Clinical trial results:
A Phase 2, Single-Arm, Open-Label, Multicenter Study of the Clinical Activity and Safety of Enzalutamide in Subjects With Advanced, Androgen Receptor-Positive, Triple-Negative Breast Cancer.

Summary

EudraCT number	2013-000698-57
Trial protocol	GB BE IT IE ES
Global end of trial date	10 January 2024

Results information

Result version number	v2 (current)
This version publication date	04 December 2024
First version publication date	11 August 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	C3431007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01889238
WHO universal trial number (UTN)	-
Other trial identifiers	Alias identifier: MDV3100-11

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	66 East Hudson boulevard, New York, United States, NY 1001
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	15 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the clinical benefit rate, defined as the proportion of evaluable subjects with androgen receptor positive (AR+) triple negative breast cancer (TNBC) with a best response of complete response (CR), partial response (PR), or stable disease (SD) greater than or equal (>=) 16 weeks.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United States: 74
Worldwide total number of subjects	118
EEA total number of subjects	26

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)	74
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Total of 118 subjects with advanced AR+ and TNBC were enrolled in this study.

Pre-assignment

Screening details:

Subjects were enrolled at total of 34 study sites in North America and Europe to attain total of 78 evaluable subjects.

Period 1

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

Arms

Arm title	Enzalutamide

Arm description:

Subjects received enzalutamide 160 milligram (mg) (as four 40 mg soft gelatin capsules), orally once daily until disease progression (DP), intolerable adverse events (AEs) (including any seizures), noncompliance with protocol requirements, initiation of a new antitumor treatment, or subject or physician decision to discontinue treatment or death due to any cause.

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

Dosage and administration details:

Enzalutamide 160 mg was administered as four 40-mg soft gelatin capsules orally once daily.

Number of subjects in period 1	Enzalutamide
Started	118
Completed	0
Not completed	118
Consent withdrawn by subject	1
Adverse event, non-fatal	6
Death	1
Unspecified	6
Disease Progression	104

Baseline characteristics

Reporting groups	
Reporting group title	Enzalutamide
Reporting group description:	
Subjects received enzalutamide 160 milligram (mg) (as four 40 mg soft gelatin capsules), orally once daily until disease progression (DP), intolerable adverse events (AEs) (including any seizures), noncompliance with protocol requirements, initiation of a new antitumor treatment, or subject or physician decision to discontinue treatment or death due to any cause.	

Reporting group values	Enzalutamide	Total	
Number of subjects	118	118	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	74	74	
From 65-84 years	44	44	
85 years and over	0	0	
Age Continuous			
Age Continuous is provided for treated subjects only			
Units: years			
arithmetic mean	58.3		
standard deviation	± 12.95	-	
Sex: Female, Male Units: Subjects			
Female	118	118	
Male	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	6	6	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	20	20	
White	91	91	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	108	108	
Unknown or Not Reported	6	6	

End points

End points reporting groups

Reporting group title	Enzalutamide

Reporting group description:

Subjects received enzalutamide 160 milligram (mg) (as four 40 mg soft gelatin capsules), orally once daily until disease progression (DP), intolerable adverse events (AEs) (including any seizures), noncompliance with protocol requirements, initiation of a new antitumor treatment, or subject or physician decision to discontinue treatment or death due to any cause.

Primary: Percentage of Subjects With Clinical Benefit (CB) at Week 16: Evaluable Population

End point title	Percentage of Subjects With Clinical Benefit (CB) at Week 16: Evaluable Population[1]

End point description:

CB at Week16: percentage of subjects with best response of CR, PR, SD for>=16 weeks on radiologic imaging per investigator using RECIST version 1.1. Estimate of percentage, its exact 2-sided 85% confidence interval calculated by Blaker method. CR: disappearance of all target, non-target lesions, normalisation of tumor marker level, all lymph nodes decreased to non-pathological in size <10 millimeter(mm) short axis. PR: >=30% decrease in sum of longest diameter(LD) of target lesions taking as reference baseline sum of LD, without progression of non-target lesions, no appearance of new lesions. SD: neither sufficient reduction to qualify as PR nor sufficient increase to qualify as PD, using smallest sum diameters during study as reference. Evaluable population:enrolled subjects with centrally assessed AR+ breast cancer (total nuclear AR expression in >=10% of tumor cells), who received at least 1 dose of study drug with atleast 1 available post baseline tumor assessment per RECIST 1.1.

End point type	Primary

End point timeframe:

Week 16

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: No statistical analyses was planned.

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Percentage of subjects				
number (confidence interval 85%)	33.3 (25.53 to 41.63)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With CB at Week 16: Intent-to-Treat (ITT) Population

End point title	Percentage of Subjects With CB at Week 16: Intent-to-Treat (ITT) Population[2]

End point description:

CB at Week 16 defined as percentage of subjects with a best response of CR, PR, or SD for >= 16 weeks on radiologic imaging based on investigator assessment using RECIST 1.1. An estimate of % and

its exact 2-sided 85% CI were calculated using Blaker method. As per RECIST 1.1, CR defined as disappearance of all target, non-target lesions and normalization of tumor marker level and all lymph nodes decreased to non-pathological in size<10 mm short axis. PR: >=30% decrease in sum of LD of target lesions taking as reference baseline sum of LD, without progression of non-target lesions, no appearance of new lesions. SD: neither sufficient reduction to qualify as PR nor sufficient increase to qualify as PD, using smallest sum diameters during study as a reference. ITT population included all enrolled subjects who had centrally assessed AR+ breast cancer and received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Week 16

Notes:

[2] - 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: No statistical analyses was planned.

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Percentage of subjects				
number (confidence interval 85%)	24.6 (18.98 to 30.88)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With CB at Week 24: Evaluable Population

End point title	Percentage of Subjects With CB at Week 24: Evaluable Population

End point description:

CB at Week 24: percentage of subjects with a best response of CR, PR, or SD for >= 24 weeks on radiologic imaging per investigator using RECIST 1.1. Estimate of percentage, its exact 2-sided 85% CI was calculated by Blaker method. CR: disappearance of all target, non-target lesions, normalization of tumor marker level, all lymph nodes decreased to non-pathological in size <10 mm short axis. PR: At least 30% decrease in sum of LD of target lesions taking as reference baseline sum of LD, without progression of non-target lesions, no appearance of new lesions. SD: neither sufficient reduction to qualify as PR nor sufficient increase to qualify as PD, using the smallest sum diameters during the study as a reference. Evaluable population: enrolled subjects with centrally assessed AR + breast cancer (total nuclear AR expression in >= 10% of tumor cells), who received at least 1 dose of study drug with atleast 1 available post baseline tumor assessment per RECIST 1.1.

End point type	Secondary

End point timeframe:

Week 24

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Percentage of subjects				
number (confidence interval 85%)	28.2 (21.04 to 36.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With CB at Week 24: ITT Population

End point title	Percentage of Subjects With CB at Week 24: ITT Population

End point description:

CB at Week 24 defined as percentage of subjects with a best response of CR, PR, or SD for >= 24 weeks on radiologic imaging based on investigator assessment using RECIST 1.1. An estimate of the percentage and its exact 2-sided 85% CI were calculated using the Blaker method. As per RECIST 1.1, CR defined as disappearance of all target, non-target lesions and normalization of tumor marker level and all lymph nodes decreased to non-pathological in size <10 mm short axis. PR: At least 30% decrease in sum of LD of target lesions taking as reference baseline sum of LD, without progression of non-target lesions, no appearance of new lesions. SD: neither sufficient reduction to qualify as PR nor sufficient increase to qualify as PD, using the smallest sum diameters during the study as a reference. ITT population included all enrolled subjects who had centrally assessed AR+ breast cancer and received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 24

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Percentage of subjects				
number (confidence interval 85%)	20.3 (15.16 to 26.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Best Objective Response: Evaluable Population

End point title	Percentage of Subjects With Best Objective Response: Evaluable Population

End point description:

Percentage of subjects with best objective response defined as percentage of subjects with a best response of CR and PR based on investigator assessment of target, non-target and new lesions using RECIST 1.1. As per RECIST 1.1, CR defined as disappearance of all target, non-target lesions and normalization of tumor marker level and all lymph nodes decreased to non-pathological in <10 mm short axis. PR: At least 30% decrease in sum of LD of target lesions taking as reference baseline sum of LD, without progression of non-target lesions, no appearance of new lesions. Evaluable population: enrolled subjects with centrally assessed AR + breast cancer (total nuclear AR expression in >= 10% of tumor cells), who received at least 1 dose of study drug with atleast 1 available post baseline tumor

assessment per RECIST 1.1. Here, Number of Subjects Analyzed signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline up to disease progression or death due to any cause (up to 87 Weeks)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Percentage of subjects				
number (confidence interval 85%)	8.5 (3.05 to 12.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS): Evaluable Population

End point title	Progression-Free Survival (PFS): Evaluable Population

End point description:

PFS was defined as the time (in weeks) from the date of first dose of study drug to the date of documented disease progression or death due to any cause whichever occurs first as determined by the investigator using RECIST 1.1. As per RECIST 1.1, progression was defined as: >=20 percent increase in sum of LD of target lesions taking as a reference the smallest sum of the LD recorded since the treatment started, or the appearance of one or more new lesions and/or unequivocal progression of existing non target-lesions. Evaluable population included all enrolled subjects who had centrally assessed AR + breast cancer (total nuclear AR expression in >= 10% of tumor cells), had at least 1 dose of study drug and had at least 1 available post baseline tumor assessment evaluable as per RECIST 1.1.

End point type	Secondary

End point timeframe:

From Baseline up to disease progression or death due to any cause (up to 87 Weeks)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Weeks				
median (confidence interval 85%)	14.3 (8.3 to 16.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Best Objective Response: ITT Population

End point title	Percentage of Subjects With Best Objective Response: ITT Population

End point description:

Percentage of subjects with best objective response defined as percentage of subjects with a best response of CR and PR based on investigator assessment of target, non-target and new lesions using RECIST 1.1. As per RECIST 1.1, CR defined as disappearance of all target, non-target lesions and normalization of tumor marker level and all lymph nodes decreased to non-pathological in <10 mm short axis. PR: At least 30% decrease in sum of LD of target lesions taking as reference baseline sum of LD, without progression of non-target lesions, no appearance of new lesions. ITT population included all enrolled subjects who had centrally assessed AR+ breast cancer and received at least 1 dose of study drug. Here, Number of Subjects Analyzed signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline up to disease progression or death due to any cause (up to 87 Weeks)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percentage of subjects				
number (confidence interval 85%)	6.2 (2.80 to 8.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival: ITT Population

End point title	Progression-Free Survival: ITT Population

End point description:

PFS was defined as the time (in weeks) from the date of first dose of study drug to the date of documented disease progression or death due to any cause whichever occurs first as determined by the investigator using RECIST 1.1. As per RECIST 1.1, progression was defined as: >=20 percent increase in sum of LD of target lesions taking as a reference the smallest sum of the LD recorded since the treatment started, or the appearance of one or more new lesions and/or unequivocal progression of existing non target-lesions. ITT population included all enrolled subjects who had centrally assessed AR+ breast cancer and received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Baseline up to disease progression or death due to any cause (up to 87 Weeks)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Weeks				
median (confidence interval 85%)	12.6 (8.1 to 15.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response: Evaluable Population

End point title	Time to Response: Evaluable Population

End point description:

The time to response is defined as the time from the date of first dose of study drug to initial CR or PR. Subjects without response of CR or PR before the data cutoff date were censored at the last tumor assessment date before the data cutoff. Kaplan-Meier method was used to summarize time to response. Evaluable population included all enrolled subjects who had centrally assessed AR + breast cancer (total nuclear AR expression in >= 10% of tumor cells), had at least 1 dose of study drug and had at least 1 available post baseline tumor assessment evaluable as per RECIST 1.1. Here, 'Number of Subjects Analyzed' signifies subjects evaluable for this endpoint. '99999' indicates median and 95%CI could not be estimated due to insufficient number of subjects with the event.

End point type	Secondary

End point timeframe:

From first dose of study drug until first documentation of CR or PR (up to 87 Weeks)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Weeks				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response: Evaluable Population

End point title	Duration of Response: Evaluable Population

End point description:

Duration of objective response was defined as the time from initial CR or PR to documented disease progression or death due to any cause, whichever occurs first. Subjects without disease progression or death due to any cause before the data cutoff date were censored at the last tumor assessment date before the data cutoff. Evaluable population included all enrolled subjects who had centrally assessed AR + breast cancer (total nuclear AR expression in >= 10% of tumor cells), had at least 1 dose of study drug and had at least 1 available post baseline tumor assessment evaluable as per RECIST 1.1. Here, 'Number of Subjects Analyzed' signifies subjects evaluable for this endpoint. '99999' indicates median and 95%CI could not be estimated due to insufficient number of subjects with the event.

End point type	Secondary

End point timeframe:

From first documentation of CR or PR until first documentation of tumor progression or death due to any cause or data censoring date, whichever occurred first (up to 87 Weeks)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Weeks				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Postbaseline Laboratory Toxicities Grade 3 or 4

End point title	Number of Subjects With Postbaseline Laboratory Toxicities Grade 3 or 4

End point description:

Laboratory parameters included hematology parameters [low lymphocytes (10^6/L), neutrophils (10^6/L) and Leukocytes (10^9/L)] and chemistry parameters [high phosphate (mmol/L), bilirubin, Alkaline phosphatase (U/L) and glucose (mmol/L)]. Number of participants with postbaseline laboratory toxicity Grade 3 or 4 as per NCI-CTCAE (version 4.0) (Grade 3= Severe, Grade 4= Life-threatening) were reported. Safety population included all subjects who received 1 dose or partial dose of study drug.

End point type	Secondary

End point timeframe:

From start of study treatment on Day 1 up to 30 days after the last dose of study drug (up to maximum of 9.6 years)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Subjects				
Hematology: Leukocytes	1			
Hematology: Lymphocytes	9			
Hematology: Neutrophils	1			
Chemistry: Alkaline Phosphatase	1			
Chemistry: Bilirubin	1			
Chemistry: Glucose	4			
Chemistry: Phosphate	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Trough Plasma Concentration of Enzalutamide and its Metabolite

End point title	Trough Plasma Concentration of Enzalutamide and its Metabolite

End point description:

M2 was the metabolite of enzalutamide. The lower limit of of quantitation (LLQ) was 0.0200 micrograms per milliliter (mcg/mL) for enzalutamide and M2. Pharmacokinetics (PK) analysis population included all subjects who received 1 dose or partial dose of study drug, and who had at least 1 enzalutamide or M2 plasma concentration assessment. Here, 'Number of Subjects' Analyzed signifies subjects evaluable for this endpoint. Here, "99999" signifies that none of the subjects had data above LLQ and as per the predefined protocol, values below the limit of quantitation (BLQ) were set to missing and hence not reported.

End point type	Other pre-specified

End point timeframe:

Predose on Day 1 (Baseline), Week 9 and Week 17

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	115			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)				
Enzalutamide Day 1	99999 (± 99999)			
M2 Day 1	99999 (± 99999)			
Enzalutamide Week 9	12.59 (± 33.46)			
M2 Week 9	13.48 (± 35.64)			
Enzalutamide Week 17	12.79 (± 37.33)			
M2 Week 17	13.88 (± 25.47)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Clinically Significant Change From Baseline in Vital Signs

End point title	Number of Subjects With Clinically Significant Change From Baseline in Vital Signs

End point description:

Criteria: Systolic blood pressure (SBP):absolute SBP<90 millimeters of mercury (mmHg) and decrease from baseline (DFB)>30mmHg, absolute SBP>180mmHg and increase from baseline (IFB)>40 mmHg, final visit or 2 consecutive visits SBP>=20 mmHg change from baseline (CFB), most extreme post-baseline SBP>=140mmHg, most extreme post-baseline SBP>=180mmHg, most extreme

SBP>=140mmHg and>=20 mmHg CFB, most extreme SBP>=180mmHg and>=20mmHg CFB; diastolic blood pressure (DBP): absolute DBP>105mmHg and IFB>30mmHg, absolute DBP<50mmHg and DFB>20mmHg, final visit or 2 consecutive visits DBP>=15mmHg CFB, most extreme post-baseline DBP>=90mmHg, most extreme post-baseline DBP>=105mmHg, most extreme DBP>=90mmHg and>=15mmHg CFB, most extreme DBP>=105mmHg and>=15mmHg CFB; heart rate<50beats per minute (BPM) and DFB>20BPM or heart rate>120BPM and IFB>30BPM. Only those categories, in which at least 1 subject had data were reported. Safety population set was used in the analysis.

End point type	Other pre-specified

End point timeframe:

From start of study treatment on Day 1 up to 30 days after the last dose of study drug (up to maximum of 9.6 years)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Subjects				
SBP: Most extreme SBP>=140 mmHg and>=20 mmHg CFB	12			
SBP: absolute SBP <90 mmHg and DFB>30 mmHg	1			
SBP: Most extreme post baseline SBP >=140 mmHg	42			
SBP: Most extreme post baseline SBP >=180 mmHg	1			
DBP: Most extreme DBP>=90 mmHg and>=15 mmHg CFB	12			
DBP: Most extreme DBP>=105 mmHg and>=15 mmHg CFB	2			
DBP: Most extreme post baseline result >=90 mmHg	24			
DBP: Most extreme post baseline result >=105 mmHg	4			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Grade 3 or Higher Adverse Events

End point title	Number of Subjects With Grade 3 or Higher Adverse Events

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Severity of the AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. As per the NCI CTCAE, version 4.0, Grade 3= severe or medically significant, Grade 4= life-threatening and Grade 5= death. Only the subjects with treatment-emergent AEs of Grade 3 (severe) or higher grade were reported in this endpoint. Safety population included all subjects who received 1 dose or partial dose of study drug

End point type	Other pre-specified

End point timeframe:

Baseline up to 87 weeks

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Subjects	36			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Study Drug Discontinuation due to Adverse Events

End point title	Number of Subjects With Study Drug Discontinuation due to Adverse Events

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Data reported here is for study drug discontinuation due to adverse events. Safety population included all subjects who received 1 dose or partial dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline up to 87 weeks

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Subjects	8			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAEs are events that were absent before treatment or that worsened relative to pretreatment state between first dose of study drug and up to 30 days after last dose of study drug or the day prior to initiation of new anti-tumor treatment. AEs included both serious and non-serious AEs. Safety population included all subjects who received 1 dose or partial dose of

study drug.

End point type	Other pre-specified

End point timeframe:

Baseline up to 87 weeks

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Subjects				
TEAEs	109			
Serious TEAEs	29			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Change From Baseline in Laboratory Parameters Grades by 2 or More Grades

End point title	Number of Subjects With Change From Baseline in Laboratory Parameters Grades by 2 or More Grades

End point description:

Laboratory tests included hematology parameters [low lymphocytes (10^6/L), white blood cells (10^9/L), neutrophils (10^6/L), hemoglobin gram per Liter(g/L) and platelets (10^9/L)] and chemistry parameters [mean albumin grams per Liter(g/L), calcium milli mole per Liter(mmol/L), Phosphate (mmol/L), alanine aminotransferase units per Liter(U/L), Aspartate aminotransferase (U/L), bilirubin micro mole per Liter, Alkaline phosphatase (U/L) and glucose (mmol/L)]. Number of participants with change from baseline in laboratory parameters Grades by 2 or More Grades as per NCI-CTCAE (version 4.0) (Grade 2=Moderate, Grade 3= Severe, Grade 4= Life-threatening) were reported. Safety population included all subjects who received 1 dose or partial dose of study drug.

End point type	Other pre-specified

End point timeframe:

From start of study treatment on Day 1 up to 30 days after the last dose of study drug (up to maximum of 9.6 years)

End point values	Enzalutamide			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Subjects				
Hematology: Hemoglobin	1			
Hematology: Leukocytes	4			
Hematology: Lymphocytes	12			
Hematology: Neutrophils	2			
Hematology: Platelets	1			
Chemistry: Alanine aminotransferase	1			
Chemistry: Albumin	4			
Chemistry: Alkaline phosphatase	5			

Chemistry: Bilirubin	2			
Chemistry: Calcium	2			
Chemistry: Glucose	5			
Chemistry: Phosphate	4			
Chemistry: Aspartate Aminotransferase	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 87 weeks

Adverse event reporting additional description:

Same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorised as serious in one subject and as non-serious in another subject or one subject may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Enzalutamide

Reporting group description:

Subjects received enzalutamide 160 mg (as four 40 mg soft gelatin capsules), orally once daily until disease progression, intolerable AEs (including any seizures), noncompliance with protocol requirements, initiation of a new antitumor treatment, or subject or physician decision to discontinue treatment (up to a maximum of 87 Weeks).

Serious adverse events	Enzalutamide		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 118 (24.58%)		
number of deaths (all causes)	88		
number of deaths resulting from adverse events	12		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	3 / 118 (2.54%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Breast cancer metastatic			
subjects affected / exposed	2 / 118 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pericardial effusion malignant			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Metastases to central nervous system				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to lung				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastatic pain				
subjects affected / exposed	3 / 118 (2.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Toxicity to various agents				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radiation oesophagitis				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				

subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic fracture				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial infarction				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	2 / 118 (1.69%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Nervous system disorders				
Cognitive disorder				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	2 / 118 (1.69%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pain				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 118 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Disease progression			
subjects affected / exposed	3 / 118 (2.54%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 118 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	3 / 118 (2.54%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Pleuritic pain			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			

subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	2 / 118 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 118 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Soft tissue infection			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Device related infection			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 118 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Enzalutamide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 118 (89.83%)		
Investigations			
Weight decrease			
subjects affected / exposed	8 / 118 (6.78%)		
occurrences (all)	11		
Vascular disorders			
Hot flush			
subjects affected / exposed	12 / 118 (10.17%)		
occurrences (all)	13		
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 118 (14.41%)		
occurrences (all)	17		
Dizziness			
subjects affected / exposed	6 / 118 (5.08%)		
occurrences (all)	10		
Neuropathy peripheral			

subjects affected / exposed	6 / 118 (5.08%)		
occurrences (all)	6		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	49 / 118 (41.53%)		
occurrences (all)	66		
Pain			
subjects affected / exposed	9 / 118 (7.63%)		
occurrences (all)	9		
Asthenia			
subjects affected / exposed	6 / 118 (5.08%)		
occurrences (all)	8		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	40 / 118 (33.90%)		
occurrences (all)	52		
Abdominal pain			
subjects affected / exposed	7 / 118 (5.93%)		
occurrences (all)	7		
Vomiting			
subjects affected / exposed	11 / 118 (9.32%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	17 / 118 (14.41%)		
occurrences (all)	17		
Diarrhoea			
subjects affected / exposed	18 / 118 (15.25%)		
occurrences (all)	23		
Reproductive system and breast disorders			
Breast Pain			
subjects affected / exposed	6 / 118 (5.08%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	13 / 118 (11.02%) 16 8 / 118 (6.78%) 8		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	 17 / 118 (14.41%) 17 7 / 118 (5.93%) 10		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 17 / 118 (14.41%) 23 6 / 118 (5.08%) 6 6 / 118 (5.08%) 7 18 / 118 (15.25%) 23 10 / 118 (8.47%) 17 9 / 118 (7.63%) 9		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis	 6 / 118 (5.08%) 6 		

subjects affected / exposed occurrences (all)	6 / 118 (5.08%) 6		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 22 / 118 (18.64%) 23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2013	1- Modified to require head imaging using magnetic resonance imaging (MRI) with contrast to rule out central nervous system (CNS) metastatic disease; head computed tomography (CT) with contrast could be considered after discussion with the medical monitor. Instructions for head imaging were provided for subjects enrolled before this amendment. 2- Increased the sample size from 80 to 95 subjects to ensure an adequate number of evaluable subjects for the primary and secondary efficacy endpoint analyses. 3- Modified exclusion criterion 10 to remove the option of using a creatinine clearance estimation by Cockcroft Gault. Renal function was to be assessed using a single parameter (serum creatinine) to enable analysis by common terminology criteria for adverse events (CTCAE) severity grading. 4- Clarified that modalities other than radiographic methods (such as physical examination) could be used for disease status assessments per RECIST 1.1; positron emission tomography (PET) imaging was not to be used. 5- Clarified that the primary efficacy endpoint of clinical benefit rate at 16 weeks was to be based on investigator determination of response using RECIST 1.1. 6- Provided guidance for late doses and updated the directions for dose modification. 7- Added instructions for reporting pregnancies. 8- Removed requirements for reporting certain adverse events as serious.
09 December 2016	1- Allows long-term follow-up that was previously continued until death to be discontinued at least 6 months after treatment discontinuation. 2- Reduces the assessments performed on patients continuing treatment after week 97 (approximately 2 years) to include only assessments of adverse events, concomitant medications, and study drug dispensation/accountability performed every 12 weeks. 3- Adds that patients continuing treatment after week 97 may enroll in an open-label extension study. 4- Adds that patients discontinuing treatment after week 97 will not participate in long-term follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported