



## 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 |                |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1             |
| This version publication date  | 11 August 2018 |
| First version publication date | 11 August 2018 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | MDV3100-11 |
|-----------------------|------------|

##### 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 | 235 E 42nd Street, New York, United States, NY 10017  |
| Public contact               | Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com  |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, 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                                       | Interim          |
| Date of interim/final analysis                       | 28 November 2016 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 01 March 2015    |
| Global end of trial reached?                         | 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 greater than or equal ( $\geq$ ) 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                               | Yes          |
| Long term follow-up rationale                             | Safety       |
| Long term follow-up duration                              | 24 Months    |
| 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         | 35                |

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: -

### Pre-assignment

Screening details:

The study was conducted at 34 centres in 7 countries. Data reported based on primary analysis date (01 March 2015).

### 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 subjectt or physician decision to discontinue treatment (up to a maximum of 87 Weeks).

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

Dosage and administration details:

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

| Number of subjects in period 1 | Enzalutamide |
|--------------------------------|--------------|
| Started                        | 118          |
| Completed                      | 109          |
| Not completed                  | 9            |
| Treatment ongoing              | 9            |

## 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 subjectt or physician decision to discontinue treatment (up to a maximum of 87 Weeks).

| Reporting group values                                | Enzalutamide | Total |  |
|---|--------------|-------|--|
| Number of subjects                                    | 118          | 118   |  |
| Age categorical                                       |              |       |  |
| Units: Subjects                                       |              |       |  |
| In utero  | 0            | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0            | 0     |  |
| Newborns (0-27 days)                                  | 0            | 0     |  |
| Infants and toddlers (28 days-23<br>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     |  |

## 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 subjectt or physician decision to discontinue treatment (up to a maximum of 87 Weeks). |              |

### 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 <sup>[1]</sup> |
|-----------------|---|

End point description:

CB at Week 16: best response of complete response (CR), partial response (PR), stable disease (SD) for  $\geq 16$  weeks on radiologic imaging per Investigator using RECIST 1.1. Estimate of percentage, its exact 2-sided 85% confidence interval were 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:  $\geq 30\%$  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 a reference. Evaluable population: enrolled subjects with centrally assessed AR + breast cancer (total nuclear AR expression in  $\geq 10\%$  of tumor cells), had at least 1 dose of study drug with  $\geq 1$  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: Only descriptive data was planned to be analyzed for the endpoint

| 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 Clinical Benefit (CB) at Week 16: Intent-to-Treat (ITT) Population

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Clinical Benefit (CB) at Week 16: Intent-to-Treat (ITT) Population <sup>[2]</sup> |
|-----------------|---|

End point description:

Clinical benefit at Week 16 defined as percentage of subjects with a best response of CR, PR, or SD for

$\geq 16$  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:  $\geq 30\%$  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 participants 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: Only descriptive data was planned to be analyzed for the endpoint

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | 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 Clinical Benefit at Week 24: Evaluable Population

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Clinical Benefit at Week 24: Evaluable Population |
|-----------------|---|

End point description:

Percentage of subjects with a clinical benefit at Week 24 defined as percentage of subjects with a best response of CR, PR, or SD for  $\geq 24$  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. Evaluable population set was used in the analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 24

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | 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 Clinical Benefit at Week 24: ITT Population

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Clinical Benefit at Week 24: ITT Population |
|-----------------|---|

End point description:

Clinical benefit at Week 24 defined as percentage of subjects with a best response of CR, PR, or SD for  $\geq 24$  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 set was used in the analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 24

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | 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. Analysis was performed on subjects from Evaluable population who had measurable disease.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From Baseline up to disease progression or death due to any cause (up to 87 Weeks) |           |

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | 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: 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. Analysis was performed on subjects from ITT population who had measurable disease.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From Baseline up to disease progression or death due to any cause (up to 87 Weeks) |           |

|                                  |                    |  |  |  |
|----------------------------------|--------------------|--|--|--|
| <b>End point values</b>          | 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 (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:  $\geq 20$  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  $\geq 10\%$  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: 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:  $\geq 20$  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

## 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 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, "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

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

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

End point description:

An AEs was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AEs 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. Treatment emergent are events between first dose of study drug and up to 87 weeks that were absent before treatment or that worsened relative to pretreatment state. 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

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| End point values            | Enzalutamide    |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 118             |  |  |  |
| Units: subjects             |                 |  |  |  |
| Adverse Events              | 109             |  |  |  |
| Serious Adverse Events      | 29              |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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

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

End point description:

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

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| 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 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 1= mild, Grade 2= moderate, Grade 3= severe, 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 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:  
Baseline up to 87 weeks

| End point values                                  | Enzalutamide    |  |  |  |
|---|-----------------|--|--|--|
| Subject group type                                | Reporting group |  |  |  |
| Number of subjects analysed                       | 118             |  |  |  |
| Units: subjects                                   |                 |  |  |  |
| SBP: absolute SBP <90 mmHg and DFB>30 mmHg        | 1               |  |  |  |
| SBP: FV or 2 CV SBP>=20 mmHg CFB                  | 9               |  |  |  |
| SBP: Most extreme post baseline SBP >=140 mmHg    | 36              |  |  |  |
| SBP: Most extreme post baseline SBP >=180 mmHg    | 1               |  |  |  |
| SBP:Most extreme SBP>=140 mmHg and>=20 mmHg CFB   | 11              |  |  |  |
| DBP: FV or 2 CV DBP>=15 mmHg CFB                  | 10              |  |  |  |
| DBP: Most extreme post baseline result >=90 mmHg  | 22              |  |  |  |
| DBP: Most extreme post baseline result >=105 mmHg | 4               |  |  |  |
| DBP:Most extreme DBP>=105 mmHg and>=15 mmHg CFB   | 2               |  |  |  |
| DBP:Most extreme DBP>=90 mmHg and>=15 mmHg CFB    | 12              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Laboratory tests included hematology parameters (low lymphocytes, WBC, neutrophils, hemoglobin and platelets) and chemistry parameters (mean albumin, Blood urea nitrogen [BUN], calcium, Lactate dehydrogenase [LDH], alanine aminotransferase, Aspartate aminotransferase, bilirubin, Alkaline phosphatase, creatinine and glucose). Number of participants with change from baseline in laboratory parameters Grades by 2 or More Grades as per National Cancer Institute Common Terminology Criteria (NCI CTC) (Grade 0= within normal limits, Grade 1=Mild, Grade 2=Moderate, Grade 3= Severe, Grade 4= Life-threatening) were reported. Safety population included all participants who receive 1 dose or partial dose of study drug.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline up to 87 weeks

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Enzalutamide    |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 118             |  |  |  |
| Units: subjects             |                 |  |  |  |
| Hemoglobin                  | 1               |  |  |  |
| Leukocytes                  | 4               |  |  |  |
| Lymphocytes                 | 12              |  |  |  |
| Neutrophils                 | 2               |  |  |  |
| Platelets                   | 1               |  |  |  |
| Alanine aminotransferase    | 1               |  |  |  |
| Albumin                     | 4               |  |  |  |
| Alkaline phosphatase        | 3               |  |  |  |
| Bilirubin                   | 2               |  |  |  |
| Calcium                     | 2               |  |  |  |
| Glucose                     | 5               |  |  |  |
| Phosphate                   | 4               |  |  |  |

### 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 categorized 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. AEs and SAEs were collected for safety population.

|                 |                |
|-----------------|----------------|
| 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)                                       | 12                |  |  |
| number of deaths resulting from adverse events                      |                   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| 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             |  |  |
| 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           |  |  |
| Injury, poisoning and procedural complications                   |                 |  |  |
| 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           |  |  |
| 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           |  |  |
| 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           |  |  |

|   |                                   |  |  |
|---|-----------------------------------|--|--|
| Toxicity to various agents<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 1 / 118 (0.85%)<br>0 / 1<br>0 / 0 |  |  |
| Traumatic fracture<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 1 / 118 (0.85%)<br>0 / 1<br>0 / 0 |  |  |
| Cardiac disorders<br>Pericardial effusion<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                   | 2 / 118 (1.69%)<br>0 / 2<br>0 / 2 |  |  |
| Myocardial infarction<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 118 (0.85%)<br>0 / 1<br>0 / 0 |  |  |
| Nervous system disorders<br>Spinal cord compression<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                         | 2 / 118 (1.69%)<br>0 / 2<br>0 / 0 |  |  |
| Cognitive disorder<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 1 / 118 (0.85%)<br>0 / 1<br>0 / 0 |  |  |
| General disorders and administration site conditions<br>Disease progression<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 3 / 118 (2.54%)<br>0 / 3<br>0 / 3 |  |  |
| 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           |  |  |
| Pain  |                 |  |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Constipation                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 118 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea  |                 |  |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| 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 |                 |  |  |
| 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           |  |  |
| 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           |  |  |
| 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           |  |  |
| Sepsis  |                 |  |  |
| subjects affected / exposed                     | 2 / 118 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cellulitis                                      |                 |  |  |
| 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           |  |  |
| 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           |  |  |
| 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           |  |  |
| 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 %

| <b>Non-serious adverse events</b>                     | Enzalutamide       |  |  |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 100 / 118 (84.75%) |  |  |
| 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<br>occurrences (all)                          | 6 / 118 (5.08%)<br>9    |  |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 6 / 118 (5.08%)<br>6    |  |  |
| General disorders and administration<br>site conditions                   |                         |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)               | 49 / 118 (41.53%)<br>64 |  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)                  | 9 / 118 (7.63%)<br>9    |  |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)              | 6 / 118 (5.08%)<br>8    |  |  |
| Gastrointestinal disorders  |                         |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                | 40 / 118 (33.90%)<br>51 |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)             | 18 / 118 (15.25%)<br>22 |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)          | 18 / 118 (15.25%)<br>18 |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)              | 11 / 118 (9.32%)<br>14  |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)        | 7 / 118 (5.93%)<br>7    |  |  |
| Reproductive system and breast<br>disorders                               |                         |  |  |
| Breast Pain<br>subjects affected / exposed<br>occurrences (all)           | 6 / 118 (5.08%)<br>6    |  |  |
| Respiratory, thoracic and mediastinal                                     |                         |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| disorders                                       |                   |  |  |
| Dyspnoea  |                   |  |  |
| subjects affected / exposed                     | 13 / 118 (11.02%) |  |  |
| occurrences (all)                               | 15                |  |  |
| Cough   |                   |  |  |
| subjects affected / exposed                     | 7 / 118 (5.93%)   |  |  |
| occurrences (all)                               | 7                 |  |  |
| Psychiatric disorders                           |                   |  |  |
| Insomnia  |                   |  |  |
| subjects affected / exposed                     | 17 / 118 (14.41%) |  |  |
| occurrences (all)                               | 17                |  |  |
| Anxiety   |                   |  |  |
| subjects affected / exposed                     | 7 / 118 (5.93%)   |  |  |
| occurrences (all)                               | 10                |  |  |
| Musculoskeletal and connective tissue disorders |                   |  |  |
| Back pain                                       |                   |  |  |
| subjects affected / exposed                     | 17 / 118 (14.41%) |  |  |
| occurrences (all)                               | 23                |  |  |
| Arthralgia                                      |                   |  |  |
| subjects affected / exposed                     | 17 / 118 (14.41%) |  |  |
| occurrences (all)                               | 19                |  |  |
| Pain in extremity                               |                   |  |  |
| subjects affected / exposed                     | 9 / 118 (7.63%)   |  |  |
| occurrences (all)                               | 16                |  |  |
| Musculoskeletal pain                            |                   |  |  |
| subjects affected / exposed                     | 10 / 118 (8.47%)  |  |  |
| occurrences (all)                               | 10                |  |  |
| Muscle spasms                                   |                   |  |  |
| subjects affected / exposed                     | 6 / 118 (5.08%)   |  |  |
| occurrences (all)                               | 7                 |  |  |
| Infections and infestations                     |                   |  |  |
| Nasopharyngitis                                 |                   |  |  |
| subjects affected / exposed                     | 6 / 118 (5.08%)   |  |  |
| occurrences (all)                               | 6                 |  |  |
| Upper respiratory tract infection               |                   |  |  |

|  |                         |  |  |
|--|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 6 / 118 (5.08%)<br>6    |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 22 / 118 (18.64%)<br>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. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

As per change in planned analysis, AR low population (all enrolled subjects who had AR nuclear staining > 0%, < 10% assessed centrally) was not analyzed for efficacy and duration of response, time to response were not analyzed for any population

Notes: