Clinical trial results:
A Randomized, Open Label, Multicenter Study of Cabazitaxel Versus an Androgen Receptor (AR)- targeted Agent (Abiraterone or Enzalutamide) in mCRPC Patients Previously Treated with Docetaxel and Who Rapidly Failed a Prior AR-targeted Agent (CARD)

Summary

EudraCT number	2014-004676-29
Trial protocol	ES BE NL IE GR FR IS AT CZ IT
Global end of trial date	15 March 2021

Results information

Result version number	v2 (current)
This version publication date	07 January 2023
First version publication date	29 March 2022
Version creation reason	• Correction of full data set Updated safety optional field

Trial information

Trial identification

Sponsor protocol code	LPS14201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02485691
WHO universal trial number (UTN)	U1111-1166-5329

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis Groupe (SAG)
Sponsor organisation address	54, rue La Boetie, Paris, France, 75008
Public contact	Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@sanofi.com
Scientific contact	Sanofi aventis recherche & développement, Trial Transparency Team, 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	13 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the radiographic Progression-Free Survival (rPFS) [Using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 for tumor lesions and Prostate Cancer Working Group 2 (PCWG2) criteria for bone scan lesions or death due to any cause] with chemotherapy (Cabazitaxel plus prednisone) (Arm A) versus Androgen Receptor (AR)-targeted therapy (enzalutamide or abiraterone acetate plus prednisone) (Arm B) in mCRPC subjects who had been treated with docetaxel and who had disease progression while receiving AR-targeted therapy within 12 months of AR treatment initiation (less than or equal to [<=] 12 months) (either before or after docetaxel).

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	09 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czechia: 19
Country: Number of subjects enrolled	France: 55
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Iceland: 9
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 29

Worldwide total number of subjects	255
EEA total number of subjects	248

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)	63
From 65 to 84 years	188
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 66 active centres in 13 countries. A total of 255 subjects were randomised between 09 November 2015 to 13 November 2018, out of which 250 subjects received treatment with the study drug.

Pre-assignment

Screening details:

Subjects were randomised to receive either cabazitaxel or AR targeted therapy (abiraterone or enzalutamide were assigned based on previous AR targeted treatment in which subjects previously treated with abiraterone were treated with enzalutamide and vice versa due to resistance).

Period 1

Period 1 title	Overall study (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

Arm description:

Subjects received cabazitaxel 25 milligrams per square metre (mg/m^2) intravenous (IV) infusion for over 1 hour on Day 1 of each 3-week treatment cycle in combination with Prednisone 10 mg orally once daily and primary prophylactic granulocyte-colony stimulating factor (G-CSF) as per investigator decision, until radiographic disease progression, unacceptable toxicity, or subject's refusal of further study treatment (median duration = 22 weeks).

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	XRP6258
Other name	Jevtana
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cabazitaxel 25 mg/m^2 IV infusion for over 1 hour on Day 1 of each 3-week treatment cycle in combination with Prednisone 10 mg orally once daily and primary prophylactic G-CSF as per investigator decision.

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

Dosage and administration details:

Prednisone 10mg given orally every 3 weeks.

Arm title	Abiraterone Acetate or Enzalutamide

Arm description:

Subjects received either abiraterone acetate 1000 mg orally once daily from Day 1 to Day 21 of each 3-week treatment cycle in combination with prednisone 5 mg orally twice daily; or enzalutamide 160 mg orally once daily continuously from Day 1 to Day 21 of each 3-week treatment cycle, until radiographic disease progression, unacceptable toxicity, or subject's refusal of further study treatment (median duration =12.5 weeks).

Arm type	Active comparator

Investigational medicinal product name	Abiraterone Acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone acetate 1000 mg orally once daily along with oral prednisone 5 mg twice daily. Abiraterone was administered to subjects who had received enzalutamide prior to study entry.

Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	
Other name	Xtandi
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Enzalutamide 160 mg orally once daily. Enzalutamide was administered to subjects who received prior abiraterone acetate.

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

Dosage and administration details:

Prednisone 5 mg given orally twice daily.

Number of subjects in period 1	Cabazitaxel	Abiraterone Acetate or Enzalutamide
Started	129	126
Treated	126	124
Completed	0	0
Not completed	129	126
Randomised and not treated	3	2
Investigator's decision	23	5
Disease progression	57	92
Adverse events	25	11
Other reason	8	9
Poor compliance to protocol	-	1
Subject's request	13	6

Baseline characteristics

Reporting groups	
Reporting group title	Cabazitaxel

Reporting group description:

Subjects received cabazitaxel 25 milligrams per square metre (mg/m^2) intravenous (IV) infusion for over 1 hour on Day 1 of each 3-week treatment cycle in combination with Prednisone 10 mg orally once daily and primary prophylactic granulocyte-colony stimulating factor (G-CSF) as per investigator decision, until radiographic disease progression, unacceptable toxicity, or subject's refusal of further study treatment (median duration = 22 weeks).

Reporting group title	Abiraterone Acetate or Enzalutamide

Reporting group description:

Subjects received either abiraterone acetate 1000 mg orally once daily from Day 1 to Day 21 of each 3-week treatment cycle in combination with prednisone 5 mg orally twice daily; or enzalutamide 160 mg orally once daily continuously from Day 1 to Day 21 of each 3-week treatment cycle, until radiographic disease progression, unacceptable toxicity, or subject's refusal of further study treatment (median duration =12.5 weeks).

Reporting group values	Cabazitaxel	Abiraterone Acetate or Enzalutamide	Total
Number of subjects	129	126	255
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	69.7	69.7	
standard deviation	± 8.3	± 7.9	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	129	126	255

End points

End points reporting groups

Reporting group title	Cabazitaxel

Reporting group description:

Subjects received cabazitaxel 25 milligrams per square metre (mg/m^2) intravenous (IV) infusion for over 1 hour on Day 1 of each 3-week treatment cycle in combination with Prednisone 10 mg orally once daily and primary prophylactic granulocyte-colony stimulating factor (G-CSF) as per investigator decision, until radiographic disease progression, unacceptable toxicity, or subject's refusal of further study treatment (median duration = 22 weeks).

Reporting group title	Abiraterone Acetate or Enzalutamide

Reporting group description:

Subjects received either abiraterone acetate 1000 mg orally once daily from Day 1 to Day 21 of each 3-week treatment cycle in combination with prednisone 5 mg orally twice daily; or enzalutamide 160 mg orally once daily continuously from Day 1 to Day 21 of each 3-week treatment cycle, until radiographic disease progression, unacceptable toxicity, or subject's refusal of further study treatment (median duration =12.5 weeks).

Primary: Radiographic Progression-Free Survival (rPFS)

End point title	Radiographic Progression-Free Survival (rPFS)

End point description:

Radiographic progression-free survival: time (in months) from randomisation to occurrence of any one of following: radiological tumor progressions using response evaluation criteria in solid tumors (RECIST 1.1), progression of bone lesions using Prostate Cancer Working Group 2 (PCWG2) criteria or occurrence of death due to any cause. Progression as per RECIST 1.1: at least a 20 percent (%) increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions. Progression of bone lesions (PCWG2 criteria): first bone scan with greater than or equal to (>=) 2 new lesions compared to Baseline observed less than (<) 12 weeks from randomisation and confirmed by a second bone scan performed >=6 weeks; first bone scan with >=2 new lesions compared to Baseline observed >=12 weeks from randomisation. per protocol, data cut-off date for final analysis of this endpoint was date when 196 rPFS events had occurred. Analysed by Kaplan-Meier method. ITT population.

End point type	Primary

End point timeframe:

From randomisation until tumor progression or bone lesion progression, death due to any cause, or data cut-off date whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126		
Units: months				
median (confidence interval 95%)	8.0 (5.7 to 9.2)	3.7 (2.8 to 5.1)		

Statistical analyses

Statistical analysis title	Cabazitaxel vs Abiraterone Acetate or Enzalutamide

Statistical analysis description:

Hazard ratio was estimated using a Cox Proportional Hazards regression model. The Cox proportional

hazard model was stratified by Eastern Cooperative Oncology Group performance status (ECOG) performance status, time from AR-targeted agent initiation progression, timing of AR targeted agent as specified at the time of randomisation.

Comparison groups	Cabazitaxel v Abiraterone Acetate or Enzalutamide
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.73

Notes:

[1] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in an order the endpoints were reported and continued when previous endpoint was statistically significant at two-sided 0.05. Only the primary and the first 4 secondary endpoints were included in the procedure.
[2] - P-value from 2-sided stratified log-rank test, stratified for ECOG performance status, time from AR-targeted agent initiation progression, timing of AR targeted agent as specified at the time of randomisation. Significance threshold was at 0.05.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time interval (in months) from the date of randomisation to the date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date subject was known to be alive or at the cut-off date whichever comes first. Analysis was performed by Kaplan-Meier method. Analysis was performed on ITT population that included any subject who had been allocated to a randomised treatment regardless of whether the treatment kit was used, analysed according to the treatment group allocated by randomisation.

End point type	Secondary

End point timeframe:

From randomisation to death due to any cause, or data cut-off date whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126		
Units: months				
median (confidence interval 95%)	13.6 (11.5 to 17.5)	11.0 (9.2 to 12.9)		

Statistical analyses

Statistical analysis title	Cabazitaxel vs Abiraterone Acetate or Enzalutamide

Statistical analysis description:

Hazard ratio was estimated using a Cox Proportional Hazards regression model. The Cox proportional hazard model was stratified by ECOG performance status, time from AR-targeted agent initiation progression, timing of AR targeted agent as specified at the time of randomisation.

Comparison groups	Cabazitaxel v Abiraterone Acetate or Enzalutamide
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0078 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.89

Notes:

[3] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints are reported and continued when previous endpoint was statistically significant at two-sided 0.05. Only the primary and the first 4 secondary endpoints were included in the procedure.
[4] - P-value from 2-sided stratified log-rank test, stratified for ECOG performance status, time from AR-targeted agent initiation progression, timing of AR-targeted agent as specified at the time of randomisation. Significance threshold was at 0.05.

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS:time duration (in months) from date of randomisation to date of first occurrence of any of following events: radiological tumor progression (RECIST 1.1); progression of bone lesions (PCWG2); symptomatic progression (developing urinary or bowel symptoms; need to change anti-cancer therapy), pain progression or death due to any cause. Tumor Progression(RECIST 1.1): at least 20% increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions. Progression of bone lesion (PCWG2 criteria): first bone scan with >=2 new lesions compared to Baseline and confirmed by second bone scan performed >=6 weeks later; pain progression: increase by >=30% from Baseline in pain intensity score (calculated using scale ranged: 0=no pain to 5=extreme pain) or increase in analgesic usage score >=30% (calculated from analgesic use data, non-narcotic medications assigned value of 1 point and narcotic medications assigned 4 points). Analysed by Kaplan-Meier method. ITT.

End point type	Secondary

End point timeframe:

From randomisation until tumor progression or bone lesion progression, pain progression, death due to any cause, or data cut-off date whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126		
Units: months				
median (confidence interval 95%)	4.4 (3.6 to 5.4)	2.7 (2.3 to 2.8)		

Statistical analyses

Statistical analysis title	Cabazitaxel vs Abiraterone Acetate or Enzalutamide

Statistical analysis description:

Hazard ratio was estimated using a Cox Proportional Hazards regression model. The Cox proportional hazard model was stratified by ECOG performance status, time from AR-targeted agent initiation progression, timing of AR targeted agent as specified at the time of randomisation.

Comparison groups	Cabazitaxel v Abiraterone Acetate or Enzalutamide
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.68

Notes:

[5] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints are reported and continued when previous endpoint was statistically significant at two-sided 0.05. Only the primary and the first 4 secondary endpoints were included in the procedure.
[6] - P-value from 2-sided stratified log-rank test, stratified for ECOG performance status, time from AR-targeted agent initiation progression, timing of AR targeted agent as specified at the time of randomisation. Significance threshold was at 0.05.

Secondary: Percentage of Subjects With Prostate Specific Antigen (PSA) Response

End point title	Percentage of Subjects With Prostate Specific Antigen (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. Analysis was performed on subset of ITT population (any subject who had been allocated to a randomised treatment, analysed according to group allocated) with PSA level >2 nanograms per millilitre (ng/mL) at Baseline, and with at least two post-baseline assessments before any further anti-cancer therapy for specified endpoint.

End point type	Secondary

End point timeframe:

Baseline up to PSA response, death due to any cause or data cut-off date whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	105		
Units: percentage of subjects				
number (confidence interval 95%)	36.3 (27.4 to 45.1)	14.3 (7.6 to 21.0)		

Statistical analyses

Statistical analysis title	Cabazitaxel vs Abiraterone Acetate or Enzalutamide
Comparison groups	Cabazitaxel v Abiraterone Acetate or Enzalutamide
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0003 [8]
Method	Cochran-Mantel-Haenszel

Notes:

[7] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints are reported and continued when previous endpoint was statistically significant at two-sided 0.05. Only the primary and the first 4 secondary endpoints were included in the procedure.

[8] - Cochran-Mantel-Haenszel test stratified by ECOG performance status, time from AR-targeted agent initiation to progression, timing of AR-targeted agent as specified at the time of randomisation. Significance threshold = 0.05.

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 having a partial response (PR) or complete response (CR) according to the RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions and normalisation of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (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. Analysis was performed on subset of ITT population (any subject who had been allocated to a randomised treatment, analysed according to group allocated) with measurable disease at Baseline and at least one post-baseline assessment before any further anti-cancer therapy for specified endpoint.

End point type	Secondary

End point timeframe:

From randomisation until disease progression, death due to any cause or data cut-off date whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	52		
Units: percentage of subjects				
number (confidence interval 95%)	36.5 (24.6 to 48.4)	11.5 (2.9 to 20.2)		

Statistical analyses

Statistical analysis title	Cabazitaxel vs Abiraterone Acetate or Enzalutamide
Comparison groups	Cabazitaxel v Abiraterone Acetate or Enzalutamide
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0004 [10]
Method	Cochran-Mantel-Haenszel

Notes:

[9] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints are reported and continued when previous endpoint was statistically significant at two-sided 0.05. Only the primary and the first 4 secondary endpoints were included in the procedure.
[10] - Cochran-Mantel-Haenszel test stratified by ECOG performance status, time from AR-targeted agent initiation to progression, timing of AR-targeted agent as specified at the time of randomisation. Significance threshold = 0.05.

Secondary: Time to PSA Progression (TTPP)

End point title	Time to PSA Progression (TTPP)

End point description:

TTPP was defined as the time duration (in months) between the date of randomisation and the date of first documented PSA progression. PSA progression (as per PCWG 2) was defined as: 1) If decline from Baseline value: an increase of >=25% (at least 2 ng/mL) over the nadir value, confirmed by a second PSA value at least 3 weeks apart; 2) If no decline from Baseline value: an increase of >=25% (at least 2 ng/mL) over the Baseline value after 12 weeks of treatment, confirmed by a second PSA value at least 3 weeks apart. Analysis performed by Kaplan-Meier method. Analysis was performed on subset of ITT population (any subject who had been allocated to a randomised treatment, analysed according to group allocated) with PSA level > 2 ng/mL at Baseline, and with at least two post-baseline assessments before any further anti-cancer therapy for specified endpoint.

End point type	Secondary

End point timeframe:

From time from randomisation until PSA progression, death due to any cause or data cut-off whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	105		
Units: months				
median (confidence interval 95%)	6.3 (4.2 to 8.3)	2.1 (1.7 to 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Tumor Response

End point title	Duration of Tumor Response

End point description:

Duration of tumor response was defined as time (in months) from date of first response (CR or PR) until date of first documentation of tumor progression or death, whichever occurs first. As per RECIST 1.1, CR: defined as disappearance of all target and non-target lesions and normalisation of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference Baseline sum diameters. Progression was defined as at least a 20% increase in sum of diameters of target lesions, unequivocal progression of existing non-target lesions. Analysed by Kaplan-Meier method. Analysis was performed on subset of subjects with overall objective tumor response. Here, '99999' is used as a space filler and denotes that upper limit of confidence interval (CI) was not estimable due to less number of subjects with overall objective tumor response.

End point type	Secondary

End point timeframe:

From the date of the first response to the date of first documented tumor progression, or death due to any cause or data cut-off date whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	6		
Units: months				
median (confidence interval 95%)	6.5 (5.6 to 11.4)	8.0 (1.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Pain Response Assessed Using Brief Pain Inventory-Short Form (BPI-SF) Pain Intensity Score

End point title	Percentage of Subjects Achieving Pain Response Assessed Using Brief Pain Inventory-Short Form (BPI-SF) Pain Intensity Score

End point description:

Pain response as per BPI-SF was defined as a decrease of at least 30% from Baseline in the average of BPI-SF pain intensity score observed at 2 consecutive evaluations >=3 weeks apart without increase in analgesic usage score (calculated from analgesic use data, with non-narcotic medications assigned value of 1 point and narcotic medications assigned 4 points). The BPI-SF is a self-administered questionnaire developed to assess the severity of pain on a 0-10 categorical scale where 0=no pain, 10=pain as bad as you can imagine. Higher scores indicated worst outcomes. Percentage of subjects achieving pain response assessed using BPI-SF pain intensity score were reported. Analysis was performed on subset of ITT population (any subject who had been allocated to a randomised treatment, analysed according to group allocated) with Baseline assessment and at least one post-baseline assessment before any further anti-cancer therapy for specified endpoint.

End point type	Secondary

End point timeframe:

Baseline until pain progression, first further anticancer therapy, or data cut-off whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	109		
Units: percentage of subjects				
number (confidence interval 95%)	45.9 (36.7 to 55.2)	19.3 (11.9 to 26.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression

End point title	Time to Pain Progression

End point description:

Time to pain progression: time duration (in months) between date of randomisation and date of 1st documented pain progression. Pain progression, in subjects with no pain or stable pain at Baseline: defined as increase of >=30% from baseline in BPI-SF pain intensity score observed at 2 consecutive evaluations >=3 weeks apart without decrease in analgesic usage score or increase in analgesic usage score (calculated from analgesic use data, with non-narcotic medications assigned value of 1 point and narcotic medications assigned 4 points) >=30%. BPI-SF: self-administered questionnaire assessed pain severity on 0-10 categorical scale where 0=no pain, 10=pain as bad as you can imagine. Higher scores: worst outcomes. Analysed by Kaplan-Meier method on subset of ITT population. '99999' is used as a space filler and denotes that median, lower and upper limit of CI was not estimable because the curve's upper CI bound had not crossed 50% survival threshold.

End point type	Secondary

End point timeframe:

Baseline until pain progression or data cut-off whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	109		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	8.5 (4.9 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Symptomatic Skeletal Events (SSE)

End point title	Number of Symptomatic Skeletal Events (SSE)

End point description:

SSE was defined as occurrence of a new symptomatic pathological fracture, use of external beam radiation to relieve bone pain, occurrence of spinal cord compression or tumor- related orthopedic surgical intervention. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline until occurrence of first SSE or data cut-off, whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126		
Units: events	24	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptomatic Skeletal Event

End point title	Time to Symptomatic Skeletal Event

End point description:

Time to SSE was defined as the time duration (in months) between the date of randomisation and the date of occurrence of the first SSE. Analysis was performed by Kaplan-Meier method on ITT population. Here, '99999' is used as a space filler and denotes that median and upper limit of CI were not estimable because of low number of subjects with events.

End point type	Secondary

End point timeframe:

From date of randomisation until first SSE, or data cut-off whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126		
Units: months				
median (confidence interval 95%)	99999 (20.0 to 99999)	16.7 (10.8 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HRQOL): Change From Baseline in Functional Assessment of Cancer Therapy-Prostate (FACT-P) Total Score at Cycle 2, 3, 4, 5, 6, 7, 8 and End of Treatment

End point title	Health-Related Quality of Life (HRQOL): Change From Baseline in Functional Assessment of Cancer Therapy-Prostate (FACT-P) Total Score at Cycle 2, 3, 4, 5, 6, 7, 8 and End of Treatment

End point description:

Health-related quality of life (HRQOL) evaluation was performed using the FACT-P questionnaire (Version 4). FACTP was a 39-item subject rated questionnaire that measures the concerns of subjects with prostate cancer. It consisted of 5 sub-scales assessing physical well-being (7 items), social/family well-being (7 items), emotional wellbeing (6 items), functional well-being (7 items), and prostate-specific concerns (12 items). FACT-P total score was the sum of all 5 subscale scores. It ranged from 0 to156 with higher score indicated better quality of life with fewer symptoms. Baseline corresponded to last evaluable assessment before treatment administration. Analysis was performed on HRQOL population which included subjects who received at least one dose of the study drug and with an evaluable FACT-P questionnaire at Baseline and at least one post-baseline evaluable FACT-P. Here 'n' = subjects in each treatment group with available data for each cycle.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8 and at End of Treatment (any time up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	114		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 (n=104,106)	2.6 (± 12.3)	-0.0 (± 12.4)		
Cycle 3 (n=99,94)	2.7 (± 16.1)	-1.0 (± 16.8)		
Cycle 4 (n=93,77)	2.8 (± 14.8)	-0.7 (± 16.8)		
Cycle 5 (n=79,56)	2.1 (± 17.9)	-1.0 (± 16.1)		
Cycle 6 (n=64,39)	-3.7 (± 18.0)	0.4 (± 18.6)		
Cycle 7 (n=58,33)	-2.2 (± 19.3)	2.7 (± 19.9)		
Cycle 8 (n=47,25)	-4.8 (± 20.4)	0.8 (± 23.0)		
End of treatment (n=51,31)	-6.3 (± 16.1)	-7.5 (± 15.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Utility Single Index and Visual Analogue Scale (VAS) Scores at Cycle 2, 3, 4, 5, 6, 7, 8 and End of Treatment

End point title	Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Utility Single Index and Visual Analogue Scale (VAS) Scores at Cycle 2, 3, 4, 5, 6, 7, 8 and End of Treatment

End point description:

EQ-5D: HRQOL questionnaire with EQ-5D descriptive system & Visual Analogue Scale (VAS). EQ-5D descriptive system had 5 dimensions: mobility, self-care, usual activities, pain/discomfort & anxiety/depression measured on 3 levels (no problem, some problems & severe problems) within particular EQ-5D dimension. 5 dimensional 3-level system converted into single index utility score. Possible values for single index utility score ranged -0.594 (severe problems in all dimensions) to 1.0 (no problem in all dimensions) on scale where 1 = best health state. EQ-5D VAS recorded subject's rating for his/her current HRQOL state, captured on a vertical VAS scale ranging 0-100, where 0=worst health state & 100=best health state, where higher states: better outcomes. Baseline: last evaluable assessment before treatment administration. Health status population: had at least 1 dose of study drug and Baseline evaluable EQ-5D-5L with at least 1 post-baseline evaluable EQ-5D-5L. 'n' = subjects with data.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8 and at End of Treatment (any time up to: 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	115		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2: VAS (n=108,109)	3.6 (± 14.4)	0.9 (± 14.6)		
Cycle 3: VAS (n=104,94)	4.5 (± 15.0)	1.5 (± 13.4)		
Cycle 4: VAS (n=100,77)	4.6 (± 16.5)	-1.1 (± 18.2)		
Cycle 5: VAS (n=84,57)	0.6 (± 17.1)	3.2 (± 17.0)		
Cycle 6: VAS (n=68,39)	-1.3 (± 22.8)	-1.5 (± 23.1)		
Cycle 7: VAS (n=60,32)	2.9 (± 18.1)	-0.2 (± 20.1)		
Cycle 8: VAS (n=49,23)	2.8 (± 18.0)	1.2 (± 19.6)		
End of treatment: VAS (n=56,33)	-3.3 (± 19.3)	-5.9 (± 23.1)		
Cycle 2: Utility Index Score (n=108,109)	0.026 (± 0.179)	-0.010 (± 0.178)		
Cycle 3: Utility Index Score (n=103,94)	0.041 (± 0.183)	-0.011 (± 0.182)		
Cycle 4: Utility Index Score (n=99,79)	0.051 (± 0.176)	-0.002 (± 0.188)		
Cycle 5: Utility Index Score (n=79,59)	0.027 (± 0.209)	-0.035 (± 0.185)		
Cycle 6: Utility Index Score (n=67,42)	0.015 (± 0.191)	-0.000 (± 0.176)		
Cycle 7: Utility Index Score (n=60,34)	0.029 (± 0.182)	0.024 (± 0.153)		
Cycle 8: Utility Index Score (n=47,24)	0.008 (± 0.213)	-0.014 (± 0.138)		
End of treatment: Utility Index Score (n=56,35)	-0.048 (± 0.188)	-0.079 (± 0.200)		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic Progression-Free Survival (rPFS) in Subjects With Presence and Absence of Biomarker

End point title	Radiographic Progression-Free Survival (rPFS) in Subjects With Presence and Absence of Biomarker

End point description:

Circulating tumor cell (CTC) counts: biomarker in liquid biopsy. rPFS in subjects with presence and absence of CTC biomarker subtypes i.e. chromosomal instability (CIN) and neuroendocrine (NE) is reported. rPFS: time (in months) from randomisation to 1st occurrence of any 1 of following: radiological tumor progressions (RECIST1.1), progression of bone lesions (PCWG2 criteria) or death due to any cause. Analysis performed on subset of subjects analyzed per the treatment group allocated by randomisation with evaluable samples. Here, 'n' = subjects in each treatment group with data for each specified category.

End point type	Secondary

End point timeframe:

From randomisation until tumor progression or bone lesion progression, death due to any cause, or data cut-off date whichever comes first (maximum duration: up to 141 weeks)

End point values	Cabazitaxel	Abiraterone Acetate or Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	106		
Units: month				
median (full range (min-max))				
Presence of CIN (n=27,27)	4.2 (2.1 to 11.2)	4.2 (0.03 to 21.0)		
Absence of CIN (n=82,79)	8.5 (0.03 to 33.1)	3.4 (0.03 to 28.0)		
Presence of NE (n=7,14)	3.0 (2.6 to 11.2)	3.9 (0.03 to 21.0)		
Absence of NE (n=102,92)	8.2 (0.03 to 33.1)	3.5 (0.03 to 28.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) data were collected from Baseline up to 30 days after the last treatment administration (up to 197 weeks), deaths were collected from Baseline up to end of study (up to 197 weeks).

Adverse event reporting additional description:

Reported AEs were TEAEs i.e., AEs that developed/worsened during the 'on-treatment period' (time from first dose of study drug until 30 days after last administration of study drug), and all deaths for the safety population (i.e., all subjects who received at least one dose of study drugs, analysed according to treatment actually received).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Enzalutamide or Abiraterone

Reporting group description:

Subjects received either abiraterone acetate 1000 mg orally once daily from Day 1 to Day 21 of each 3-week treatment cycle in combination with prednisone 5 mg orally twice daily; or enzalutamide 160 mg orally once daily continuously from Day 1 to Day 21 of each 3-week treatment cycle, until radiographic disease progression, unacceptable toxicity, or subject's refusal of further study treatment (median duration =12.5 weeks).

Reporting group title	Cabazitaxel

Reporting group description:

Subjects received cabazitaxel 25 mg/m^2 IV infusion for over 1 hour on Day 1 of each 3-week treatment cycle in combination with Prednisone 10 mg orally once daily and primary prophylactic G-CSF as per investigator decision, until radiographic disease progression, unacceptable toxicity, or subject's refusal of further study treatment (median duration = 22 weeks).

Serious adverse events	Enzalutamide or Abiraterone	Cabazitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 124 (40.32%)	49 / 126 (38.89%)	
number of deaths (all causes)	102	96	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	2 / 124 (1.61%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine Carcinoma Of The Skin			

subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic Complication			
subjects affected / exposed	1 / 124 (0.81%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour Pain			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (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	1 / 124 (0.81%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease Progression			
subjects affected / exposed	8 / 124 (6.45%)	4 / 126 (3.17%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 3	

General Physical Health Deterioration			
subjects affected / exposed	2 / 124 (1.61%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 124 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic Obstructive Pulmonary Disease			

subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Inflammation			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (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	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Product issues			
Device Dislocation			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
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			
Femoral Neck Fracture			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head Injury			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal Compression Fracture			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity To Various Agents			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina Pectoris			

subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 124 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Complete			
subjects affected / exposed	2 / 124 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	2 / 124 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Carotid Artery Stenosis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cognitive Disorder			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			

subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
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 / 124 (0.81%)	0 / 126 (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	3 / 124 (2.42%)	4 / 126 (3.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 124 (0.81%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	0 / 124 (0.00%)	4 / 126 (3.17%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperfibrinolysis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 124 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea Haemorrhagic			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus Paralytic			

subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (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 / 124 (2.42%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 124 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 124 (1.61%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	4 / 124 (3.23%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematuria			

subjects affected / exposed	3 / 124 (2.42%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 124 (0.81%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelocaliectasis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (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	3 / 124 (2.42%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary Retention			
subjects affected / exposed	1 / 124 (0.81%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			
subjects affected / exposed	2 / 124 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	4 / 124 (3.23%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			

subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	2 / 124 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	1 / 124 (0.81%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Pain			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device Related Sepsis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter Sepsis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			

subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Infection			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal Cellulitis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 124 (0.81%)	4 / 126 (3.17%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Sepsis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 124 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tooth Infection			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	3 / 124 (2.42%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary Tract Infection Bacterial			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 124 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 124 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 124 (0.81%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Enzalutamide or Abiraterone	Cabazitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 124 (83.87%)	114 / 126 (90.48%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	9 / 124 (7.26%)	9 / 126 (7.14%)	
occurrences (all)	10	15	

Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 124 (6.45%)	5 / 126 (3.97%)	
occurrences (all)	8	12	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 124 (16.94%)	36 / 126 (28.57%)	
occurrences (all)	27	65	
Asthenia			
subjects affected / exposed	26 / 124 (20.97%)	33 / 126 (26.19%)	
occurrences (all)	37	69	
Oedema Peripheral			
subjects affected / exposed	11 / 124 (8.87%)	10 / 126 (7.94%)	
occurrences (all)	12	13	
Pain			
subjects affected / exposed	6 / 124 (4.84%)	8 / 126 (6.35%)	
occurrences (all)	7	8	
Pyrexia			
subjects affected / exposed	7 / 124 (5.65%)	7 / 126 (5.56%)	
occurrences (all)	7	10	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 124 (2.42%)	7 / 126 (5.56%)	
occurrences (all)	5	8	
Investigations			
Weight Decreased			
subjects affected / exposed	7 / 124 (5.65%)	5 / 126 (3.97%)	
occurrences (all)	7	6	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 124 (4.03%)	15 / 126 (11.90%)	
occurrences (all)	7	18	
Neuropathy Peripheral			
subjects affected / exposed	3 / 124 (2.42%)	8 / 126 (6.35%)	
occurrences (all)	3	11	
Polyneuropathy			

subjects affected / exposed	0 / 124 (0.00%)	8 / 126 (6.35%)	
occurrences (all)	0	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 124 (11.29%)	38 / 126 (30.16%)	
occurrences (all)	24	75	
Leukopenia			
subjects affected / exposed	1 / 124 (0.81%)	8 / 126 (6.35%)	
occurrences (all)	3	12	
Neutropenia			
subjects affected / exposed	1 / 124 (0.81%)	28 / 126 (22.22%)	
occurrences (all)	3	35	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	3 / 124 (2.42%)	10 / 126 (7.94%)	
occurrences (all)	3	12	
Constipation			
subjects affected / exposed	13 / 124 (10.48%)	19 / 126 (15.08%)	
occurrences (all)	18	27	
Diarrhoea			
subjects affected / exposed	8 / 124 (6.45%)	50 / 126 (39.68%)	
occurrences (all)	8	88	
Nausea			
subjects affected / exposed	26 / 124 (20.97%)	29 / 126 (23.02%)	
occurrences (all)	31	49	
Stomatitis			
subjects affected / exposed	2 / 124 (1.61%)	10 / 126 (7.94%)	
occurrences (all)	3	13	
Vomiting			
subjects affected / exposed	14 / 124 (11.29%)	16 / 126 (12.70%)	
occurrences (all)	18	21	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 124 (0.00%)	7 / 126 (5.56%)	
occurrences (all)	0	7	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	5 / 124 (4.03%)	18 / 126 (14.29%)	
occurrences (all)	6	27	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 124 (16.13%)	10 / 126 (7.94%)	
occurrences (all)	35	14	
Back Pain			
subjects affected / exposed	27 / 124 (21.77%)	20 / 126 (15.87%)	
occurrences (all)	41	22	
Bone Pain			
subjects affected / exposed	7 / 124 (5.65%)	4 / 126 (3.17%)	
occurrences (all)	7	4	
Pain In Extremity			
subjects affected / exposed	13 / 124 (10.48%)	6 / 126 (4.76%)	
occurrences (all)	18	7	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	4 / 124 (3.23%)	10 / 126 (7.94%)	
occurrences (all)	4	10	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	19 / 124 (15.32%)	16 / 126 (12.70%)	
occurrences (all)	21	21	
Hypokalaemia			
subjects affected / exposed	7 / 124 (5.65%)	5 / 126 (3.97%)	
occurrences (all)	14	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2015	Changed secondary objectives: FACT-P questionnaire was added. Changed exploratory objectives: New biomarkers to study was identified. For scientifically interpretable data, collection of germline DNA derived from saliva at Baseline was found necessary. Changed inclusion criteria: Minimum dose exposure to docetaxel was specified. At least 3 cycles were needed to consider prior treatment with docetaxel. Specified docetaxel administration in combination with ADT in metastatic hormone-sensitive disease was considered prior exposure. Per ESMO guidelines, ADT+docetaxel: recommended as first-line treatment of metastatic hormone-naive disease in men fit enough for chemotherapy. Time to progression with first AR-targeted agent was extended from 6-12 months (with stratification [0;6 months] versus[6;12 months]) to evaluate optimal management of such subjects. Published retrospective data suggested that subjects with acquired resistance to AR-targeted agents poorly respond to another targeted agent. Unpublished retrospective data suggested that subjects having disease progression within 6-12 months with first AR-targeted agent in post-docetaxel setting may poorly respond to another AR-targeted agent. In pre-docetaxel setting, subjects having disease progression within 6-12 months with abiraterone or enzalutamide were considered 'rapid progressors' and could also poorly respond to another AR-targeted agent. Changed exclusion criteria. Clarified immunotherapy, previous immunotherapy was allowed. Modified as per NoMA request to give more details on contraception. Creatinine clearance <50 mL/min was removed per last SmPC update. Cabazitaxel is minimally excreted through kidney. No dose adjustment was necessary in subjects with renal impairment, not requiring hemodialysis. Per SmPC clarified exclusion of subjects with symptomatic peripheral neuropathy Grade 2 as well as subjects with Grade >2 and concomitant vaccination with yellow fever vaccine was added (also per NoMA request).
11 May 2018	Introduced name and address of: Coordinating Investigator and Sponsor in cover page. Clarified definition of rPFS in the Primary Objective and Primary Endpoint sections. Clarified definition of PFS. Clarified & adapted the Inclusion criteria based on recent guidelines updates: As per ESMO guidelines, prostate cancer diagnosis was to be confirmed by histology, (cytology is not mentioned). Per ESMO guidelines on management of metastatic CRPC, the sentence: "If the subject has been treated with LHRH agonists or antagonist (i.e., without orchiectomy), then this therapy should be continued" was added. LHRH agonists or antagonists were already allowed in section concomitant treatments, but to avoid any ambiguity and add clarity. Abiraterone acetate + androgen deprivation therapy (ADT) was now indicated in Europe for the treatment of metastatic hormone-sensitive prostate cancer. Such subjects were thus eligible in CARD if they have progressed within 12 months with this regimen. It has also been clarified that subjects having PSA progression only (as per PCWG 2) within 12 months, were eligible, even if total treatment duration with the AR-targeted agent was more than 12 months. Revised statistical power and accrual rates assumptions, and as a consequence reduced the sample size. Introduced the 500mg dosage of the Investigational Medicinal Product(s)– abiraterone acetate (Zytiga) and adapt dose modification and dose delay accordingly and to align dose adaptation rules with revised abiraterone acetate European labelling. Introduced time window of + or - 1 week for tumor assessment during treatment and in follow up if applicable, as well as all follow up visit to increase compliance and flexibility for subjects. Clarified change to procedure and consequence for subject withdrawal from study. Corrected inconsistencies throughout the protocol with regards to general guidelines for reporting AEs.
08 November 2018	This amendment had introduced mainly a new format of Abiraterone acetate 500 mg tablets (available in two formats (wallets 60 or 56 tablets, previously only 60 tablets), with no changes concerning the immediate packaging or daily dose), and introduced the new address of coordinating investigator.

01 March 2019	Inclusion criteria was updated and harmonised for the three arms of treatment, based on the approved label (for abiraterone and enzalutamide) and cabazitaxel IB. Subjects with reproductive potential who did not agree, in conjunction with their partner, to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of "effective method of contraception" described hereafter: oral contraceptives, combined hormonal intravaginal, transdermal, intra uterine device or condoms was be based on respective study treatment labelling and country-specific regulatory requirements, and were documented in the Informed Consent Form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported