Clinical trial results:
A Multi-center, Single-arm Study of Enzalutamide in Patients With Progressive Metastatic Castration-resistant Prostate Cancer Previously Treated With Abiraterone Acetate

Summary

EudraCT number	2013-002271-17
Trial protocol	BE DE GB ES
Global end of trial date	29 September 2017

Results information

Result version number	v2 (current)
This version publication date	09 September 2018
First version publication date	25 July 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	9785-CL-0410

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02116582
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.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	29 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate Radiographic Progression-free Survival (rPFS) in participants with progressive metastatic castration-resistant prostate cancer (mCRPC) previously treated with abiraterone acetate.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2014
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	Belgium: 15
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 66
Worldwide total number of subjects	215
EEA total number of subjects	215

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	176
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

Male participants with progressive metastatic castration-resistant prostate cancer were enrolled in this study.

Pre-assignment

Screening details:

A total of 272 participants were screened for enrollment & signed an informed consent form, & 57 of those screen failed. The primary reason for screening failure was not fulfilling inclusion/exclusion criteria (52 participants, 19.1%), followed by withdrawal (5 participants, 1.8%).

Period 1

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

Arms

Arm title	Enzalutamide

Arm description:

Participants received 160 mg of enzalutamide orally once daily until they experienced an adverse event, disease progression, started new anti-cancer therapy, withdrew consent, or other protocol-specified criteria.

Arm type	Experimental
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	MDV3100
Other name	Xtandi
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Participants received 160 mg of enzalutamide orally once daily.

Number of subjects in period 1	Enzalutamide
Started	215
Treated	214
Completed	0
Not completed	215
Transitioned to 9785-CL-0123	12
Adverse Event	22
Death	9
Progressive Disease	148
Miscellaneous	11
Withdrawal by Subject	8
Protocol Violation	3

Enrolled but Never Received Study Drug	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide
Reporting group description:	
Participants received 160 mg of enzalutamide orally once daily until they experienced an adverse event, disease progression, started new anti-cancer therapy, withdrew consent, or other protocol-specified criteria.	

Reporting group values	Enzalutamide	Total	
Number of subjects	215	215	
Age categorical			
Units: Subjects			
Age continuous			
The analysis population for this baseline measure consisted of all participants who were enrolled in the study.			
Units: years			
log mean	73.2		
standard deviation	± 7.6	-	
Gender categorical			
The analysis population for this baseline measure consisted of all participants who were enrolled in the study.			
Units:			
Male	215	215	
Female	0	0	
Race/Ethnicity			
Race was not collected in France, because of country regulations. Ethnicity was not collected for this study. The analysis population for this baseline measure consisted of all participants who were enrolled in the study.			
Units: Subjects			
White	165	165	
Black or African American	2	2	
Other	1	1	
Not Reported	47	47	

End points

End points reporting groups

Reporting group title	Enzalutamide

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily until they experienced an adverse event, disease progression, started new anti-cancer therapy, withdrew consent, or other protocol-specified criteria.

Primary: Radiographic progression-free survival (rPFS)

End point title	Radiographic progression-free survival (rPFS)[1]

End point description:

Radiographic PFS, was defined as the time from first dose to the first objective evidence of radiographic disease progression or death from any cause, whichever occurred first. For patients with no documented progression event, it was censored on the date of the last disease assessment performed prior to the analysis data cut-off point. Radiographic progression (RP) for soft tissue disease was defined by Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 criteria. RP for bone disease was determined according to the consensus guidelines of a modification of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) guidelines. The 50th percentile of Kaplan-Meier (KM) estimates was used as the estimate of the rPFS median. A 2-sided 95% Confidence Interval (CI) was provided for this estimate using the Brookmeyer & Crowley (BC) method. The analysis population consisted of the safety analysis set (SAF) which consisted of all participants who took at least 1 dose of study drug.

End point type	Primary

End point timeframe:

From the first dose of study drug administration up to treatment discontinuation or the data cut-off date of 08 May 2016, whichever occurred first; the median duration of treatment was 5.7 months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All variables were presented using descriptive statistics only. No formal statistical analysis was conducted.

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	214			
Units: Months				
median (confidence interval 95%)	8.1 (6.11 to 8.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from first dose to death from any cause. All events of death were included. If patients discontinued study drug before the analysis data cut-off point, only OS status was assessed every 12 weeks until the data cut-off point date or until death, whichever occurred first. For patients who were alive at the time of the analysis data cut-off point, the OS time was censored on the last date

the patient was known to be alive. Death from any cause was included, regardless of whether the event occurred while the patient was still taking study drug or after the patient discontinued study drug. OS median was estimated using the KM method. A 2-sided 95% CI was provided for this estimate using the BC method. The analysis population consisted of the SAF. Data not available is denoted as "99999"; the data could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From the first dose of study drug administration up to the data cut-off date of 08 May 2016; up to 2 years.

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	214			
Units: Months				
median (confidence interval 95%)	99999 (18.14 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Prostate-specific Antigen (PSA) Response

End point title	Percentage of Participants with a Prostate-specific Antigen (PSA) Response

End point description:

PSA response was defined as at least a 50% decrease from baseline in PSA, and was a binary variable for achieving this criteria (or not) based on the lowest PSA value observed postbaseline. Participants with no postbaseline PSA value were regarded as non-responders. 95% CI for PSA response rate was computed using the Clopper-Pearson method based on the exact binomial distribution. The analysis population consisted of the SAF.

End point type	Secondary

End point timeframe:

From the first dose of study drug administration up to the data cut-off date for end-of-study completion 29 Sep 2017; the median duration of treatment was 5.7 months.

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	214			
Units: Percentage of participants				
number (confidence interval 95%)	22.0 (16.61 to 28.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA progression

End point title	Time to PSA progression

End point description:

The time to PSA progression was calculated as the time interval from the date of first dose to the date of first observation of PSA progression. PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (i.e., 2 ng/mL or more) above the nadir or above the baseline value for patients who did not have a decline in PSA postbaseline values, and which was confirmed by a second consecutive value obtained at least 3 or more weeks later (i.e., a confirmed rising trend) (PCWG2 criteria). The 50th percentile of KM estimates was used as the estimate of the time to PSA progression median. A 2-sided 95% CI was provided for this estimate using the BC method. The analysis population consisted of the SAF.

End point type	Secondary

End point timeframe:

From the first dose of study drug administration up to the data cut-off date of 08 May 2016; the median duration of treatment was 5.7 months.

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	214			
Units: Months				
median (confidence interval 95%)	5.7 (5.55 to 5.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

A treatment-emergent adverse event (TEAE) was defined as an adverse event occurring or worsening between the start of study treatment date and the latest date of 30 days after the last dose date or the 30-day follow-up visit date, and not later than the data cut-off date or the date of death. AEs, including abnormal clinical laboratory values, were graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) guidelines (V4.03). The analysis population consisted of the SAF.

End point type	Secondary

End point timeframe:

From the first dose of study drug administration up to data cut-off date for end-of-study completion (29 Sep 2017); the median duration of treatment was 5.7 months.

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	214			
Units: Participants				
Any TEAE	199			
NCI-CTCAE Grade ≥3	95			
Study Drug-Related	127			
Study Drug-Related NCI-CTCAE Grade ≥3	18			
TEAEs with Death as an Outcome	22			
Serious Adverse Event (SAE)	82			
Study Drug-related SAE	8			
TEAEs Leading to Study Drug Discontinuation	76			
Study Drug-Related TEAEs Leading to Drug Disc.	23			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug administration up to data cut-off date for end-of-study completion (29 Sep 2017); the median duration of treatment was 5.7 months.

Adverse event reporting additional description:

The total number of deaths (all causes) includes deaths reported after the time frame above.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Enzalutamide Total

Reporting group description:

Participants received 160 mg of enzalutamide orally once daily until they experienced an adverse event, disease progression, started new anti-cancer therapy, withdrew consent, or other protocol-specified criteria.

Serious adverse events	Enzalutamide Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 214 (38.32%)		
number of deaths (all causes)	73		
number of deaths resulting from adverse events	22		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			

subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	13 / 214 (6.07%)		
occurrences causally related to treatment / all	0 / 15		
deaths causally related to treatment / all	0 / 9		
Metastases to central nervous system			
subjects affected / exposed	2 / 214 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to lymph nodes			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic pain			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral neoplasm benign			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			

subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureteric cancer			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Ileostomy closure			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Implantable defibrillator insertion			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shoulder arthroplasty			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 214 (1.40%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Device occlusion				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	10 / 214 (4.67%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 3			
Inflammation				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 214 (0.93%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	3 / 214 (1.40%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			

Epiglottic mass				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	2 / 214 (0.93%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	5 / 214 (2.34%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 1			
Pulmonary hypertension				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disorientation				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				

Monoclonal immunoglobulin present			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural intestinal perforation			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Cardiac failure				
subjects affected / exposed	3 / 214 (1.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Cardiovascular disorder				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mitral valve incompetence				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Aphasia				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Encephalitis				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Loss of consciousness				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Monoparesis				

subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nerve root compression				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	7 / 214 (3.27%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vertebral artery thrombosis				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	5 / 214 (2.34%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Anaemia of malignant disease				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				

subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	2 / 214 (0.93%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal distension				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 214 (0.93%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				

subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Drug eruption				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Bladder tamponade				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	7 / 214 (3.27%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				

subjects affected / exposed	2 / 214 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	5 / 214 (2.34%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Ureteric stenosis			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary incontinence			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 214 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	3 / 214 (1.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	4 / 214 (1.87%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Groin pain			

subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	2 / 214 (0.93%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis of jaw				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal disorder				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchopneumonia				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				

subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dental fistula				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterobacter sepsis				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 214 (0.93%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	4 / 214 (1.87%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Pulmonary sepsis				

subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pyelonephritis				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 214 (0.93%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fluid retention				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 214 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Enzalutamide Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	182 / 214 (85.05%)		
Investigations			
Weight decreased			
subjects affected / exposed	26 / 214 (12.15%)		
occurrences (all)	28		
Vascular disorders			
Hot flush			
subjects affected / exposed	12 / 214 (5.61%)		
occurrences (all)	12		
Hypertension			
subjects affected / exposed	19 / 214 (8.88%)		
occurrences (all)	22		
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 214 (6.54%)		
occurrences (all)	14		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 214 (10.75%)		
occurrences (all)	36		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	38 / 214 (17.76%)		
occurrences (all)	51		
Fatigue			
subjects affected / exposed	72 / 214 (33.64%)		
occurrences (all)	89		
Oedema peripheral			
subjects affected / exposed	18 / 214 (8.41%)		
occurrences (all)	19		
Gastrointestinal disorders			
Constipation			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	28 / 214 (13.08%) 32 27 / 214 (12.62%) 29 32 / 214 (14.95%) 38 11 / 214 (5.14%) 17		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	11 / 214 (5.14%) 12		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	12 / 214 (5.61%) 12		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	15 / 214 (7.01%) 18		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all)	34 / 214 (15.89%) 40 37 / 214 (17.29%) 41 27 / 214 (12.62%) 34 12 / 214 (5.61%) 16		

Musculoskeletal pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	23 / 214 (10.75%) 25 25 / 214 (11.68%) 29		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	53 / 214 (24.77%) 65		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2014	The changes include: ● Updated definition of bone disease progression: Provided an exception for the requirement of a confirmatory scan if progression after week 13 showed unequivocal evidence of bone disease progression (i.e., if multiple new lesions of uptake were observed). ● Updated inclusion criteria numbers 4 and 6: Added timing of bone scan and CT/MRI to allow historical scans within ≤ 30 days prior to day 1 if these were already available. ● Updated inclusion criterion number 7: Changed minimum time period of prior treatment with abiraterone acetate from 6 months to 24 weeks and clarified previous treatment of abiraterone acetate should be within its approved label indication. ● Clarified OS assessment before the data analysis cut-off point: Provided 2 different scenarios in the flow chart and reworded (Section 5.3.2 of the protocol to clarify follow-up assessments for patients who discontinued before versus after the analysis data cut-off point. ● The schedule of assessments was updated: Updated the schedule of assessments to reflect the revisions in substantial amendment 1. ● Updated the timing of AE collection: AEs were collected from time of informed consent instead of from time of study drug administration on day 1. ● Updated sponsor contact information. ● Updated planned study period: The planned study period moved 1 quarter from Q1 2014-Q1 2016 to Q2 2014-Q2 2016. ● Updated planned total number of study centers: The planned total number of study centers was updated from approximately 40 to 55 centers in Europe. ● Clarified frequency of safety assessment after data analysis cut-off point: Clarified the frequency of the safety assessment after data analysis cut-off point as 24 weeks rather than 6 months. ● Updated the requirements of BPI-SF: Allowed for a repeat of the BPI-SF once during the screening period.
21 June 2016	The changes include: ● Revised the study design: Subjects who were free of radiographic progression, continuing to derive clinical benefit from treatment with enzalutamide based on the investigator’s medical opinion and did not meet any of the treatment discontinuation criteria as outlined in Section 6.1 of the protocol may have been eligible to continue receiving treatment with enzalutamide in open-label extension Study 9785-CL-0123 (NCT02960022) upon approval of the 9785-CL-0123 protocol and activation of this study at the participating institution. Subjects who chose not to participate or were not eligible for Study 9785-CL-0123 completed their participation in Study 9785-CL-0410 by completing the safety follow-up visit upon activation of Study 9785-CL-0123 at the institution. ● Updated sponsor contact information: Details for the Astellas Medical Expert/Medical Monitor were updated. ● Updated planned study period: The planned study period was updated from Q2 2016 to Q1 2017. ● Minor administrative-type changes were made (e.g., typos, punctuation, formatting). These minor changes were not detailed in the Summary of Changes section of this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For participants on treatment after the primary analysis data cut-off point (08 May 2016), only AEs were assessed every 24 weeks until treatment discontinuation or death, this was not required for those that enrolled into 9785-CL-0123 (NCT02960022).

Notes: