Clinical trial results:
A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination with Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone

Summary

EudraCT number	2013-004011-41
Trial protocol	NL ES
Global end of trial date	01 June 2023

Results information

Result version number	v1 (current)
This version publication date	14 June 2024
First version publication date	14 June 2024

Trial information

Trial identification

Sponsor protocol code	1280.8

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02204072
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.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	22 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2019
Global end of trial reached?	Yes
Global end of trial date	01 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase Ib dose escalation: Determine the safety and tolerability of xentuzumab in combination with enzalutamide following progression on docetaxel-based chemotherapy and abiraterone.
Phase Ib expansion cohort: Evaluate the anti-tumour activity of xentuzumab and enzalutamide in patients naive to taxane-based chemotherapy and abiraterone.
Phase II: Evaluate the anti-tumour activity of xentuzumab in combination with enzalutamide versus enzalutamide alone following progression on docetaxel-based chemotherapy and abiraterone.

Protection of trial subjects:

All patients were informed that they were free to withdraw their consent at any time during the study without penalty or prejudice. The patients were informed that their personal trial related data would be considered confidential and used by BI in accordance with the local data protection laws. The level of disclosure was explained to the patients. The patients were also informed that their medical records could be examined by Clinical Quality Assurance auditors appointed by BI, by members of the appropriate IEC/IRB, and by inspectors from regulatory authorities. Confidentiality of patient data was ensured by the use of depersonalised patient identification codes (patient numbers).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 70
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Taiwan: 17
Worldwide total number of subjects	154
EEA total number of subjects	42

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)	34
From 65 to 84 years	117
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A multicentre, open-label, randomised study to determine the safety, tolerability and anti-tumour activity of xentuzumab (BI 836845) in combination with enzalutamide in patients with advanced prostate cancer that has spread. The trial consists of 3 parts: Phase 1b dose escalation part, Phase 1b expansion part, Phase 2 two arm, parallel design.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated. Population was based on the treated set.

Period 1

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

Blinding implementation details:

Open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide

Arm description:

750 milligram (mg) xentuzumab (10mg/milliliter (mL)) was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib escalation part.

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

Dosage and administration details:

750 milligram (mg) xentuzumab (10mg/milliliter (mL)) was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events.

Investigational medicinal product name	Xentuzumab
Investigational medicinal product code	
Other name	BI 836845
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 milligram (mg) xentuzumab (10mg/milliliter (mL)) was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment

until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events.

Arm title	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide

Arm description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib escalation part.

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

Dosage and administration details:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events.

Investigational medicinal product name	Xentuzumab
Investigational medicinal product code	
Other name	BI 836845
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events.

Arm title	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide

Arm description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib expansion part.

Arm type	Experimental
Investigational medicinal product name	Xentuzumab
Investigational medicinal product code	
Other name	BI 836845
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg

(total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events.

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

Dosage and administration details:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events.

Arm title	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide

Arm description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase II part.

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

Dosage and administration details:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events

Investigational medicinal product name	Xentuzumab
Investigational medicinal product code	
Other name	BI 836845
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events.

Arm title	Phase II: 160 mg Enzalutamide

Arm description:

Four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Phase II part.

Arm type	Experimental

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

Dosage and administration details:

Four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities.

Number of subjects in period 1[1]	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide
Started	3	7	24
Treated	3	7	24
Discon. Xen. due to progressive disease	2	4	21
Discon. Xen. due to adverse event	0	3	0
Discon. Xen due to withdrawal by subject	1	0	2
Discon. Xen. due to other reason	0	0	1
Completed	0	0	0
Not completed	3	7	24
Discon. Enz. due to progressive disease	2	4	19
Dison. Enz. due to other reason	-	-	2
Discon. Enz. due to adverse events	-	3	1
Discon. Enz. due to withdrawal by subject	1	-	2

Number of subjects in period 1[1]	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide
Started	43	43
Treated	43	43
Discon. Xen. due to progressive disease	24	0
Discon. Xen. due to adverse event	7	0
Discon. Xen due to withdrawal by subject	9	0
Discon. Xen. due to other reason	1 [2]	0
Completed	2	0
Not completed	41	43
Discon. Enz. due to progressive disease	26	31
Dison. Enz. due to other reason	-	-
Discon. Enz. due to adverse events	6	6
Discon. Enz. due to withdrawal by subject	9	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Worldwide 154 patients were enrolled into the trial, whereof 120 patients actually started the trial.

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

Justification: 43 subjects were treated in this arm, whereof 41 discontinued all treatment medication and 2 subjects were on treatment at the time of the final analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

750 milligram (mg) xentuzumab (10mg/milliliter (mL)) was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib escalation part.

Reporting group title	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib escalation part.

Reporting group title	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib expansion part.

Reporting group title	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase II part.

Reporting group title	Phase II: 160 mg Enzalutamide

Reporting group description:

Four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Phase II part.

Reporting group values	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide
Number of subjects	3	7	24
Age categorical			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0

Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	1	2
From 65-84 years	2	6	21
85 years and over	0	0	1
Age Continuous			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: years			
arithmetic mean	68.67	70.71	73.38
standard deviation	± 11.85	± 7.09	± 7.81
Sex: Female, Male			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
Female	0	0	0
Male	3	7	24
Ethnicity (NIH/OMB)			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
Hispanic or Latino	0	0	4
Not Hispanic or Latino	3	7	20
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	3	7	23
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Phase Ib expansion part: Prostate Surface Antigen (PSA) at baseline			
Treated Set (TS): All patients who were documented to have received and taken at least one dose of study medication during treatment cycles (from Day 1). Only phase Ib expansion. 99999 = Not applicable.			
Units: Microgram / Liter			
median	99999	99999	35.95
inter-quartile range (Q1-Q3)	99999 to 99999	99999 to 99999	14.13 to 73.39

Reporting group values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide	Total
Number of subjects	43	43	120
Age categorical			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			

In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	10	25
From 65-84 years	31	33	93
85 years and over	1	0	2
Age Continuous			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: years			
arithmetic mean	68.58	69.91	
standard deviation	± 8.80	± 7.92	-
Sex: Female, Male			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
Female	0	0	0
Male	43	43	120
Ethnicity (NIH/OMB)			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
Hispanic or Latino	5	12	21
Not Hispanic or Latino	37	31	98
Unknown or Not Reported	1	0	1
Race (NIH/OMB)			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	15	10	25
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	27	33	93
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Phase Ib expansion part: Prostate Surface Antigen (PSA) at baseline			
Treated Set (TS): All patients who were documented to have received and taken at least one dose of study medication during treatment cycles (from Day 1). Only phase Ib expansion. 99999 = Not applicable.			
Units: Microgram / Liter			
median	99999	99999	
inter-quartile range (Q1-Q3)	99999 to 99999	99999 to 99999	-

Subject analysis sets

Subject analysis set title	Xentuzumab + Enzalutamide
Subject analysis set type	Full analysis

Subject analysis set description:

This arm comprises all dose groups from Phase Ib escalation phase (750 mg Xentuzumab + 160 mg Enzalutamide and 1000 mg Xentuzumab + 160 mg Enzalutamide)

Reporting group values	Xentuzumab + Enzalutamide		
Number of subjects	9		
Age categorical			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: years arithmetic mean standard deviation	±		
Sex: Female, Male			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
Female Male			
Ethnicity (NIH/OMB)			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race (NIH/OMB)			
Treated Set: All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles.			
Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Phase Ib expansion part: Prostate Surface Antigen (PSA) at baseline			
Treated Set (TS): All patients who were documented to have received and taken at least one dose of study medication during treatment cycles (from Day 1). Only phase Ib expansion. 99999 = Not applicable.			
Units: Microgram / Liter			
median	99999		
inter-quartile range (Q1-Q3)	99999 to 99999		

End points

End points reporting groups

Reporting group title	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

750 milligram (mg) xentuzumab (10mg/milliliter (mL)) was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib escalation part.

Reporting group title	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib escalation part.

Reporting group title	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib expansion part.

Reporting group title	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase II part.

Reporting group title	Phase II: 160 mg Enzalutamide

Reporting group description:

Four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Phase II part.

Subject analysis set title	Xentuzumab + Enzalutamide
Subject analysis set type	Full analysis

Subject analysis set description:

This arm comprises all dose groups from Phase Ib escalation phase (750 mg Xentuzumab + 160 mg Enzalutamide and 1000 mg Xentuzumab + 160 mg Enzalutamide)

Primary: Phase Ib expansion part: Prostate Specific Antigen (PSA) response

End point title	Phase Ib expansion part: Prostate Specific Antigen (PSA) response[1][2]

End point description:

The primary endpoint of the Phase Ib expansion part was PSA response. PSA response was defined as a decline in PSA value >50% compared to baseline which was confirmed by the next available value occurring at least 3 weeks later. The confirmatory value had to be at least 50% lower than the baseline, but could be higher than the first PSA value taken into account for response. However the confirmatory value was not allowed to be 50% higher than this first PSA value. If it was ≥ 50% higher than the first PSA value, the next available sample was to be taken to determine if response had been achieved. The date of response was the date that the first 50% (or greater) decline was observed. Number of subjects

with response is reported.

Treated Set (TS): All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Phase Ib expansion part.

End point type	Primary

End point timeframe:

At Cycle 1 Day 1 before study treatment and from Cycle 3 Day 1 and Day 1 of every cycle thereafter until the end of treatment, up to 35 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: This endpoint was analyzed descriptively.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase Ib expansion part only.

End point values	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Subjects				
Yes, Confirmed	1			
Yes, Unconfirmed	1			
No	21			
Missing	1			

Statistical analyses

No statistical analyses for this end point

Primary: Phase Ib escalation part: Number of patients with dose limiting toxicities (DLTs)

End point title	Phase Ib escalation part: Number of patients with dose limiting toxicities (DLTs)[3][4]

End point description:

Number of patients with DLTs were used to determine the maximum tolerated dose (MTD) in the Phase Ib escalation part. The MTD in this study was defined as the highest protocol dose level of xentuzumab in combination with enzalutamide, at which no more than 1 out of 6 patients in a cohort experienced a DLT during the MTD evaluation period.

MTD-set: The MTD set defined the set of patients in the Phase Ib escalation part who were fully evaluable for determination of the MTD in the first treatment course. 1 patient in the 1000 mg Xentuzumab + 160 mg Enzalutamide arm was not evaluable for the MTD determination due to missed doses. Phase Ib escalation part.

End point type	Primary

End point timeframe:

From first administration of xentuzumab up to start of Cycle 2, up to 28 days.

Notes:

[3] - 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: Endpoint is assessed for Phase Ib escalation part only.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase Ib escalation part only.

End point values	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b esclation part: Maximum tolerated dose (MTD) based on the occurrence of dose limiting toxicity (DLT) during the first treatment course

End point title	Phase 1b esclation part: Maximum tolerated dose (MTD) based on the occurrence of dose limiting toxicity (DLT) during the first treatment course[5]

End point description:

Maximum tolerated dose (MTD) based on the occurrence of dose limiting toxicity (DLT) during the first treatment course. The MTD in this study was defined as the highest protocol dose level of xentuzumab in combination with enzalutamide, at which no more than 1 out of 6 patients in a cohort experienced a DLT during the MTD evaluation period.

MTD-set: The MTD set defined the set of patients in the Phase Ib escalation part who were fully evaluable for determination of the MTD in the first treatment course. 1 patient in the 1000 mg Xentuzumab + 160 mg Enzalutamide arm was not evaluable for the MTD determination due to missed doses. Phase Ib escalation part.

End point type	Primary

End point timeframe:

From first administration of xentuzumab up to start of Cycle 2, up to 28 days.

Notes:

[5] - 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: This endpoint was analyzed descriptively.

End point values	Xentuzumab + Enzalutamide			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Milligram	1000			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II part: Progression Free Survival (PFS) based on investigator

assessment	
End point title	Phase II part: Progression Free Survival (PFS) based on investigator assessment[6]

End point description:

PFS was defined as the time from randomisation until radiological tumour progression in bone (based on Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria) or soft tissue (based on modified RECIST 1.1) or death from any cause, whichever occurred earlier. Clinical disease progression was not considered for determination of a PFS event, unless the outcome of the progression was death. Median PFS time in months is reported. PFS was calculated as follows:
For patients with 'event' as an outcome for PFS: PFS [days] = date of outcome - date of randomisation + 1. For patients with 'censored' as an outcome for PFS: PFS (censored) [days] = date of outcome - date of randomisation + 1.

Randomised Set (RS): All randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Phase II part.

End point type	Primary

End point timeframe:

From randomisation until radiological tumor progression or death from any cause, whichever occurred earlier, up to 1269 days.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Months				
median (confidence interval 95%)	7.4 (3.5 to 8.7)	6.2 (3.5 to 11.1)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide v Phase II: 160 mg Enzalutamide
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9549
Method	Two-sided log-rank test.
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.7

Secondary: Phase Ib expansion part: Progression free survival (PFS) based on investigator assessment

End point title	Phase Ib expansion part: Progression free survival (PFS) based on investigator assessment[7]

End point description:

PFS was defined as the time from randomisation until radiological tumour progression in bone (based on Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria) or soft tissue (based on modified RECIST 1.1) or death from any cause, whichever occurred earlier. Clinical disease progression was not considered for determination of a PFS event, unless the outcome of the progression was death. Median PFS time in months is reported.

PFS was calculated as follows:
For patients with 'event' as an outcome for PFS:
PFS [days] = date of outcome - date of first treatment administration + 1.
For patients with 'censored' as an outcome for PFS:
PFS (censored) [days] = date of outcome - date of first treatment administration + 1.

Treated Set (TS): All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Phase Ib expansion part.

End point type	Secondary

End point timeframe:

From first treatment administration of any study medication until radiological tumor progression or death from any cause, whichever occurred earlier, up to 1114 days.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase Ib expansion part only.

End point values	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Months				
median (confidence interval 95%)	8.2 (3.5 to 14.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II part: Overall survival (OS)

End point title	Phase II part: Overall survival (OS)[8]

End point description:

Overall survival (OS) defined as the time from randomisation to death from any cause. Median survival time in months is reported.
Overall survival at cut-off date for final analysis (24-Oct-2019) is reported.

Randomised Set: All randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Phase II part.

End point type	Secondary

End point timeframe:

From randomisation until radiological tumor progression or death from any cause (until cut-off date for final analysis), whichever occurred earlier, up to 1269 days.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Months				
median (confidence interval 95%)	13.6 (8.7 to 19.4)	13.6 (8.7 to 21.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide v Phase II: 160 mg Enzalutamide
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5534
Method	Two-sided log-rank test.
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.9

Secondary: Phase Ib expansion part: Changes in circulating tumour cells (CTC) response – CTC reduction from >=5 to <5 cells per 7.5 mL blood for at least one post-baseline time point

End point title	Phase Ib expansion part: Changes in circulating tumour cells (CTC) response – CTC reduction from >=5 to <5 cells per 7.5 mL blood for at least one post-baseline time point[9]

End point description:

Changes in circulating tumour cells (CTC) response – CTC reduction from >=5 to <5 cells per 7.5 mL blood for at least one post-baseline time point. Number of subjects with CTC Response (yes/no) is reported.

Treated Set (TS): All patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Only subjects with baseline CTC value >= 5 cells per 7.5mL were included in the analysis. Phase Ib expansion part.

End point type	Secondary

End point timeframe:

Prior to study drug administration at Day 1 Cycle 1, Day 1 Cycle 2, Day 1 Cycle 3, Day 1 Cycle 5, Day 1 Cycle 7 and every 12 weeks thereafter, up to end of treatment. Up to 35 months.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase Ib expansion part only.

End point values	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
Yes	1			
No	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II part: Radiological Progression Free Survivial (PFS), based on central review

End point title	Phase II part: Radiological Progression Free Survivial (PFS), based on central review[10]

End point description:

PFS was defined as the time from randomisation until radiological tumour progression in bone (based on Prostate Cancer Clinical Trials Working Group 2 criteria) or soft tissue or death from any cause, whichever occurred earlier. Clinical disease progression was not considered for determination of a PFS event, unless the outcome of the progression was death.
Median PFS time in months is reported.
PFS was calculated as follows:
For patients with 'event' as an outcome for PFS:
PFS [days] = date of outcome - date of first treatment administration + 1.
For patients with 'censored' as an outcome for PFS: PFS (censored) [days] = date of outcome - date of first treatment administration + 1.

Randomised Set: All randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Phase II part.

End point type	Secondary

End point timeframe:

From randomisation until radiological tumor progression or death from any cause, whichever occurred earlier, up to 1269 days.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Months				
median (confidence interval 95%)	3.6 (3.5 to 8.1)	7.1 (3.6 to 8.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide v Phase II: 160 mg Enzalutamide
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5425
Method	Two-sided log-rank test.
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.06

Secondary: Phase II part: Maximum decline in Prostate Specific Antigen (PSA)

End point title	Phase II part: Maximum decline in Prostate Specific Antigen (PSA)[11]

End point description:

Maximum decline in (PSA) compared to baseline. The maximum decline in PSA is defined as the change in PSA between the baseline PSA
value and the minimum post-baseline PSA value. The change from baseline is defined as:
Change from baseline in PSA (ng/mL) = PSA value post-baseline - PSA value at baseline.
Maximum decline in PSA is defined as:
Maximum decline in PSA (ng/mL) = min(PSA value post-baseline) – PSA value at baseline.

Randomised Set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Phase II part.

End point type	Secondary

End point timeframe:

At screening, at Cycle 1 Day 1 and from Cycle 3 Day 1 and at Day 1 of every cycle thereafter until end of treatment, up to 40.1 months.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	37		
Units: Microgram / Liter				
arithmetic mean (standard deviation)	-102.20 (± 580.59)	-94.13 (± 1020.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II part: Time to Prostate Specific Antigen (PSA) progression

End point title	Phase II part: Time to Prostate Specific Antigen (PSA) progression[12]

End point description:

For the definition of time to PSA progression, the following rules are used:
- Decline from baseline in PSA before increasing:
Time to PSA progression is defined as the time from the date of randomisation until the date where a 25% or greater increase in PSA and an absolute increase of 2 ng/mL or more from baseline, is documented (which is confirmed by the next available value occurring at least 3 weeks later).
- No decline from baseline in PSA:
Time to PSA progression is defined as the time from the date of randomisation until the date where a 25% or greater increase in PSA and an absolute increase of 2 ng/mL or more from baseline, is documented. However, only values after 12 weeks of therapy are considered.
Time to PSA progression [days] = date of PSA progression - date of randomisation + 1.
For patients not presenting with PSA progression or being lost to follow-up:
Time to PSA progression (censored) [days] = date of censoring - date of randomisation + 1.
Randomised Set.

End point type	Secondary

End point timeframe:

At screening, at Cycle 1 Day 1 and from Cycle 3 Day 1 and at Day 1 of every cycle thereafter until end of treatment, up to 40.1 months.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Months				
median (confidence interval 95%)	4.6 (2.8 to 5.7)	3.7 (2.8 to 4.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide v Phase II: 160 mg Enzalutamide
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1514
Method	Two-sided log-rank test.
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.18

Secondary: Phase II part: Percentage change in Prostate Specific Antigen (PSA) at Week 12

End point title	Phase II part: Percentage change in Prostate Specific Antigen (PSA) at Week 12[13]

End point description:

Percentage change in PSA from baseline to Week 12. Percentage change in PSA from baseline to week 12 of treatment is defined as:
Percentage change in PSA (%) = 100*(PSA value at week 12 - PSA value at baseline)/PSA value at baseline
For this assessment, it is allowed to take a value:
- until one week later than week 12, in case the PSA assessment was delayed
- one day earlier due to the one day window allowed by the protocol
Values from assessments between day 84 and day 92 after first treatment administration will therefore be taken into account (according to the protocol schedule for visits at week 12).

Randomised Set: All randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Only subjects with non-missing values were included in the analysis. Phase II part.

End point type	Secondary

End point timeframe:

At baseline and at Week 12.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	30		
Units: Percentage change				
arithmetic mean (standard deviation)	10.13 (± 83.25)	49.72 (± 109.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II part: Prostate Specific Antigen (PSA) response

End point title	Phase II part: Prostate Specific Antigen (PSA) response[14]

End point description:

PSA response – defined as a decline in PSA value >50% (which is confirmed by a second value 3 to 4 weeks apart).
PSA response was defined as a decline in PSA value >50% compared to baseline which was confirmed by the next available value occurring at least 3 weeks later. The confirmatory value had to be at least 50% lower than the baseline, but could be higher than the first PSA value taken into account for response. However the confirmatory value was not allowed to be 50% higher than this first PSA value. If it was ≥ 50% higher than the first PSA value, the next available sample was to be taken to determine if response had been achieved. Number of participants with response is reported.

Randomised Set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Phase II part.

End point type	Secondary

End point timeframe:

At Cycle 1 Day 1 and from Cycle 3 Day 1 and at Day 1 of every cycle thereafter until end of treatment, up to 40.1 months.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Subjects				
Yes - confirmed	7	8		
Yes - unconfirmed	2	0		
No	31	29		
Missing	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II part: Circulating tumour cells (CTC) reduction defined as CTC decline from ≥5 to <5 cells per 7.5 mL blood for at least one post-baseline time-

point	
End point title	Phase II part: Circulating tumour cells (CTC) reduction defined as CTC decline from ≥5 to <5 cells per 7.5 mL blood for at least one post-baseline time-point[15]

End point description:

CTC reduction is defined as CTC decline from ≥5 to <5 cells per 7.5 mL blood for at least one post-baseline time-point. Patients with a CTC value < 5 cells per 7.5mL blood at baseline, or with missing baseline values were not taken into consideration for this endpoint. Baseline value is the value collected before a patient starts treatment with trial medication.

Number of participants per category is reported.

Randomised Set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Only patients with baseline CTC value >=5 cells per 7.5mL were included in the analysis. Phase II part.

End point type	Secondary

End point timeframe:

Prior to study drug administration at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1 and then every 12 weeks thereafter, until end of treatment. Up to 40.1 months.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	19		
Units: Subjects				
Yes	4	2		
No	19	15		
Missing on treatment	2	2		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide v Phase II: 160 mg Enzalutamide
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6186
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.579
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.269
upper limit	12.515

Secondary: Phase II part: Circulating tumour cells (CTC) status at Week 12

End point title	Phase II part: Circulating tumour cells (CTC) status at Week

End point description:

CTC status (≥5 or <5 cells per 7.5mL blood) at Week 12. Number of participants per category is reported.

Randomised Set: All randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Phase II part.

End point type	Secondary

End point timeframe:

At Week 12.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Subjects				
≥5 cells per 7.5ml blood	26	20		
<5 cells per 7.5ml blood	11	16		
Missing on treatment	6	7		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide v Phase II: 160 mg Enzalutamide
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.192
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.891
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.727
upper limit	5.059

Secondary: Phase II part: Maximum decline (%) in circulating tumour cells (CTC) counts

End point title	Phase II part: Maximum decline (%) in circulating tumour cells (CTC) counts[17]

End point description:

Maximum decline in CTC counts (in number of cells) compared with baseline that occurred at any point after treatment start , defined as the difference between the minimum post-baseline CTC value and the baseline CTC value. Patients with missing baseline value are considered missing for this criterion. Baseline value is the value collected before a patient starts treatment with trial medication.

Randomised Set: All randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. Only subjects with baseline CTC value were included in the analysis. Phase II part.

End point type	Secondary

End point timeframe:

Prior to study drug administration at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1 and then every 12 weeks thereafter, until end of treatment. Up to 40.1 months.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint is assessed for Phase II part only.

End point values	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	28		
Units: Percentage				
arithmetic mean (standard deviation)	41.96 (± 289.085)	21.33 (± 201.353)		

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

[All cause mortality]: Up to 430 days for Phase 1b escalation, 1107 days for Phase 1b expansion and up to 1322 days for Phase II part.
[Serious/other AE]: Up to 370 days for Phase 1b escalation, 1107 days for Phase 1b expansion, 1262 days for Phase II.

Adverse event reporting additional description:

Treated Set (TS): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1).
All-cause mortality includes all death throughout the whole study period, also including death reports after the cut-off date of the final analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

750 milligram (mg) xentuzumab (10mg/milliliter (mL)) was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib escalation part.

Reporting group title	Phase II: 160 mg Enzalutamide

Reporting group description:

Four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Phase II part.

Reporting group title	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase II part.

Reporting group title	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib escalation part.

Reporting group title	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide

Reporting group description:

1000 milligram (mg) xentuzumab (10mg/mL was supplied in 20mL vials and diluted in physiological sodium chloride solution (0.9%)) as liquid formulation was administered as weekly 1-hour intravenous (i.v.) infusion on Days 1, 8, 15 and 22 together with four liquid-filled soft gelatin capsules of 40mg (total: 160mg) enzalutamide administered orally once daily during each 28-day cycle of treatment until disease progression or occurrence of undue toxicities. Infusion duration of xentuzumab could be extended to more than 1 hour in case of infusion reaction or adverse events. Phase Ib expansion part.

Serious adverse events	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	17 / 43 (39.53%)	19 / 43 (44.19%)
number of deaths (all causes)	1	31	34
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Circulatory collapse			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 3 (33.33%)	4 / 43 (9.30%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cauda equina syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 3 (33.33%)	1 / 43 (2.33%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 3 (33.33%)	1 / 43 (2.33%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	8 / 24 (33.33%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Condition aggravated			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (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			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infusion related reaction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	2 / 7 (28.57%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypersomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (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	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteomyelitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (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 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Phase Ib escalation: 750 mg Xentuzumab + 160 mg Enzalutamide	Phase II: 160 mg Enzalutamide	Phase II: 1000 mg Xentuzumab + 160 mg Enzalutamide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	43 / 43 (100.00%)	43 / 43 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	1 / 43 (2.33%)
occurrences (all)	0	2	1
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	4 / 43 (9.30%)	3 / 43 (6.98%)
occurrences (all)	0	4	5
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	7 / 43 (16.28%)	3 / 43 (6.98%)
occurrences (all)	0	7	3
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	4 / 43 (9.30%)	2 / 43 (4.65%)
occurrences (all)	0	4	2
Pain			
subjects affected / exposed	0 / 3 (0.00%)	6 / 43 (13.95%)	3 / 43 (6.98%)
occurrences (all)	0	7	4
Peripheral swelling			
subjects affected / exposed	0 / 3 (0.00%)	3 / 43 (6.98%)	1 / 43 (2.33%)
occurrences (all)	0	6	1
Fatigue			
subjects affected / exposed	3 / 3 (100.00%)	21 / 43 (48.84%)	29 / 43 (67.44%)
occurrences (all)	13	40	50
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	11 / 43 (25.58%)	7 / 43 (16.28%)
occurrences (all)	0	22	13
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 43 (11.63%)	4 / 43 (9.30%)
occurrences (all)	0	5	4
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	0	2	1

General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	1 / 43 (2.33%)
occurrences (all)	0	2	1
Chest discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 3 (33.33%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	3	3	4
Perineal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 3 (33.33%)	2 / 43 (4.65%)	1 / 43 (2.33%)
occurrences (all)	1	2	1
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	4 / 43 (9.30%)	4 / 43 (9.30%)
occurrences (all)	1	4	4
Cough			
subjects affected / exposed	1 / 3 (33.33%)	5 / 43 (11.63%)	7 / 43 (16.28%)
occurrences (all)	1	7	8
Dysphonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 3 (0.00%)	4 / 43 (9.30%)	0 / 43 (0.00%)
occurrences (all)	0	4	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	7 / 43 (16.28%)	6 / 43 (13.95%)
occurrences (all)	0	8	6
Nightmare			
subjects affected / exposed	1 / 3 (33.33%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0

Distractibility			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	0	2	6
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 43 (6.98%)	0 / 43 (0.00%)
occurrences (all)	0	3	0
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	4 / 43 (9.30%)	2 / 43 (4.65%)
occurrences (all)	0	6	4
Weight decreased			
subjects affected / exposed	2 / 3 (66.67%)	5 / 43 (11.63%)	16 / 43 (37.21%)
occurrences (all)	2	6	20
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 43 (6.98%)	4 / 43 (9.30%)
occurrences (all)	0	6	4
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 43 (6.98%)	0 / 43 (0.00%)
occurrences (all)	0	3	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	2 / 43 (4.65%)
occurrences (all)	0	3	2
Blood calcium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	0	3	4
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Humerus fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	0	2	3
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)	4 / 43 (9.30%)	5 / 43 (11.63%)
occurrences (all)	1	4	5
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 43 (6.98%)	3 / 43 (6.98%)
occurrences (all)	0	3	3
Headache			
subjects affected / exposed	0 / 3 (0.00%)	4 / 43 (9.30%)	3 / 43 (6.98%)
occurrences (all)	0	6	5
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	4 / 43 (9.30%)
occurrences (all)	0	2	4
Neuropathy peripheral			

subjects affected / exposed	0 / 3 (0.00%)	3 / 43 (6.98%)	0 / 43 (0.00%)
occurrences (all)	0	3	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 43 (9.30%)	1 / 43 (2.33%)
occurrences (all)	0	6	2
Somnolence			
subjects affected / exposed	1 / 3 (33.33%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Taste disorder			
subjects affected / exposed	1 / 3 (33.33%)	3 / 43 (6.98%)	1 / 43 (2.33%)
occurrences (all)	1	3	1
Restless legs syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	19 / 43 (44.19%)	15 / 43 (34.88%)
occurrences (all)	1	52	57
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	3 / 43 (6.98%)
occurrences (all)	0	1	6
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	2 / 43 (4.65%)
occurrences (all)	0	1	3
Constipation			

subjects affected / exposed	1 / 3 (33.33%)	14 / 43 (32.56%)	11 / 43 (25.58%)
occurrences (all)	2	16	12
Abdominal discomfort			
subjects affected / exposed	1 / 3 (33.33%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	9 / 43 (20.93%)	9 / 43 (20.93%)
occurrences (all)	0	14	15
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	12 / 43 (27.91%)	11 / 43 (25.58%)
occurrences (all)	2	21	13
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	10 / 43 (23.26%)	10 / 43 (23.26%)
occurrences (all)	1	14	16
Dyspepsia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 43 (0.00%)	3 / 43 (6.98%)
occurrences (all)	5	0	3
Abdominal pain lower			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Anal incontinence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gingival pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 3 (33.33%)	5 / 43 (11.63%)	2 / 43 (4.65%)
occurrences (all)	2	5	2
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	2 / 43 (4.65%)	8 / 43 (18.60%)
occurrences (all)	2	2	10
Rash			
subjects affected / exposed	0 / 3 (0.00%)	6 / 43 (13.95%)	6 / 43 (13.95%)
occurrences (all)	0	7	11
Skin ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 3 (33.33%)	3 / 43 (6.98%)	3 / 43 (6.98%)
occurrences (all)	1	3	3
Urinary retention			
subjects affected / exposed	1 / 3 (33.33%)	2 / 43 (4.65%)	1 / 43 (2.33%)
occurrences (all)	1	2	2
Pollakiuria			
subjects affected / exposed	1 / 3 (33.33%)	3 / 43 (6.98%)	1 / 43 (2.33%)
occurrences (all)	3	3	1
Haematuria			
subjects affected / exposed	1 / 3 (33.33%)	1 / 43 (2.33%)	6 / 43 (13.95%)
occurrences (all)	3	1	10
Proteinuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			

Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	0	2	3
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 43 (4.65%)	5 / 43 (11.63%)
occurrences (all)	3	2	6
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	3 / 43 (6.98%)
occurrences (all)	0	1	4
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	4 / 43 (9.30%)
occurrences (all)	0	3	6
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	5 / 43 (11.63%)	2 / 43 (4.65%)
occurrences (all)	0	6	3
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	3 / 43 (6.98%)	4 / 43 (9.30%)
occurrences (all)	0	3	4
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	2 / 43 (4.65%)
occurrences (all)	0	1	2
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	6 / 43 (13.95%)	2 / 43 (4.65%)
occurrences (all)	0	9	4
Back pain			
subjects affected / exposed	1 / 3 (33.33%)	17 / 43 (39.53%)	13 / 43 (30.23%)
occurrences (all)	1	27	24
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	10 / 43 (23.26%)	7 / 43 (16.28%)
occurrences (all)	0	15	8
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	19 / 43 (44.19%)	13 / 43 (30.23%)
occurrences (all)	0	32	22
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Sacral pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	2
Infections and infestations			
Viral infection			
subjects affected / exposed	1 / 3 (33.33%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	1	2	0
Urinary tract infection			
subjects affected / exposed	2 / 3 (66.67%)	5 / 43 (11.63%)	3 / 43 (6.98%)
occurrences (all)	3	7	5
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 43 (2.33%)	6 / 43 (13.95%)
occurrences (all)	0	1	7
Oral candidiasis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 43 (2.33%)	2 / 43 (4.65%)
occurrences (all)	2	1	2
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	5 / 43 (11.63%)	4 / 43 (9.30%)
occurrences (all)	1	5	6
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	3 / 43 (6.98%)	3 / 43 (6.98%)
occurrences (all)	0	4	3
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Infected skin ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	1	2	0
Hyponatraemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	1	3	8
Hypokalaemia			

subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	0	3	16
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	0	3	3
Decreased appetite			
subjects affected / exposed	3 / 3 (100.00%)	26 / 43 (60.47%)	26 / 43 (60.47%)
occurrences (all)	6	35	43

Non-serious adverse events	Phase Ib escalation: 1000 mg Xentuzumab + 160 mg Enzalutamide	Phase Ib expansion: 1000 mg Xentuzumab + 160 mg Enzalutamide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	24 / 24 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	13	
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	5 / 7 (71.43%)	9 / 24 (37.50%)	
occurrences (all)	22	15	

Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	7	
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
General physical health deterioration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Perineal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Cough			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Dysphonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

Depressed mood			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Insomnia			
subjects affected / exposed	3 / 7 (42.86%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Nightmare			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Distractibility			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	8	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
White blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	2 / 7 (28.57%)	4 / 24 (16.67%)	
occurrences (all)	2	5	
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood calcium decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	5	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 7 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	1	4	
Fall			
subjects affected / exposed	1 / 7 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	5	6	
Infusion related reaction			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	5	
Humerus fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	5 / 24 (20.83%)	
occurrences (all)	0	6	
Dysgeusia			

subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 7 (14.29%)	6 / 24 (25.00%)	
occurrences (all)	1	7	
Lethargy			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Taste disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Hypoaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	4 / 24 (16.67%)	
occurrences (all)	7	5	
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	4	4	

Lymphadenopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	5 / 7 (71.43%)	5 / 24 (20.83%)	
occurrences (all)	8	5	
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	3 / 7 (42.86%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	3 / 24 (12.50%)	
occurrences (all)	2	5	
Nausea			
subjects affected / exposed	4 / 7 (57.14%)	8 / 24 (33.33%)	
occurrences (all)	6	11	
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	3 / 24 (12.50%)	
occurrences (all)	4	3	
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Abdominal pain lower			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Anal incontinence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Dry mouth			

subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Rash			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	1	3	
Skin ulcer			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Pollakiuria			

subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Haematuria			
subjects affected / exposed	1 / 7 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	3	4	
Proteinuria			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	2 / 7 (28.57%)	2 / 24 (8.33%)	
occurrences (all)	2	3	
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	2	4	
Muscular weakness			
subjects affected / exposed	2 / 7 (28.57%)	3 / 24 (12.50%)	
occurrences (all)	2	3	
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	4	
Groin pain			
subjects affected / exposed	0 / 7 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	6	
Bone pain			
subjects affected / exposed	1 / 7 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Back pain			

subjects affected / exposed	3 / 7 (42.86%)	12 / 24 (50.00%)	
occurrences (all)	6	21	
Pain in extremity			
subjects affected / exposed	2 / 7 (28.57%)	6 / 24 (25.00%)	
occurrences (all)	2	7	
Arthralgia			
subjects affected / exposed	4 / 7 (57.14%)	14 / 24 (58.33%)	
occurrences (all)	5	17	
Flank pain			
subjects affected / exposed	2 / 7 (28.57%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Sacral pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	4 / 24 (16.67%)	
occurrences (all)	2	5	
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Lower respiratory tract infection			
subjects affected / exposed	2 / 7 (28.57%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Infected skin ulcer			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 24 (0.00%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	7	
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)	9 / 24 (37.50%)	
occurrences (all)	5	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2014	Amendment 1: At the request of the Medicines and Healthcare products Regulatory Agency (MHRA), the option of de-escalation of the enzalutamide dose in Phase 1b was removed. Furthermore, the use of contraception for patients and their partners during the study was clarified and expanded. This amendment was issued before the first patient was recruited for the trial. The amendment was implemented after approval of the Institutional review board (IRB)/ (Independent ethics committee) IEC/ Competent Authorities.
20 March 2015	Amendment 2 (Part 1): This amendment was issued before commencing the Phase Ib expansion part and the Phase II part of the trial. It was implemented after approval of the IRB/IEC/Competent Authorities. To bring the Phase Ib expansion part in line with US practice, patients entering the expansion cohort were no longer allowed to have received prior taxane therapy. Furthermore, several inclusion/exclusion criteria were updated. Reasons were the change of the patient population in the expansion cohort, updating according to the current enzalutamide Summary of product characteristics (SmPC), and site feedback. Bone scans were made mandatory at screening, and should then be followed up every 12 weeks if clinically indicated. In the previous version of the protocol bone scans were only required at screening if clinically indicated. The requirement for an additional Computed tomography (CT) scan 6 weeks later to confirm progression was removed if progression was seen at the first tumour assessment. This update was in line with RECIST 1.1 requirements.
20 March 2015	Amendment 2 (Part 2): The requirements for fresh tissue biopsies changed. From this point onwards, they were only mandatory at baseline and Cycle 1 Day 15 and then optional at End of treatment (EOT) for the Phase Ib expansion cohort and optional at all time points in Phase II. This was changed to allow more flexibility for patients. An additional blood sample was added at Cycle 4 Day 1 to collect circulating DNA. The handling of restricted medications was updated in line with the current enzalutamide SmPC. Originally, the Clinical Trial Protocol (CTP) contained an exhaustive list of CYP inducers/inhibitors and substrates and investigators needed to get approval from Boehringer Ingelheim (BI) to keep patient on one of these medications. The CTP was updated to refer investigators to the enzalutamide SmPC to make a decision on whether a patient should stay on any medications involving the CYP pathway. After elective surgery, patients were now allowed to restart treatment within 3 d as there had not been concern with wound healing following treatment with xentuzumab. The quality of life questionnaire Functional Assessment of Cancer Therapy-Prostate (FACT-P) was added to the Phase II part of the trial at several time points as it was considered important to collect this data to compare quality of life between the two treatment arms.

09 April 2015	Amendment 3: Exclusion criterion no. 22 was re-written by Amendment 2 (formerly exclusion criterion no. 1) as the original wording in the CTP was considered unclear. In error the new language was worded as an inclusion criterion rather than an exclusion criterion. This was corrected by Amendment 3. This amendment was issued before commencing the Phase Ib expansion part and the Phase II part of the trial. The amendment was implemented after approval of the IRB/IEC/Competent Authorities.
15 September 2015	Amendment 4 (Part 1): This amendment was issued before commencing the Phase Ib expansion part and the Phase II part of the trial. It was implemented after approval of the IRB/IEC/Competent Authorities. The primary endpoint of the Phase II part was changed from Progression-free survival (PFS) assessed by central imaging to PFS assessed by investigator. The change was based on data available from the Phase Ib dose escalation part of the trial as well as feedback on the discrepancy seen between central imaging and investigator assessment in other prostate cancer trials. This raised concern that the planned number of 90 PFS events might not be met. As this was a Phase II trial, PFS assessed by central imaging was not required as a primary endpoint. PFS assessed by central imaging was made a secondary endpoint. The frequency of the imaging assessments, both CT/Magnetic resonance imaging (MRI) and bone scans was changed from being at baseline and thereafter every 12 weeks to baseline and then every 8 weeks until Week 24 (Week 8, Week 16, Week 24) and then every 12 weeks thereafter. This change was implemented based on data showing the PFS for this type of patient is around 3-5 months and therefore it was important to be able to capture any early progressions. Circulating tumour cells (CTC), Prostate-specific antigen (PSA) and FACT-P assessments were amended in line with the imaging assessments so that efficacy assessments were performed at the same time points.

15 September 2015	Amendment 4 (Part 2): Inclusion criterion no. 6 was changed to only allow patients with Eastern Cooperative Oncology Group (ECOG) 0 and 1 in the trial and no longer allow patients with ECOG 2. The rationale for this change was that patients should be fit enough to manage weekly infusions and be able to stay on treatment for long enough to potentially receive benefit. To avoid unnecessary Serious adverse event (SAE) reporting, it was added that an adverse event (AE) did not meet the SAE criteria for hospitalization if the patient was treated in the emergency room but was not admitted for an overnight stay, if they were hospitalized for diagnostic reasons without AE, or if the hospitalization was due to pre-planned treatments or procedures, social circumstances, or administrative reasons. For the same reason, an exemption was added so that disease progression unrelated to treatments no longer needed to be reported. These changes were implemented according to updated company standards. The section on the primary analysis was updated to allow analysis to be performed in the case that 90 radiological progression events are not reached. If it became foreseeable that 90 PFS events would not be reached, analysis for PFS was to be performed around 23 months after the first patient had been randomised in the Phase II part. The scheduling of the pharmacogenomic sample was changed and an additional sample was added at Cycle 3 Day 1. For this protocol version, a note to file was issued to document an error in an appendix table showing the time points of Pharmacokinetics (PK) and biomarker sample collection. The correct information was available in the flow chart and the main part of the clinical trial report (CTR) as well as in the laboratory manual and PK/ Pharmacodynamics (PD) worksheets that were distributed to the investigational sites.
19 November 2015	Amendment 5: Based on feedback from the FDA, two changes were implemented: Firstly, the number of patients in the Phase Ib expansion part was changed from at least 21 to 25 to ensure that 21 evaluable patients would be available for analysis. And secondly, an exclusion criterion was added for the Phase Ib expansion part to exclude patients who were in immediate need of chemotherapy (e.g. for visceral disease, or intractable pain). The amendment was implemented after approval of the IRB/IEC/Competent Authorities.
31 May 2016	Amendment 6: Due to new statistical estimations, a project level decision, and new project standards, the number of patients in the Phase II part was changed from 120 to 80 with the number of targeted PFS events decreased from 90 to 60 events. Furthermore, in- and exclusion criteria were updated to address changes in PSA and international normalised ratio (INR) value requirements. Luteinizing hormone releasing hormone (LHRH) antagonists were added as an accepted concomitant treatment during the trial. The amendment was implemented after approval of the IRB/IEC/Competent Authorities.
06 February 2018	Amendment 7: This amendment involved logistical or administrative aspects only. It was implemented without IRB/IEC/Competent Authority approval.

15 July 2019	Amendment 8: Amendment 8 was issued when all data required to achieve the trial objectives had been collected. The amount of procedures and data collected was reduced: procedures were limited to those necessary to continue with trial treatment; data collection was limited to those data necessary to ensure patient safety and to support safety reporting to authorities. However, CTP version 9 (based on Amendment 8) was rejected by a health authority because, as patients were on experimental therapy, the safety laboratory tests should be clearly defined in the CTP rather than being per standard of care. CTP Version 9 was therefore not implemented by any sites with ongoing patients.
13 September 2019	Amendment 9: Instead the CTP was updated to Version 10 (based on Amendment 9) to include safety lab testing on Day 1 of every cycle, at EOT, and at the follow-up visit for all patients ongoing on trial treatment.
11 August 2020	Amendment 10: CTP updated to provide additional guidance in response to the COVID-19 pandemic to ensure patient's safety by decreasing patient visits to site if needed by permitting direct shipment of enzalutamide from site to patient, local safety lab analyses and remote patient visits.
06 June 2022	Amendment 11: CTP updated to include the rationale for discontinuation of the clinical development program with xentuzumab in Castration-resistant prostate cancer (CRPC), including how the trial would proceed towards termination.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported