randomized by Interactive Voice Response System (IVRS) in 1:1 ratio (Cabazitaxel 20 mg/m²: Cabazitaxel 25 mg/m²).

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cabazitaxel 20 mg/m²

Arm description:

Cabazitaxel 20 mg/m² on Day 1 of each 21-day cycle in combination with prednisone or prednisolone 10 mg orally daily until DP, unacceptable toxicity, subject’s refusal of further study treatment or for a maximum of 10 cycles.

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	XRP6258
Other name	Jevtana®
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cabazitaxel 20 mg/m² intravenous (IV) infusion over one hour.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone or prednisolone 10 mg daily administered according to its labelling.

Arm title	Cabazitaxel 25 mg/m²

Arm description:

Cabazitaxel 25 mg/m²on Day 1 of each 21-day cycle in combination with prednisone or prednisolone 10 mg orally daily until DP, unacceptable toxicity, subject’s refusal of further study treatment or for a maximum of 10 cycles.

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	XRP6258
Other name	Jevtana®
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cabazitaxel 25 mg/m² IV infusion over one hour.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone or prednisolone 10 mg daily administered according to its labelling.

Number of subjects in period 1	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²
Started	598	602
Treated	587	588 [1]
Completed	586	595
Not completed	12	7
Lost to follow-up	12	7

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: By EudraCT Results Validation Rules warning is intended to state: "It is expected the number of subjects will be greater than, or equal to the number that started minus those that left." Completed group = subjects with survival follow-up until death/end of study (randomized minus lost to follow-up). Completed subjects included those who withdrew treatment consent but agreed to be followed for survival. Treated subjects appear by random assignment, was not actual treatment received in some cases.

Baseline characteristics

Reporting groups	
Reporting group title	Cabazitaxel 20 mg/m²
Reporting group description:	
Cabazitaxel 20 mg/m² on Day 1 of each 21-day cycle in combination with prednisone or prednisolone 10 mg orally daily until DP, unacceptable toxicity, subject's refusal of further study treatment or for a maximum of 10 cycles.	

Reporting group title	Cabazitaxel 25 mg/m²
Reporting group description:	
Cabazitaxel 25 mg/m²on Day 1 of each 21-day cycle in combination with prednisone or prednisolone 10 mg orally daily until DP, unacceptable toxicity, subject's refusal of further study treatment or for a maximum of 10 cycles.	

Reporting group values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²	Total
Number of subjects	598	602	1200
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	182	180	362
From 65-84 years	412	418	830
85 years and over	4	4	8
Gender categorical Units: Subjects			
Female	0	0	0
Male	598	602	1200

End points

End points reporting groups

Reporting group title	Cabazitaxel 20 mg/m²

Reporting group description:

Cabazitaxel 20 mg/m² on Day 1 of each 21-day cycle in combination with prednisone or prednisolone 10 mg orally daily until DP, unacceptable toxicity, subject's refusal of further study treatment or for a maximum of 10 cycles.

Reporting group title	Cabazitaxel 25 mg/m²

Reporting group description:

Cabazitaxel 25 mg/m²on Day 1 of each 21-day cycle in combination with prednisone or prednisolone 10 mg orally daily until DP, unacceptable toxicity, subject's refusal of further study treatment or for a maximum of 10 cycles.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time interval from the date of randomization to the date of death due to any cause. In absence of confirmation of death, survival time was censored at the earlier of the last date the subject was known to be alive or the study cut-off date. The cut-off date for the final analysis of OS was the date when the 988th death had been observed. Analysis was performed by Kaplan-Meier method. Analysis was performed on Intent-to-Treat (ITT) population, which included all randomized subjects.

End point type	Primary

End point timeframe:

From baseline up to death due to any cause or study cut-off date, whichever was earlier (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	602		
Units: months				
median (confidence interval 95%)	13.4 (12.19 to 14.88)	14.5 (13.47 to 15.28)		

Statistical analyses

Statistical analysis title	HR Cabazitaxel 20 mg/m² vs Cabazitaxel 25 mg/m²

Statistical analysis description:

Hazard ratio (HR) for OS was estimated using Cox proportional hazards regression model. This model was adjusted by measurability of disease at baseline, Eastern Cooperative Oncology Group performance status (ECOG PS) score at baseline, & region at the time of randomization. Cabazitaxel 20 mg/m² relative to 25 mg/m² dose group was considered non-inferior if upper bound of 1-sided 98.89% confidence interval of hazard ratio (20 mg/m² versus 25 mg/m²) was less than non-inferiority margin of 1.214.

Comparison groups	Cabazitaxel 20 mg/m² v Cabazitaxel 25 mg/m²

Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.024
Confidence interval	
level	Other: 98.89 %
sides	1-sided
upper limit	1.184

Notes:

[1] - Non-inferiority margin of 1.214

Statistical analysis title	HR Cabazitaxel 20 mg/m² vs Cabazitaxel 25 mg/m²

Statistical analysis description:

The HR for OS was estimated using the Cox proportional hazards regression model. The Cox proportional hazard model was adjusted by measurability of the disease at baseline, ECOG PS score at baseline, and region at the time of randomization. Cabazitaxel 25 mg/m² was considered to be superior to 20 mg/m² dose if the lower bound of 1-sided 95% confidence interval of hazard ratio was greater than 1.

Comparison groups	Cabazitaxel 20 mg/m² v Cabazitaxel 25 mg/m²
Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.024
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.922

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was evaluated from the date of randomization to the date of the first documentation of any of the following events: Radiological tumor progression according to Response Evaluation Criteria In Solid Tumors (RECIST 1.1); Prostate-Specific Antigen (PSA) progression; pain progression or death due to any cause. Analysis was performed by Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

From baseline up to DP or death due to any cause or study cut-off date, whichever was earlier (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	602		
Units: months				
median (confidence interval 95%)	2.9 (2.79 to 3.45)	3.5 (3.12 to 3.94)		

Statistical analyses

Statistical analysis title	HR Cabazitaxel 20 mg/m² vs Cabazitaxel 25 mg/m²

Statistical analysis description:

HR was estimated using a Cox Proportional Hazards regression model. The Cox proportional hazard model was adjusted by measurability of the disease at baseline, ECOG PS score at baseline, and region at the time of randomization.

Comparison groups	Cabazitaxel 20 mg/m² v Cabazitaxel 25 mg/m²
Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.974
upper limit	1.24

Secondary: Time to Tumor Progression

End point title	Time to Tumor Progression

End point description:

Time to Tumor progression was defined as the first occurrence of radiological tumor progression according to RECIST 1.1. Analysis was performed by Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

From baseline up to tumor progression or death due to any cause or study cut-off date, whichever was earlier (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	602		
Units: months				
median (confidence interval 95%)	9 (8.38 to 9.79)	9.3 (8.61 to 9.92)		

Statistical analyses

Statistical analysis title	HR Cabazitaxel 20 mg/m² vs Cabazitaxel 25 mg/m²

Statistical analysis description:

HR was estimated using a Cox Proportional Hazards regression model. The Cox proportional hazard model was adjusted by measurability of the disease at baseline, ECOG PS score at baseline, and region at the time of randomization.

Comparison groups	Cabazitaxel 20 mg/m² v Cabazitaxel 25 mg/m²
Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.902
upper limit	1.331

Secondary: Percentage of Subjects With Overall Objective Tumor Response

End point title	Percentage of Subjects With Overall Objective Tumor Response

End point description:

Overall objective tumor response was defined as either a partial response (PR) or complete response (CR) according to the RECIST 1.1 criteria, as assessed by the investigator. CR was defined as disappearance of all target and non-target lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) had reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. ITT population. Number of subjects analyzed= subjects evaluable for tumor response with measurable disease at baseline and at least one valid post baseline value.

End point type	Secondary

End point timeframe:

From baseline up to DP or death due to any cause or study cut-off date, whichever was earlier (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	256		
Units: percentage of subjects				
number (confidence interval 95%)	18.5 (13.8 to 23.1)	23.4 (18.2 to 28.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA Progression

End point title	Time to PSA Progression

End point description:

Time to PSA progression was time interval between randomization & first occurrence of PSA progression. PSA progression defined as: 1) PSA responders (>50% decline from baseline PSA ≥10 ng/mL): increase of >25% (≥2 ng/mL) over nadir value, confirmed by second PSA ≥3 weeks later; 2) PSA non-responders (did not achieve >50% decline from baseline PSA ≥10 ng/mL): increase of ≥25% (≥2 ng/mL) over baseline value, confirmed by second PSA ≥3 weeks later; 3) In subjects not eligible for PSA response (baseline PSA <10 ng/mL): (a) subjects with baseline PSA >0 ng/mL & <10 ng/mL: increase in PSA by 25% (≥2 ng/mL) above baseline level, confirmed by second PSA value ≥3 weeks apart; (b) subjects with baseline value=0 ng/mL: post-baseline PSA value ≥2 ng/mL. Note (for 1-3): Rise in PSA in first 12 weeks was progression only if met definition above and was associated with other sign of DP or if it continued beyond 12 weeks. Analysis was performed by Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

From baseline up to PSA progression or death due to any cause or study cut-off date, whichever was earlier (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	602		
Units: months				
median (confidence interval 95%)	5.7 (4.96 to 6.47)	6.8 (6.11 to 7.46)		

Statistical analyses

Statistical analysis title	HR Cabazitaxel 20 mg/m² vs Cabazitaxel 25 mg/m²

Statistical analysis description:

HR was estimated using a Cox Proportional Hazards regression model. The Cox proportional hazard model was adjusted by measurability of the disease at baseline, ECOG PS score at baseline, and region at the time of randomization.

Comparison groups	Cabazitaxel 20 mg/m² v Cabazitaxel 25 mg/m²

Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.025
upper limit	1.393

Secondary: Percentage of Subjects With PSA Response

End point title	Percentage of Subjects With PSA Response

End point description:

PSA response was defined as ≥50% decrease from baseline in serum PSA levels, confirmed by a second PSA value at least 3 weeks later in subjects with baseline PSA value ≥10 ng/mL. ITT population. Number of subjects analyzed= subjects evaluable for PSA response with PSA value ≥10 ng/mL at baseline and at least one valid post baseline value.

End point type	Secondary

End point timeframe:

From baseline up to PSA progression or death due to any cause or study cut-off date, whichever was earlier (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	543	538		
Units: percentage of subjects				
number (confidence interval 95%)	29.5 (25.6 to 33.3)	42.9 (38.8 to 47.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression

End point title	Time to Pain Progression

End point description:

Pain Progression was defined as an increase of ≥1 point in the median Present Pain Intensity (PPI) from its nadir confirmed by a second assessment at least 3 weeks later or ≥25 % increase in the mean analgesic score (AS) compared with the baseline score confirmed by a second assessment at least 3 weeks later or requirement for local palliative radiotherapy. PPI was rated by subject in a diary using a scale of 0=no pain, 1=mild, 2=discomforting, 3=distressing, 4=horrible, 5=excruciating. Analgesic use was recorded by the subject in a diary. AS was calculated from the analgesic use data based on a table of analgesic medications, with non-narcotic medications assigned a value of 1 point and narcotic medications assigned a value of 4 points. Analysis was performed by Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

From baseline until DP, start of another anti-cancer therapy, death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	602		
Units: months				
median (confidence interval 95%)	6.2 (5.22 to 7.39)	6.4 (5.55 to 7.26)		

Statistical analyses

Statistical analysis title	HR Cabazitaxel 20 mg/m² vs Cabazitaxel 25 mg/m²

Statistical analysis description:

HR was estimated using a Cox Proportional Hazards regression model. The Cox proportional hazard model was adjusted by measurability of the disease at baseline, ECOG PS score at baseline, and region at the time of randomization.

Comparison groups	Cabazitaxel 20 mg/m² v Cabazitaxel 25 mg/m²
Number of subjects included in analysis	1200
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.874
upper limit	1.251

Secondary: Percentage of Subjects With Pain Response

End point title	Percentage of Subjects With Pain Response

End point description:

Pain response was defined as either a ≥2-point decrease from baseline median PPI score without increase in AS, or a ≥50% decrease from baseline mean AS without increase in the PPI score, maintained for 2 consecutive evaluations at least 3 weeks apart. Increase in pain during the first 12 weeks were ignored in determining pain response. ITT population. Number of subjects analyzed= subjects evaluable for pain response with pain score with median PPI ≥2 and/or mean AS ≥10 points at baseline and at least one valid post baseline value.

End point type	Secondary

End point timeframe:

From baseline until DP, start of another anti-cancer therapy, death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	284		
Units: percentage of subjects				
number (confidence interval 95%)	34.7 (28.8 to 40.6)	37.3 (31.7 to 42.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Prostate (FACT-P): Trial Outcome Index (TOI) as a Measure of Health Related Quality of Life (HRQoL)

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Prostate (FACT-P): Trial Outcome Index (TOI) as a Measure of Health Related Quality of Life (HRQoL)

End point description:

FACT-P is a 39-item subject questionnaire that measures the concerns of subjects with prostate cancer. It consists of 5 sub-scales assessing physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and prostate-specific concerns (12 items). FACT-P Trial Outcome Index combines physical well-being, functional well-being, and prostate-specific concerns sub-scales for a total possible score range of 0-104, where higher values represent better HRQoL. Analysis was performed on Fact-P population that included randomized subjects who completed FACT-P questionnaire at baseline & in at least one post baseline assessment. Number of subjects analyzed= subjects with evaluable FACT-P TOI for specified outcome measure. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

From baseline until DP, start of another anti-cancer therapy, death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	494		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Change at Cycle 1 (n=521, 494)	4.69 (2.95 to 6.44)	5.08 (3.32 to 6.84)		
Change at cycle 2 (n = 500, 494)	4.4 (2.67 to 6.14)	5.55 (3.81 to 7.3)		
Change at Cycle 3 (n=456, 451)	3.75 (2 to 5.5)	5.46 (3.7 to 7.23)		
Change at Cycle 4 (n=420, 415)	2.57 (0.8 to 4.33)	3.82 (2.04 to 5.6)		

Change at Cycle 5 (n=339, 361)	1.78 (-0.03 to 3.59)	3.06 (1.26 to 4.87)		
Change at Cycle 6 (n=275, 318)	2.57 (0.72 to 4.43)	2.03 (0.2 to 3.86)		
Change at Cycle 7 (n=225, 262)	2.51 (0.6 to 4.42)	2.73 (0.85 to 4.6)		
Change at Cycle 8 (n=196, 227)	1.44 (-0.5 to 3.39)	2.08 (0.16 to 3.99)		
Change at Cycle 9 (n=165, 172)	0.94 (-1.06 to 2.94)	1.46 (-0.55 to 3.46)		
Change at Cycle 10 (n=137, 141)	0.02 (-2.05 to 2.1)	1.31 (-0.76 to 3.39)		
Change at Follow-up 1 (n=136, 152)	-2.27 (-4.35 to -0.19)	-1.16 (-3.21 to 0.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FACT-P: Total Score as a Measure of HRQoL

End point title	Change From Baseline in FACT-P: Total Score as a Measure of HRQoL

End point description:

FACT-P is a 39-item subject questionnaire that measures the concerns of subjects with prostate cancer. It consists of 5 sub-scales assessing physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and prostate-specific concerns (12 items). FACT-P Total Score sums all 5 sub-scales to give a score in the range of 0 to 156, where higher values represent better HRQoL. Fact-P population. Number of subjects analyzed= subjects with evaluable FACT-P Total Score for specified outcome measure. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

From baseline until DP, start of another anti-cancer therapy, death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	495		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Change at Cycle 1 (n=521, 495)	5.6 (3.43 to 7.78)	5.75 (3.55 to 7.95)		
Change at Cycle 2 (n=502, 492)	5.39 (3.23 to 7.55)	6.23 (4.05 to 8.42)		
Change at Cycle 3 (n=459, 452)	4.39 (2.21 to 6.57)	6.09 (3.89 to 8.3)		
Change at Cycle 4 (n=421, 415)	2.94 (0.73 to 5.14)	4.2 (1.98 to 6.42)		
Change at Cycle 5 (n=339, 365)	1.79 (-0.46 to 4.04)	3.33 (1.08 to 5.59)		
Change at Cycle 6 (n=275, 320)	2.57 (0.26 to 4.88)	2.35 (0.06 to 4.64)		

Change at Cycle 7 (n=229, 267)	2.62 (0.25 to 4.99)	2.72 (0.38 to 5.06)		
Change at Cycle 8 (n=196, 226)	1.35 (-1.08 to 3.78)	1.98 (-0.42 to 4.37)		
Change at Cycle 9 (n=164, 172)	1.1 (-1.4 to 3.6)	1 (-1.5 to 3.51)		
Change at Cycle 10 (n=137, 141)	0.02 (-2.57 to 2.61)	1.33 (-1.26 to 3.93)		
Change at Follow-up 1 (n=137, 153)	-3.1 (-5.69 to -0.51)	-2.09 (-4.65 to 0.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With FACT-P Total Score Response

End point title	Percentage of Subjects With FACT-P Total Score Response

End point description:

FACT-P is a 39-item subject questionnaire that measures the concerns of subjects with prostate cancer. It consists of 5 sub-scales assessing physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and prostate-specific concerns (12 items). FACT-P Total Score sums all 5 sub-scales to give a score in the range of 0 to 156, where higher values represent better HRQoL. Responder of FACT-P was defined as at least one occurrence of 7-point improvement from baseline in FACT-P total score during treatment period. Fact-P population. Number of subjects analyzed= subjects with evaluable FACT-P total score for specified outcome measure.

End point type	Secondary

End point timeframe:

From baseline until DP, start of another anti-cancer therapy, death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	540	525		
Units: percentage of subjects				
number (confidence interval 95%)	57.2 (53 to 61.4)	59.4 (55.2 to 63.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Definitive Deterioration of Score by 10% From Baseline on FACT-P Sub-Scales

End point title	Time to Definitive Deterioration of Score by 10% From Baseline on FACT-P Sub-Scales

End point description:

The time to definitive deterioration (10% decrease in score from baseline) was assessed for the individual sub-scales (Physical Well-Being; Social/Family Well-Being; Emotional Well-Being; Functional

Well-Being; Prostate-Specific Concerns). Analysis was performed by Kaplan-Meier method. Fact-P population.

End point type	Secondary

End point timeframe:

From baseline until DP, start of another anti-cancer therapy, death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	557	543		
Units: months				
median (confidence interval 95%)				
Physical well-being	6.6 (5.85 to 7.82)	8.3 (7.16 to 8.74)		
Social/family well-being	10.8 (9.26 to 13.37)	12.4 (8.97 to 13.83)		
Emotional well-being	9.7 (7.36 to 11.3)	9.9 (8.54 to 12.52)		
Functional well-being	6.6 (5.55 to 7.43)	6.7 (6.01 to 8.34)		
Prostate specific concern	8.7 (7.62 to 9.66)	9.7 (8.77 to 10.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Definitive Deterioration of ECOG PS Score From Baseline

End point title	Time to Definitive Deterioration of ECOG PS Score From Baseline

End point description:

The ECOG PS was used to evaluate subject's DP and the effect of the disease on the subject's activities of daily living. Time to definitive deterioration in ECOG PS score from baseline was defined as a change from 0, 1 to ≥2, or from 2 to ≥3. Analysis was performed by Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

From baseline until death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	602		
Units: months				
median (confidence interval 95%)	14.9 (11.43 to 23.59)	14.1 (12.22 to 20.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Definitive Weight Loss by 5% and 10% From Baseline

End point title	Time to Definitive Weight Loss by 5% and 10% From Baseline

End point description:

Time to definitive weight loss was defined as the time to first occurrence of ≥5% or ≥10% decrease in body weight from baseline. Analysis was performed by Kaplan-Meier method. ITT population. Here, 99999 signifies that median and upper bound of the confidence interval of Cabazitaxel 20 mg/m² arm and upper bound of the confidence interval of Cabazitaxel 25 mg/m² arm for weight loss by 10% could not be calculated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From baseline until death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	602		
Units: months				
median (confidence interval 95%)				
Weight Loss by 5%	10.6 (9.26 to 13.17)	11.1 (10.12 to 12.42)		
Weight Loss by 10%	99999 (12.65 to 99999)	20.3 (14.23 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Definitive Consumption of Narcotic Medication

End point title	Time to First Definitive Consumption of Narcotic Medication

End point description:

Concomitant medications used were recorded for all subjects, and time of first definitive consumption of narcotic medication (if it occurred) was determined. This measure summarizes the time from baseline to first definitive consumption of narcotic medication. Analysis was performed by Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

From baseline until DP, start of another anti-cancer therapy, death or study cut-off date (maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	602		
Units: months				
median (confidence interval 95%)	2.2 (0.99 to 3.65)	0.8 (0.3 to 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-emergent Adverse Events (TEAE)

End point title	Percentage of Subjects With Treatment-emergent Adverse Events (TEAE)

End point description:

Any untoward medical occurrence in a subject receiving investigational medicinal product was considered an adverse event (AE) without regard to possibility of causal relationship with treatment. TEAEs: AEs developed/worsened/became serious during on-treatment period (time from first dose of treatment to 30 days after last dose of treatment [either Cabazitaxel or Prednisone]).Serious adverse event (SAE):any untoward medical occurrence resulted in any of following: death,life-threatening,required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered medically important event. Any TEAE included subjects with both SAE and non-serious AEs. National Cancer Institute Common Terminology Criteria (NCI-CTCAE) v.4.03 (Grade 3=severe; Grade 4=life-threatening) was used to grade clinical AEs. Safety population included all randomized subjects who received ≥1 dose of study drug during study treatment period.

End point type	Secondary

End point timeframe:

From first administration of study treatment until 30 days after the last administration of study treatment (Maximum duration: 48 months)

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	580	595		
Units: percentage of subjects				
number (not applicable)				
Any Grade TEAE	91.2	93.9		
Any Grade 3-4 TEAE	39.7	54.5		
Grade 3-4 TEAE excluding laboratory TEAE	35.7	48.1		
Grade 3-4 TEAE excluding DP TEAEs	39	53.9		
Grade 3-4 TEAE excluding laboratory and DP TEAEs	35	47.4		
Any Serious TEAE	30.5	43.2		

Any TEAE leading to permanent discontinuation	16.4	19.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Clearance (CL) for Cabazitaxel

End point title	Plasma Clearance (CL) for Cabazitaxel

End point description:

Blood samples for pharmacokinetic (PK) analysis were obtained from a subset of the study subjects (approximately 150 subjects/group, by protocol) according to a sparse sampling strategy. Analysis was performed on PK population that included subjects who had evaluable PK data. Number of subjects analyzed = subjects with PK assessment at specified time-points.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1: 5 minutes before the end of infusion (EOI), 15 minutes, 1 to 4 hour, 6 to 24 hours, 48 to 168 hour after EOI

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	166		
Units: Litre/hour				
arithmetic mean (standard deviation)	44.832 (± 15.075)	49.662 (± 17.613)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Steady State Volume of Distribution (Vss) for Cabazitaxel

End point title	Plasma Steady State Volume of Distribution (Vss) for Cabazitaxel

End point description:

Blood samples for PK analysis were obtained from a subset of the study subjects (approximately 150 subjects/group, by protocol) according to a sparse sampling strategy. PK population. Number of subjects analyzed= subjects with PK assessment at specified time-points.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1: 5 minutes before the end of infusion (EOI), 15 minutes, 1 to 4 hour, 6 to 24 hours, 48 to 168 hour after EOI

End point values	Cabazitaxel 20 mg/m²	Cabazitaxel 25 mg/m²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	166		
Units: litre				
arithmetic mean (standard deviation)	7381.46 (± 4488.72)	7040.1 (± 5133.12)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to the final visit (48 months) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are TEAEs that is AEs that developed/worsened and death that occurred during the 'on treatment period' (time from first dose of study drug until 30 days after the last administration of study drug). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Cabazitaxel 25 mg/m²

Reporting group description:

Cabazitaxel 25 mg/m² on Day 1 of each 21-day cycle in combination with prednisone or prednisolone 10 mg orally daily until DP, unacceptable toxicity, subject's refusal of further study treatment or for a maximum of 10 cycles.

Reporting group title	Cabazitaxel 20 mg/m²

Reporting group description:

Cabazitaxel 20 mg/m² on Day 1 of each 21-day cycle in combination with prednisone or prednisolone 10 mg orally daily until DP, unacceptable toxicity, subject's refusal of further study treatment or for a maximum of 10 cycles.

Serious adverse events	Cabazitaxel 25 mg/m²	Cabazitaxel 20 mg/m²	
Total subjects affected by serious adverse events			
subjects affected / exposed	257 / 595 (43.19%)	177 / 580 (30.52%)	
number of deaths (all causes)	497	487	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder Cancer			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer Pain			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Carcinoma			

subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Squamous Cell Carcinoma			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases To Central Nervous System			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases To Spine			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Pain			
subjects affected / exposed	1 / 595 (0.17%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Carcinoma			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Associated Fever			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	3 / 595 (0.50%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism Venous			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic Shock			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous Thrombosis Limb			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 595 (0.67%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Site Inflammation			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Discomfort			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Occlusion			

subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Disease Progression			
subjects affected / exposed	13 / 595 (2.18%)	8 / 580 (1.38%)	
occurrences causally related to treatment / all	0 / 13	0 / 8	
deaths causally related to treatment / all	0 / 8	0 / 8	
Fatigue			
subjects affected / exposed	5 / 595 (0.84%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	2 / 595 (0.34%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Site Extravasation			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			

subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 595 (1.01%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	3 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Cardiac Death			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden Death			
subjects affected / exposed	2 / 595 (0.34%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Oedema Genital			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Pain			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute Respiratory Distress Syndrome			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	2 / 595 (0.34%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 595 (0.50%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Consolidation			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 595 (0.00%)	3 / 580 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia Aspiration			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	8 / 595 (1.34%)	7 / 580 (1.21%)	
occurrences causally related to treatment / all	2 / 8	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	3 / 595 (0.50%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Status Changes			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic Attack			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood Creatinine Increased			
subjects affected / exposed	2 / 595 (0.34%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases Increased			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical Cystitis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis Radiation			
subjects affected / exposed	4 / 595 (0.67%)	4 / 580 (0.69%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured Sacrum			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Radiation			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-Traumatic Pain			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Fracture			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation Proctitis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			

subjects affected / exposed	0 / 595 (0.00%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Anastomotic Leak			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	2 / 595 (0.34%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	3 / 595 (0.50%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiorenal Syndrome			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial Effusion			

subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Haematoma			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ataxia			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Encephalopathy			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			

subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lumbosacral Plexopathy			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve Compression			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Sensorimotor Neuropathy			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Motor Neuropathy			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			

subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	6 / 595 (1.01%)	6 / 580 (1.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 595 (0.00%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 595 (2.02%)	13 / 580 (2.24%)	
occurrences causally related to treatment / all	8 / 13	9 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated Intravascular Coagulation			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Febrile Bone Marrow Aplasia			

subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	48 / 595 (8.07%)	10 / 580 (1.72%)	
occurrences causally related to treatment / all	48 / 48	10 / 10	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haemolytic Uraemic Syndrome			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Anaemia			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	27 / 595 (4.54%)	3 / 580 (0.52%)	
occurrences causally related to treatment / all	26 / 28	3 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 595 (0.50%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual Acuity Reduced			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	5 / 595 (0.84%)	5 / 580 (0.86%)	
occurrences causally related to treatment / all	4 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 595 (0.50%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	13 / 595 (2.18%)	5 / 580 (0.86%)	
occurrences causally related to treatment / all	14 / 15	4 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Constipation			
subjects affected / exposed	0 / 595 (0.00%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum Intestinal Haemorrhagic			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular Perforation			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Duodenal Ulcer			

subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	3 / 595 (0.50%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical Fistula			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive Oesophagitis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Ischaemia			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus Paralytic			

subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Inguinal Hernia			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Haemorrhage			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Perforation			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric Vein Thrombosis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 595 (0.50%)	3 / 580 (0.52%)	
occurrences causally related to treatment / all	3 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Colitis			
subjects affected / exposed	2 / 595 (0.34%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	2 / 595 (0.34%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small Intestinal Obstruction			

subjects affected / exposed	2 / 595 (0.34%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 595 (0.84%)	7 / 580 (1.21%)	
occurrences causally related to treatment / all	4 / 7	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder Obstruction			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Failure			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	6 / 595 (1.01%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Azotaemia			

subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis Haemorrhagic			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis Noninfective			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 595 (0.00%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	21 / 595 (3.53%)	13 / 580 (2.24%)	
occurrences causally related to treatment / all	9 / 23	8 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	7 / 595 (1.18%)	6 / 580 (1.03%)	
occurrences causally related to treatment / all	1 / 7	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Colic			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 595 (0.00%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal Impairment			

subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric Obstruction			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Bladder Toxicity			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Incontinence			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	6 / 595 (1.01%)	6 / 580 (1.03%)	
occurrences causally related to treatment / all	0 / 6	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Inflammation			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 595 (0.84%)	3 / 580 (0.52%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			

subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	5 / 595 (0.84%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	8 / 595 (1.34%)	4 / 580 (0.69%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Haemorrhage			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Pain			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			

subjects affected / exposed	2 / 595 (0.34%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck Pain			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	4 / 595 (0.67%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral Foraminal Stenosis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Pain			
subjects affected / exposed	0 / 595 (0.00%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal Infection			

subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic Dysentery			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis Bacterial			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 595 (0.17%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Infective			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial Infection			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Bacteraemia			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			

subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Sepsis			
subjects affected / exposed	2 / 595 (0.34%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Infection			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	0 / 595 (0.00%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			

subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Infection			
subjects affected / exposed	17 / 595 (2.86%)	8 / 580 (1.38%)	
occurrences causally related to treatment / all	17 / 18	8 / 9	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pelvic Abscess			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			
subjects affected / exposed	14 / 595 (2.35%)	7 / 580 (1.21%)	
occurrences causally related to treatment / all	14 / 14	7 / 7	
deaths causally related to treatment / all	3 / 3	2 / 2	
Peritonitis			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis Infective			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	7 / 595 (1.18%)	6 / 580 (1.03%)	
occurrences causally related to treatment / all	4 / 7	4 / 7	
deaths causally related to treatment / all	1 / 2	1 / 1	
Pyelonephritis			
subjects affected / exposed	2 / 595 (0.34%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal Infection			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	2 / 595 (0.34%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	7 / 595 (1.18%)	5 / 580 (0.86%)	
occurrences causally related to treatment / all	5 / 7	4 / 5	
deaths causally related to treatment / all	2 / 2	1 / 1	
Septic Shock			
subjects affected / exposed	5 / 595 (0.84%)	4 / 580 (0.69%)	
occurrences causally related to treatment / all	4 / 5	2 / 4	
deaths causally related to treatment / all	1 / 2	0 / 1	
Sinusitis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			

subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Infection			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 595 (0.00%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	17 / 595 (2.86%)	9 / 580 (1.55%)	
occurrences causally related to treatment / all	6 / 17	2 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Staphylococcal			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 595 (0.34%)	3 / 580 (0.52%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	2 / 595 (0.34%)	2 / 580 (0.34%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 595 (0.17%)	3 / 580 (0.52%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 595 (0.17%)	0 / 580 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 595 (0.00%)	1 / 580 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cabazitaxel 25 mg/m²	Cabazitaxel 20 mg/m²	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	507 / 595 (85.21%)	450 / 580 (77.59%)	
Investigations			
Weight Decreased			
subjects affected / exposed	44 / 595 (7.39%)	24 / 580 (4.14%)	
occurrences (all)	45	24	
Injury, poisoning and procedural complications			
Wrong Technique In Drug Usage Process			
subjects affected / exposed	32 / 595 (5.38%)	2 / 580 (0.34%)	
occurrences (all)	37	2	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	63 / 595 (10.59%)	41 / 580 (7.07%)	
occurrences (all)	87	48	
Dizziness			
subjects affected / exposed	32 / 595 (5.38%)	24 / 580 (4.14%)	
occurrences (all)	37	24	
Peripheral Sensory Neuropathy			
subjects affected / exposed	63 / 595 (10.59%)	38 / 580 (6.55%)	
occurrences (all)	73	39	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	40 / 595 (6.72%)	15 / 580 (2.59%)	
occurrences (all)	46	16	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	114 / 595 (19.16%)	88 / 580 (15.17%)	
occurrences (all)	164	119	
Fatigue			
subjects affected / exposed	156 / 595 (26.22%)	142 / 580 (24.48%)	
occurrences (all)	201	161	
Oedema Peripheral			
subjects affected / exposed	53 / 595 (8.91%)	38 / 580 (6.55%)	
occurrences (all)	64	40	
Pyrexia			

subjects affected / exposed	32 / 595 (5.38%)	26 / 580 (4.48%)	
occurrences (all)	38	30	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	48 / 595 (8.07%)	29 / 580 (5.00%)	
occurrences (all)	66	33	
Constipation			
subjects affected / exposed	107 / 595 (17.98%)	102 / 580 (17.59%)	
occurrences (all)	150	130	
Diarrhoea			
subjects affected / exposed	231 / 595 (38.82%)	175 / 580 (30.17%)	
occurrences (all)	442	318	
Stomatitis			
subjects affected / exposed	30 / 595 (5.04%)	27 / 580 (4.66%)	
occurrences (all)	35	30	
Nausea			
subjects affected / exposed	188 / 595 (31.60%)	140 / 580 (24.14%)	
occurrences (all)	304	192	
Vomiting			
subjects affected / exposed	105 / 595 (17.65%)	78 / 580 (13.45%)	
occurrences (all)	176	104	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	43 / 595 (7.23%)	29 / 580 (5.00%)	
occurrences (all)	52	31	
Cough			
subjects affected / exposed	35 / 595 (5.88%)	34 / 580 (5.86%)	
occurrences (all)	37	36	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	36 / 595 (6.05%)	15 / 580 (2.59%)	
occurrences (all)	36	15	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	24 / 595 (4.03%)	31 / 580 (5.34%)	
occurrences (all)	25	34	

Haematuria			
subjects affected / exposed	108 / 595 (18.15%)	73 / 580 (12.59%)	
occurrences (all)	152	90	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	37 / 595 (6.22%)	46 / 580 (7.93%)	
occurrences (all)	44	54	
Bone Pain			
subjects affected / exposed	42 / 595 (7.06%)	42 / 580 (7.24%)	
occurrences (all)	45	57	
Back Pain			
subjects affected / exposed	78 / 595 (13.11%)	63 / 580 (10.86%)	
occurrences (all)	92	68	
Pain In Extremity			
subjects affected / exposed	40 / 595 (6.72%)	30 / 580 (5.17%)	
occurrences (all)	48	34	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	51 / 595 (8.57%)	33 / 580 (5.69%)	
occurrences (all)	70	35	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	108 / 595 (18.15%)	74 / 580 (12.76%)	
occurrences (all)	138	91	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2010	Amendment 1: It included the following changes: - Removed the body surface area (BSA) capping at 2.1 m² for the calculation of the dose, following the Food and Drug Association (FDA) request. Based on FDA review of the EFC6193 trial, subjects whose BSA was greater than 2.1 m² and did not had their cabazitaxel dose capped had a lower rate of >Grade 3 neutropenia compared to subjects with BSA greater than 2.1 m² and dose-capping and to subjects with BSA <2.1 m².
10 March 2011	Amendment 2: It included the following changes: - Implemented the recommendations made by the renal expert board. - Added pharmacogenomics for subjects with PK in selected site. - Included an exploratory objective to evaluate circulating free plasma DNA (total and tumor specific) for biomarker studies in selected sites. - Updated the Written Subject Information in order to reflect the changes within the protocol.
14 December 2011	Amendment 3: It included the following changes: - Allowed premedication with oral antihistamines in countries where no intravenous formulation was available. - Incorporated updated information on preparation and administration of cabazitaxel, and storage of the premix and infusion solution according to Investigational Brochure edition 13.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported