Clinical trial results:
A Phase III, Multicenter, Randomized Study of Atezolizumab (Anti-Pd-L1 Antibody) in Combination with Enzalutamide Versus Enzalutamide Alone in Patients with Metastatic Castration-Resistant Prostate Cancer After Failure of an Androgen Synthesis Inhibitor and Failure of, Ineligibility for, or Refusal of a Taxane Regimen.

Summary

EudraCT number	2016-003092-22
Trial protocol	HU CZ DK DE AT GB ES PL BE GR FR IT
Global end of trial date	20 December 2022

Results information

Result version number	v1 (current)
This version publication date	29 December 2023
First version publication date	29 December 2023

Trial information

Trial identification

Sponsor protocol code	CO39385

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, Roche Trial Information Hotline, +41 61 6878333,
Scientific contact	Medical Communications, Hoffmann-La Roche, +41 800 8218590, genentech@druginfo.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the safety and efficacy of atezolizumab in combination with enzalutamide compared with enzalutamide alone in patients with mCRPC after failure of an androgen
synthesis inhibitor (e.g., abiraterone) and failure of,
ineligibility for, or refusal of a taxane regimen.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) guidelines according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2017
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	Australia: 30
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Canada: 50
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	China: 42
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Spain: 99
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	United Kingdom: 38
Country: Number of subjects enrolled	Greece: 27
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Japan: 49
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 9
Country: Number of subjects enrolled	Poland: 81
Country: Number of subjects enrolled	Russian Federation: 33

Country: Number of subjects enrolled	Taiwan: 29
Country: Number of subjects enrolled	United States: 136
Worldwide total number of subjects	759
EEA total number of subjects	338

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)	187
From 65 to 84 years	534
85 years and over	38

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study recruited predefined subject population as per inclusion and exclusion criteria

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Atezolizumab + Enzalutamide

Arm description:

Participants received atezolizumab along with enzalutamide until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab and Enzalutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Solution for injection
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Atezolizumab along with enzalutamide until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity.

Arm title	Enzalutamide

Arm description:

Participants received enzalutamide alone until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Enzalutamide alone until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity.

Number of subjects in period 1	Atezolizumab + Enzalutamide	Enzalutamide
Started	379	380
Completed	17	10
Not completed	362	370
Adverse event, serious fatal	210	184
Terminated by the Sponsor	100	126
Physician decision	1	3
Consent withdrawn by subject	37	44
Lost to follow-up	12	12
Started new therapy, loss of contact	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Atezolizumab + Enzalutamide
Reporting group description:	
Participants received atezolizumab along with enzalutamide until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity.	
Reporting group title	Enzalutamide
Reporting group description:	
Participants received enzalutamide alone until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity.	

Reporting group values	Atezolizumab + Enzalutamide	Enzalutamide	Total
Number of subjects	379	380	759
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	97	90	187
>=65 years	282	290	572
Age Continuous Units: Years			
arithmetic mean	70.3	70.6	
standard deviation	± 8.3	± 8.5	-
Sex: Female, Male Units: Participants			
Female	0	0	0
Male	379	380	759
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	71	65	136
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	7	7	14
White	279	287	566
More than one race	2	0	2
Unknown or Not Reported	19	20	39
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	18	11	29
Not Hispanic or Latino	337	345	682
Unknown or Not Reported	24	24	48

End points

End points reporting groups

Reporting group title	Atezolizumab + Enzalutamide
Reporting group description:	
Participants received atezolizumab along with enzalutamide until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity.	
Reporting group title	Enzalutamide
Reporting group description:	
Participants received enzalutamide alone until investigator-assessed confirmed radiographic disease progression per PCWG3 criteria or unacceptable toxicity.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall Survival is defined as the time from randomization to death from any cause.	
End point type	Primary
End point timeframe:	
Baseline until death from any cause (up to approximately 42 months)	

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	380		
Units: Months				
median (confidence interval 95%)	15.2 (14.0 to 17.0)	16.6 (14.7 to 18.4)		

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description:	
Stratified Analysis	
Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide
Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2786
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.118

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.913
upper limit	1.37

Statistical analysis title	Overall Survival (OS)
Statistical analysis description:	
Unstratified Analysis	
Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide
Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.094
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.184
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.971
upper limit	1.445

Secondary: Percentage of Participants who Survived at Month 6 and 12

End point title	Percentage of Participants who Survived at Month 6 and 12
End point description:	
OS (Overall Survival is defined as the time from randomization to death from any cause) probability at 6 and 12 months	
End point type	Secondary
End point timeframe:	
Months 6, 12	

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	380		
Units: Percentage of Participants				
number (confidence interval 95%)				
6 Months	85.12 (81.45 to 88.78)	85.32 (81.67 to 88.97)		
12 Months	60.61 (55.52 to 65.71)	64.65 (59.60 to 69.70)		

Statistical analyses

Statistical analysis title	Percentage of Overall survival
Statistical analysis description:	
Difference in Event Free Rate - 6 months	
Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide
Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9391
Method	z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.38
upper limit	4.97

Secondary: Time to First Symptomatic Skeletal Event (SSE)

End point title	Time to First Symptomatic Skeletal Event (SSE)
End point description:	
An SSE is defined as external beam radiation therapy to relieve skeletal symptoms (including initiation of radium-223 dichloride or other types of radionuclide therapy to treat symptoms of bone metastases), new symptomatic pathologic bone fracture, clinically apparent occurrence of spinal cord compression, or tumor related orthopedic surgical intervention. 9999 value represents Not Available data	
End point type	Secondary
End point timeframe:	
Baseline up to end of study (up to approximately 42 months)	

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	380		
Units: Months				
median (confidence interval 95%)	24.1 (24.1 to 9999)	24.9 (24.9 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic Progression-Free Survival (rPFS), as Assessed by the Investigator and Adapted From the PCWG3 Criteria

End point title	Radiographic Progression-Free Survival (rPFS), as Assessed by the Investigator and Adapted From the PCWG3 Criteria

End point description:

rPFS is defined as the time from randomization to the earliest occurrence of one of the following:
- A participant is considered to have progressed by bone scan if: The first bone scan with ≥2 new lesions compared to baseline is observed < 12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared to baseline); the date of progression is the date of the first post-treatment scan, OR After the first post-treatment scan, ≥2 new lesions are observed relative to the first post-treatment scan, which is confirmed on a subsequent scan ≥6 weeks later; the date of progression is the date of the post-treatment scan when ≥2 new lesions were first documented.
- Progression of soft tissue lesions, as defined per PCWG3 modified RECIST v1.1
- Death from any cause

End point type	Secondary

End point timeframe:

Baseline until disease progression or death from any cause (up to approximately 42 months)

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	380		
Units: Months				
median (confidence interval 95%)	4.2 (4.1 to 5.3)	4.1 (3.7 to 4.5)		

Statistical analyses

Statistical analysis title	r-Progression free survival

Statistical analysis description:

Unstratified Analysis

Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide
Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3157
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.775
upper limit	1.086

Statistical analysis title	OS
Statistical analysis description:	
Stratified Analysis	
Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide
Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2366
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.899
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.754
upper limit	1.072

Secondary: Percentage of Participants With Greater Than (>) 50 Percent (%) Decrease in Prostate-Specific Antigen (PSA) From Baseline

End point title	Percentage of Participants With Greater Than (>) 50 Percent (%) Decrease in Prostate-Specific Antigen (PSA) From Baseline
End point description:	
PSA response rate, defined as a > 50% decrease in PSA from baseline that is confirmed after ≥ 3 weeks by a consecutive confirmatory PSA measurement	
End point type	Secondary
End point timeframe:	
Baseline until disease progression (up to approximately 42 months)	

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	380		
Units: Percentage of Participants				
number (confidence interval 95%)	25.9 (21.5 to 30.5)	24.2 (20.0 to 28.7)		

Statistical analyses

Statistical analysis title	With >50% Decrease in PSA From Baseline
Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide

Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in 50% Decrease Response Rate
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	7.8

Secondary: Percentage of Participants Who are Radiographic Progression-Free, as Assessed by the Investigator and Adapted From the PCWG3 Criteria

End point title	Percentage of Participants Who are Radiographic Progression-Free, as Assessed by the Investigator and Adapted From the PCWG3 Criteria

End point description:

rPFS is defined as the time from randomization to the earliest occurrence of one of the following:
- A participant is considered to have progressed by bone scan if: The first bone scan with ≥2 new lesions compared to baseline is observed < 12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared to baseline); the date of progression is the date of the first post-treatment scan, OR After the first post-treatment scan, ≥2 new lesions are observed relative to the first post-treatment scan, which is confirmed on a subsequent scan ≥6 weeks later; the date of progression is the date of the post-treatment scan when ≥2 new lesions were first documented.
- Progression of soft tissue lesions, as defined per PCWG3 modified RECIST v1.1
- Death from any cause

End point type	Secondary

End point timeframe:

Months 6, 12

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	380		
Units: Percentage of Participants				
number (confidence interval 95%)				
6 months	41.84 (36.09 to 47.60)	39.64 (33.86 to 45.42)		
12 months	14.89 (10.74 to 19.05)	13.45 (9.42 to 17.49)		

Statistical analyses

Statistical analysis title	Percentage of r- progression free survival

Statistical analysis description:

Difference in Event Free Rate - 12 months

Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide

Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6262
Method	z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.35
upper limit	7.23

Statistical analysis title	Radiographic progression free survival
Statistical analysis description:	
Difference in Event Free Rate - 6 months	
Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide
Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5959
Method	z-test
Parameter estimate	Difference in Event Free Rate
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.95
upper limit	10.37

Secondary: Percentage of Participant With Objective Response, as Determined by the Investigator Through use of PCWG3 Criteria

End point title	Percentage of Participant With Objective Response, as Determined by the Investigator Through use of PCWG3 Criteria
End point description:	
Objective response rate in soft tissue lesions, defined as the percentage of participants with either a CR or PR on two consecutive occasions ≥ 6 weeks apart, as determined by the investigator through use of PCWG3 criteria	
End point type	Secondary
End point timeframe:	
Baseline until disease progression or death from any cause (up to approximately 42 months)	

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: Percentage of Participants				
number (confidence interval 95%)	13.7 (8.4 to 20.7)	7.4 (3.7 to 13.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA Progression, Assessed as per PCWG3 Criteria

End point title	Time to PSA Progression, Assessed as per PCWG3 Criteria

End point description:

In participants with no PSA decline from baseline, PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the baseline value, ≥12 weeks after baseline. In participants with an initial PSA decline from baseline, PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir value, which is confirmed by a consecutive second value obtained ≥3 weeks later.

End point type	Secondary

End point timeframe:

Baseline until disease progression (up to approximately 42 months)

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379	380		
Units: Months				
median (confidence interval 95%)	2.8 (2.8 to 2.9)	2.8 (2.8 to 2.9)		

Statistical analyses

Statistical analysis title	Time to PSA Progression

Statistical analysis description:

Stratified Analysis

Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide
Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6857
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.037

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.869
upper limit	1.238

Statistical analysis title	Time to PSA Progression
Statistical analysis description:	
Unstratified Analysis	
Comparison groups	Atezolizumab + Enzalutamide v Enzalutamide
Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5359
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.251

Secondary: Percentage of Participants With Adverse Events	
End point title	Percentage of Participants With Adverse Events
End point description:	
Verbatim description of adverse events will be coded to MedDRA preferred terms and graded according to NCI CTCAE v4.0.	
End point type	Secondary
End point timeframe:	
Baseline up to end of study (up to approximately 42 month)	

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	374	376		
Units: Percentage of Participants				
number (not applicable)				
Participants with at least one adverse event	96.8	92.3		
Participants with at least 1 treatment AE	78.1	51.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Atezolizumab

End point title	Minimum Observed Serum Concentration (Cmin) of Atezolizumab

End point description:

Atezolizumab serum concentration data (minimum [Cmin]) will be reported and summarized for each cycle where collected as appropriate. 9999 value represents Not Available data

End point type	Secondary

End point timeframe:

Pre-infusion (0 hour[hr]) on Day 1 Cycles 1, 2, 3, 4, 8, 12, 16 (Cycle length: 21 days); treatment discontinuation visit, 120 days after last dose (up to approximately 42 months)

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	376		
Units: microgram/mL				
number (not applicable)				
Cycle 1, Day 1, pre-dose	9999	9999		
Cycle 1, Day 1, 30 min post-dose	160	9999		
Cycle 2, Day 1, pre-dose	0.0300	9999		
Cycle 3, Day 1, pre-dose	0.0300	9999		
Cycle 4, Day 1, pre-dose	3.46	9999		
Cycle 8, Day 1, pre-dose	0.0300	9999		
Cycle 12, Day 1, pre-dose	0.0300	9999		
Cycle 16, Day 1, pre-dose	0.0300	9999		
Safety visit	0.0300	9999		
Study Completion/Early Discontinuation	0.0300	9999		
Study Completion/Early Discontinuation pre-dose	35.2	9999		
Unscheduled	50.5	9999		
Unscheduled Predose	4.24	9999		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Atezolizumab

End point title	Maximum Observed Serum Concentration (Cmax) of Atezolizumab

End point description:

Atezolizumab serum concentration data (maximum [Cmax]) will be reported and summarized for each cycle where collected as appropriate. 9999 value represents Not Available data

End point type	Secondary

End point timeframe:

Pre-infusion (0 hr) on Day 1 Cycles 1, 2, 3, 4, 8, 12, 16 (Cycle length: 21 days); 0.5 hr post-infusion

(infusion duration: 60 minutes [min]) on Day 1 Cycle 1; treatment discontinuation visit, 120 days after last dose (up to approximately 42 months)

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	376		
Units: Microgram/mL				
number (not applicable)				
Cycle 1, Day 1, pre-dose	0	9999		
Cycle 1, Day 1, 30 min post-dose	1420	9999		
Cycle 2, Day 1, pre-dose	637	9999		
Cycle 3, Day 1, pre-dose	643	9999		
Cycle 4, Day 1, pre-dose	941	9999		
Cycle 8, Day 1, pre-dose	832	9999		
Cycle 12, Day 1, pre-dose	534	9999		
Safety visit	72.1	9999		
Study Completion/Early Discontinuation	391	9999		
Study Completion/Early Discontinuation pre-dose	121	9999		
Unscheduled	50.5	9999		
Unscheduled pre-dose	146	9999		
Cycle 16, Day 1, pre-dose	465	9999		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Enzalutamide

End point title	Plasma Concentration of Enzalutamide

End point description:

Plasma concentrations of Enzalutamide will be reported and summarized using descriptive statistics for each cycle and treatment arm, as appropriate. 9999 value represents Not Available data

End point type	Secondary

End point timeframe:

Predose (0 hr) and 1 hr postdose on Day 1 Cycle 1 and 3 (Cycle length: 21 days); pre-dose (within 1 hr) on Day 1 Cycle 8

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	137		
Units: Microgram/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 Predose	9999 (± 9999)	9999 (± 9999)		

Cycle 1 Day 1 1 Hr Post	2.69 (± 1.61)	3.86 (± 2.86)		
Cycle 3 Day 1 Predose	13.6 (± 3.41)	14.0 (± 2.82)		
Cycle 3 Day 1 1 Hr Post	14.7 (± 3.47)	16.3 (± 3.13)		
Cycle 8 Day 1 Predose	12.8 (± 3.62)	13.1 (± 3.40)		
Unscheduled Predose	9999 (± 9999)	10.5 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of N-Desmethyl Enzalutamide

End point title	Plasma Concentration of N-Desmethyl Enzalutamide

End point description:

Plasma concentrations of N-Desmethyl Enzalutamide will be reported and summarized using descriptive statistics for each cycle and treatment arm, as appropriate. 9999 value represents Not Available data

End point type	Secondary

End point timeframe:

Predose (0 hr) and 1 hr postdose on Day 1 Cycle 1 and 3 (Cycle length: 21 days); pre-dose (within 1 hr) on Day 1 Cycle 8

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141[1]	137		
Units: Microgram/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 Predose	9999 (± 9999)	9999 (± 9999)		
Cycle 1 Day 1 1 Hr Post	9999 (± 9999)	9999 (± 9999)		
Cycle 3 Day 1 Predose	11.9 (± 3.75)	12.3 (± 3.20)		
Cycle 3 Day 1 1 Hr Post	11.1 (± 3.55)	11.3 (± 3.13)		
Cycle 8 Day 1 Predose	13.6 (± 4.68)	13.8 (± 4.86)		
Unscheduled Predose	9999 (± 9999)	13.3 (± 9999)		

Notes:

[1] - 9999 value represents Not Available data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Drug Antibodies (ADAs) to Atezolizumab

End point title	Number of Participants With Anti-Drug Antibodies (ADAs) to Atezolizumab

End point description:

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized by treatment group.

End point type	Secondary

End point timeframe:

Predose (0 hr) on Day 1 Cycles 1, 2, 3, 4, 8, 12, 16 (Cycle length: 21 days); at atezolizumab discontinuation visit (30 days after last dose); 120 days after last dose of atezolizumab; up to 42 months

End point values	Atezolizumab + Enzalutamide	Enzalutamide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	379[2]	380[3]		
Units: Number of Participants				
number (not applicable)				
With Positive Sample at Baseline	2	9999		
Without Positive Sample at Baseline	368	9999		
Positive ADA treatment induced	52	9999		
Positive ADA: treatment enhanced	0	9999		
Patients with no positive samples at baseline	368	9999		
Post-baseline evaluable patients	372	9999		
Participants negative for Treatment Emergent ADA	52	9999		
Negative ADA treatment induced	52	9999		
Negative ADA treatment enhanced	0	9999		
Patients negative for Treatment Emergent ADA	320	9999		
Negative ADA Treatment unaffected	2	9999		

Notes:

[2] - ITT population 386 analyzed

[3] - ITT population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline to Up To 4 years and 11 Months	
Adverse event reporting additional description:	
ATEZOLIZUMAB + ENZALUTAMIDE and ENZALUTAMIDE Arms	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	ENZALUTAMIDE
Reporting group description:	
ENZALUTAMIDE	
Reporting group title	ATEZOLIZUMAB + ENZALUTAMIDE
Reporting group description:	
ATEZOLIZUMAB + ENZALUTAMIDE	

Serious adverse events	ENZALUTAMIDE	ATEZOLIZUMAB + ENZALUTAMIDE	
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 376 (23.14%)	139 / 374 (37.17%)	
number of deaths (all causes)	191	219	
number of deaths resulting from adverse events	1	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	1 / 376 (0.27%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour rupture			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Bladder neoplasm surgery			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 376 (0.53%)	5 / 374 (1.34%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 376 (0.27%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication of device insertion			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	2 / 376 (0.53%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fatigue			
subjects affected / exposed	3 / 376 (0.80%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	1 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 376 (0.53%)	6 / 374 (1.60%)	
occurrences causally related to treatment / all	0 / 7	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unevaluable event			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypercapnia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 376 (0.53%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary embolism			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Respiratory arrest			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pleuritic pain			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 376 (0.27%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			

subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 376 (0.27%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 376 (0.27%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 376 (0.53%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Autoimmune myocarditis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 376 (0.53%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			

subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 376 (0.53%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	1 / 376 (0.27%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cranial nerve palsies multiple			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	2 / 376 (0.53%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenic syndrome			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Paraesthesia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			

subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Heparin-induced thrombocytopenia			

subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	11 / 376 (2.93%)	9 / 374 (2.41%)	
occurrences causally related to treatment / all	1 / 15	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Uveitis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			

subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal ulcer			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 376 (0.53%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 376 (0.53%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 376 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 376 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 376 (0.27%)	5 / 374 (1.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haematuria			
subjects affected / exposed	5 / 376 (1.33%)	7 / 374 (1.87%)	
occurrences causally related to treatment / all	0 / 7	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 376 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			

subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 376 (0.53%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	5 / 376 (1.33%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 376 (0.53%)	7 / 374 (1.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 376 (0.00%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			

subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 376 (0.00%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neck pain			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torticollis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	4 / 376 (1.06%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	10 / 376 (2.66%)	10 / 374 (2.67%)	
occurrences causally related to treatment / all	0 / 13	3 / 10	
deaths causally related to treatment / all	0 / 3	1 / 2	
Nosocomial infection			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 376 (0.27%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infected cyst			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 376 (0.27%)	2 / 374 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 376 (0.27%)	4 / 374 (1.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 376 (0.53%)	3 / 374 (0.80%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 376 (0.00%)	1 / 374 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 376 (0.27%)	0 / 374 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ENZALUTAMIDE	ATEZOLIZUMAB + ENZALUTAMIDE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	309 / 376 (82.18%)	339 / 374 (90.64%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 376 (5.85%)	27 / 374 (7.22%)	
occurrences (all)	22	33	
Hot flush			
subjects affected / exposed	21 / 376 (5.59%)	11 / 374 (2.94%)	
occurrences (all)	23	11	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 376 (2.39%)	31 / 374 (8.29%)	
occurrences (all)	9	37	
Pain			
subjects affected / exposed	13 / 376 (3.46%)	24 / 374 (6.42%)	
occurrences (all)	13	26	
Oedema peripheral			
subjects affected / exposed	28 / 376 (7.45%)	33 / 374 (8.82%)	
occurrences (all)	31	38	
Fatigue			
subjects affected / exposed	103 / 376 (27.39%)	128 / 374 (34.22%)	
occurrences (all)	116	148	
Asthenia			
subjects affected / exposed	63 / 376 (16.76%)	82 / 374 (21.93%)	
occurrences (all)	68	99	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	17 / 376 (4.52%)	24 / 374 (6.42%)	
occurrences (all)	19	26	
Cough			
subjects affected / exposed	17 / 376 (4.52%)	21 / 374 (5.61%)	
occurrences (all)	18	22	

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	29 / 376 (7.71%) 30	29 / 374 (7.75%) 29	
Investigations Weight decreased subjects affected / exposed occurrences (all)	32 / 376 (8.51%) 33	51 / 374 (13.64%) 54	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	19 / 376 (5.05%) 27	21 / 374 (5.61%) 26	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	19 / 376 (5.05%) 21 21 / 376 (5.59%) 27	31 / 374 (8.29%) 34 26 / 374 (6.95%) 31	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	49 / 376 (13.03%) 58	83 / 374 (22.19%) 98	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	32 / 376 (8.51%) 35 66 / 376 (17.55%) 73 41 / 376 (10.90%) 51 62 / 376 (16.49%) 65	31 / 374 (8.29%) 35 86 / 374 (22.99%) 95 86 / 374 (22.99%) 109 78 / 374 (20.86%) 88	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	10 / 376 (2.66%)	51 / 374 (13.64%)	
occurrences (all)	10	59	
Pruritus			
subjects affected / exposed	8 / 376 (2.13%)	36 / 374 (9.63%)	
occurrences (all)	8	43	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	5 / 376 (1.33%)	21 / 374 (5.61%)	
occurrences (all)	5	22	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	39 / 376 (10.37%)	26 / 374 (6.95%)	
occurrences (all)	46	32	
Musculoskeletal chest pain			
subjects affected / exposed	15 / 376 (3.99%)	21 / 374 (5.61%)	
occurrences (all)	16	25	
Bone pain			
subjects affected / exposed	34 / 376 (9.04%)	27 / 374 (7.22%)	
occurrences (all)	38	31	
Back pain			
subjects affected / exposed	55 / 376 (14.63%)	80 / 374 (21.39%)	
occurrences (all)	63	98	
Arthralgia			
subjects affected / exposed	64 / 376 (17.02%)	80 / 374 (21.39%)	
occurrences (all)	94	108	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	18 / 376 (4.79%)	20 / 374 (5.35%)	
occurrences (all)	21	24	
Nasopharyngitis			
subjects affected / exposed	21 / 376 (5.59%)	13 / 374 (3.48%)	
occurrences (all)	24	15	
Upper respiratory tract infection			
subjects affected / exposed	14 / 376 (3.72%)	19 / 374 (5.08%)	
occurrences (all)	15	21	

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 104 / 376 (27.66%) 120	 115 / 374 (30.75%) 129	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2017	V2
04 April 2017	V3
29 June 2017	V4
02 March 2018	V5
23 August 2018	V6
05 August 2019	V7
14 February 2020	V8

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported