# Clinical trial results:
# A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Enzalutamide in Subjects with Advanced Hepatocellular Carcinoma

## Summary

| | |
|---|---|
| EudraCT number | 2014-004283-37 |
| Trial protocol | GB ES IT |
| Global end of trial date | 09 February 2021 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 28 January 2022 |
| First version publication date | 28 January 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 9785-CL-3021 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02528643 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Astellas Pharma Global Development, Inc. |
| Sponsor organisation address | 1 Astellas Way, Northbrook, IL, United States, 60062 |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 09 February 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 09 February 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of enzalutamide in participants with advanced HCC, as measured by overall survival (OS).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 November 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | Hong Kong: 3 |
| Country: Number of subjects enrolled | Italy: 47 |
| Country: Number of subjects enrolled | Korea, Republic of: 59 |
| Country: Number of subjects enrolled | Puerto Rico: 2 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Taiwan: 10 |
| Country: Number of subjects enrolled | United Kingdom: 19 |
| Country: Number of subjects enrolled | United States: 14 |
| Worldwide total number of subjects | 165 |
| EEA total number of subjects | 53 |

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) | 87 |
| From 65 to 84 years | 76 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled from 37 sites in 9 countries in Europe, Asia, and North America. Participants with hepatocellular carcinoma (HCC) of any etiology whose disease had progressed on or who were intolerant to sorafenib or other antivascular endothelial growth factor (VEGF) therapy in the advanced setting were enrolled.

### Pre-assignment

Screening details:

Eligible participants were stratified by geographic region (Asia vs other) and Eastern Cooperative Oncology Group (ECOG) performance (0 vs 1) and randomized in a 2:1 ratio. Participants who discontinued treatment entered a follow-up period.

Double blind treatment (DB)
Open Label (OL)

### Period 1

| | |
|---|---|
| Period 1 title | DB (Median duration up to 14.65 months) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Placebo |

Arm description:

Participants received enzalutamide matching placebo orally, once daily (QD) during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

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

Dosage and administration details:

Participants received enzalutamide matching placebo, orally once daily (QD) until disease progression, unacceptable toxicity, or any other discontinuation criterion was met.

| | |
|---|---|
| **Arm title** | Enzalutamide 160 mg |

Arm description:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

| | |
|---|---|
| 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:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind

treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met.

| **Number of subjects in period 1** | Placebo | Enzalutamide 160 mg |
|---|---|---|
| Started | 55 | 110 |
| Treated | 55 | 107 |
| Completed | 0 | 0 |
| Not completed | 55 | 110 |
| Adverse event, serious fatal | 1 | 6 |
| Consent withdrawn by subject | 2 | 8 |
| Adverse event, non-fatal | 5 | 8 |
| Progressive Disease | 44 | 82 |
| Miscellaneous | 3 | 5 |
| Lost to follow-up | - | 1 |

## Period 2

| | |
|---|---|
| Period 2 title | OL (Median duration up to 27.56 months) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

## Arms

| **Arm title** | Enzalutamide 160 mg |
|---|---|

Arm description:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

| | |
|---|---|
| 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:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met.

| **Number of subjects in period 2** | Enzalutamide 160 mg |
|---|---|
| Started | 1 |
| Completed | 0 |
| Not completed | 1 |
| Progressive Disease | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received enzalutamide matching placebo orally, once daily (QD) during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days. | |
| Reporting group title | Enzalutamide 160 mg |
| Reporting group description: | |
| Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days. | |

| Reporting group values | Placebo | Enzalutamide 160 mg | Total |
|---|---|---|---|
| Number of subjects | 55 | 110 | 165 |
| Age categorical<br>Units: Subjects | | | |
| Age<br>Units: years | | | |
| arithmetic mean | 62.6 | 63.7 | |
| standard deviation | ± 12.5 | ± 10.9 | - |
| Sex<br>Units: Subjects | | | |
| Female | 6 | 15 | 21 |
| Male | 49 | 95 | 144 |
| Race<br>Units: Subjects | | | |
| White | 26 | 52 | 78 |
| Black or African American | 3 | 5 | 8 |
| Asian | 25 | 52 | 77 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Other | 1 | 0 | 1 |
| Ethnicity<br>Units: Subjects | | | |
| HISPANIC OR LATINO | 0 | 3 | 3 |
| NOT HISPANIC OR LATINO | 55 | 107 | 162 |
| UNKNOWN | 0 | 0 | 0 |
| Geographic Region<br>Units: Subjects | | | |
| Asia | 24 | 48 | 72 |
| Other | 31 | 62 | 93 |
| Eastern Cooperative Oncology Group (ECOG) PS (0, 1) | | | |
| ECOG PS was measured on 6 point scale<br>0-Fully active, able to carry on all pre-disease performance without restriction<br>1- Restricted in physically strenuous activity but ambulatory & able to carry out work of a light or | | | |

sedentary nature
2-Ambulatory & capable of all self-care but unable to carry out any work activities Up & about more than 50% of waking hours
3-Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4-Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5-Dead
Participants were categorized based on ECOGPS 0 or 1

| Units: Subjects | | | |
|---|---|---|---|
| ECOG PS = 0 | 23 | 43 | 66 |
| ECOG PS = 1 | 32 | 67 | 99 |

## End points

### End points reporting groups

| Reporting group title | Placebo |
|---|---|

Reporting group description:

Participants received enzalutamide matching placebo orally, once daily (QD) during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

| Reporting group title | Enzalutamide 160 mg |
|---|---|

Reporting group description:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

| Reporting group title | Enzalutamide 160 mg |
|---|---|

Reporting group description:

Participants received enzalutamide 160 milligrams (mg) capsules, orally QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

### Primary: Overall Survival (OS)

| End point title | Overall Survival (OS) |
|---|---|

End point description:

OS was defined as the time from the date of randomization until the documented date of death from any cause. Participants who were still alive at the time of the data cut-off date was censored on the last date known to be alive or at the data cutoff date, whichever occurs first. Results based on Kaplan-Meier estimates.

Analysis Population Description (APD): The analysis population was the FAS.

| End point type | Primary |
|---|---|

End point timeframe:

From date of randomization up to data cut-off date 02 Oct 2017 (approximately 22 months); median follow-up time was 14.65 months for enzalutamide and 13.83 for placebo.

| End point values | Placebo | Enzalutamide 160 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 110 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.69 (5.82 to 13.77) | 7.75 (6.05 to 9.92) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Stratified Analysis. The null hypothesis was stated as: OS distributions of the 2 arms are equivalent. The alternative hypothesis was stated as: OS is prolonged in enzalutamide arm. The null hypothesis was tested using a stratified one-sided log-rank test at the 0.10 level. Stratification factors were ECOG performance status and region from eCRF.

| | |
|---|---|
| Comparison groups | Placebo v Enzalutamide 160 mg |
| Number of subjects included in analysis | 165 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.248 [1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.146 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.774 |
| upper limit | 1.696 |

Notes:

[1] - One-sided p-value.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Unstratified Analysis. The null hypothesis was stated as: OS distributions of the 2 arms are equivalent. The alternative hypothesis was stated as: OS is prolonged in enzalutamide arm. The null hypothesis was tested using a one-sided log-rank test at the 0.10 level.

| | |
|---|---|
| Comparison groups | Placebo v Enzalutamide 160 mg |
| Number of subjects included in analysis | 165 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.252 [2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.142 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.773 |
| upper limit | 1.688 |

Notes:

[2] - One-sided p-value.

## Secondary: Number of Participants with Adverse Events (AEs)

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

End point description:

Safety was assessed by AEs, which included abnormalities identified during a medical test (laboratory tests, vital signs, ECG) if the abnormality induced clinical signs or symptoms, needed active intervention, interruption or discontinuation of study drug or was clinically significant. A treatment-emergent AE (TEAE) was defined as an AE observed after starting administration of the study drug up to 30 days after last dose of study drug or initiation of new treatment, whichever comes first. AEs were considered as serious if resulted in in death, was life-threatening resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, resulted in

congenital anomaly or birth defect, required inpatient hospitalization or led to prolongation of hospitalization & other medically important events. APD: Safety analysis set (SAF), which consisted of all participants who have received at least 1 or partial capsule of study drug.

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

End point timeframe:

From first dose of study drug up to 30days after last dose of study drug median (minimum, maximum) treatment duration was 64.0 (6, 1736) days for enzalutamide and 64.0 (12, 490) for placebo

| **End point values** | Placebo | Enzalutamide 160 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 107 | | |
| Units: Participants | | | | |
| TEAE | 50 | 105 | | |
| Drug-related TEAEs | 24 | 69 | | |
| Deaths | 45 | 82 | | |
| TEAE Leading to Death | 6 | 12 | | |
| Drug-related TEAEs Leading to Death | 0 | 0 | | |
| Serious TEAEs | 22 | 47 | | |
| Drug-related Serious TEAEs | 3 | 7 | | |
| TEAEs Leading to Treatment Withdrawal | 14 | 34 | | |
| Drug-related TEAEs Leading to Treatment Withdrawal | 4 | 7 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Trough Concentrations of Enzalutamide

| End point title | Plasma Trough Concentrations of Enzalutamide[3] |
|---|---|

End point description:

Blood samples were collected for analysis.

APD: The analysis population was the pharmacokinetics analysis set (PKAS), consisted of the subset of the SAF population for whom at least 1 quantifiable enzalutamide and N-desmethyl enzalutamide concentration value was available. Participants who had available concentration data were included in the analysis.

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

End point timeframe:

Predose at weeks 5, 9 and 13

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were analyzed only in the arms where study drug was administered.

| End point values | Enzalutamide 160 mg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 96 | | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 5 | 14.29 (± 4.15) | | | |
| Week 9 | 12.15 (± 4.68) | | | |
| Week 13 | 12.45 (± 5.44) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Trough Concentrations N-desmethyl Enzalutamide (M2 Metabolite)

| End point title | Plasma Trough Concentrations N-desmethyl Enzalutamide (M2 Metabolite)[4] |
|---|---|

End point description:

Blood samples were collected for analysis.

APD: The analysis population was the PKAS, with participants who had available concentration data.

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

End point timeframe:

Predose at weeks 5, 9 and 13

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK parameters were analyzed only in the arms where study drug was administered.

| End point values | Enzalutamide 160 mg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 96 | | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 5 | 11.01 (± 3.63) | | | |
| Week 9 | 12.65 (± 3.89) | | | |
| Week 13 | 12.21 (± 4.94) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Trough Concentrations of MDPC0001 (M1 Metabolite)

| End point title | Plasma Trough Concentrations of MDPC0001 (M1 Metabolite)[5] |
|---|---|

End point description:

Blood samples were collected for analysis.

APD: The analysis population was the PKAS, with participants who had available concentration data.

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

End point timeframe:

Predose at weeks 5, 9 and 13

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK parameters were analyzed only in the arms where study drug was administered.

| **End point values** | Enzalutamide 160 mg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 96 | | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 5 | 4.70 (± 3.86) | | | |
| Week 9 | 5.60 (± 5.63) | | | |
| Week 13 | 6.12 (± 4.24) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS)

| End point title | Progression Free Survival (PFS) |
|---|---|

End point description:

PFS was defined as the time from date of randomization until date of documented radiographic disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as determined by investigator or death from any cause on study, whichever occurred first. The earliest of censoring times was used: Participants with (1) no evaluable postbaseline imaging assessments or did not die were censored at randomization date; (2) no radiographical progression or did not die before analysis cutoff date were censored at last radiological assessment date before analysis cutoff date; (3) with no radiographical progression or did not die before new HCC treatment was censored at the last radiological assessment date before start of new HCC treatment. Based on Kaplan-Meier. APD: FAS population.

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

End point timeframe:

From date of randomization up to data cut-off date 02 Oct 2017 (approximately 22 months); median follow-up time was 14.65 months for enzalutamide and 13.83 for placebo.

| **End point values** | Placebo | Enzalutamide 160 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 110 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.87 (1.84 to 3.45) | 2.23 (1.87 to 3.52) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Unstratified Analysis. The null hypothesis was stated as: PFS distributions of the 2 arms are equivalent. The alternative hypothesis was stated as: PFS is prolonged in enzalutamide arm. The null hypothesis was tested using a one-sided log-rank test at the 0.10 level.

| | |
|---|---|
| Comparison groups | Placebo v Enzalutamide 160 mg |
| Number of subjects included in analysis | 165 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.586 [6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.959 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.684 |
| upper limit | 1.345 |

Notes:

[6] - One-sided p-value.

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Stratified Analysis. The null hypothesis was stated as: PFS distributions of the 2 arms are equivalent. The alternative hypothesis was stated as: PFS is prolonged in enzalutamide arm. The null hypothesis was tested using a stratified one-sided log-rank test at the 0.10 level. Stratification factors were ECOG performance status and region from eCRF.

| | |
|---|---|
| Comparison groups | Placebo v Enzalutamide 160 mg |
| Number of subjects included in analysis | 165 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.396 [7] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.732 |
| upper limit | 1.474 |

Notes:

[7] - One-sided p-value.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30days after last dose of study drug  median (minimum, maximum) treatment duration was 64.0 (6, 1736) days for enzalutamide and 64.0 (12, 490) for placebo

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | v16.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Participants received enzalutamide matching placebo orally,  QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met.  Median treatment duration was 64 days.

| | |
|---|---|
| Reporting group title | Enzalutamide |

Reporting group description:

Participants received enzalutamide 160 mg capsules, orally, QD during double blind treatment period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Eligible participants received enzalutamide 160 mg capsules, orally QD during open label period until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Median treatment duration was 64 days.

| Serious adverse events | Placebo | Enzalutamide | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 55 (40.00%) | 47 / 107 (43.93%) | |
| number of deaths (all causes) | 45 | 82 | |
| number of deaths resulting from adverse events | 6 | 12 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 55 (10.91%) | 14 / 107 (13.08%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 20 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 11 | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 3 / 107 (2.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial pain | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 107 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 107 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 107 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dysaesthesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 107 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 3 / 107 (2.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymph node pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 8 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 107 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 7 / 107 (6.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 5 / 107 (4.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 107 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 107 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 3 / 107 (2.80%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 3 / 107 (2.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 2 / 107 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis B | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid intake reduced | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | Enzalutamide | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 55 (83.64%) | 96 / 107 (89.72%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 6 / 107 (5.61%) | |
| occurrences (all) | 0 | 14 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 11 / 55 (20.00%) | 11 / 107 (10.28%) | |
| occurrences (all) | 12 | 26 | |
| Fatigue | | | |
| subjects affected / exposed | 10 / 55 (18.18%) | 38 / 107 (35.51%) | |
| occurrences (all) | 11 | 49 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 6 / 107 (5.61%) | |
| occurrences (all) | 3 | 7 | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 8 / 107 (7.48%) | |
| occurrences (all) | 5 | 9 | |
| Reproductive system and breast disorders | | | |
| Gynaecomastia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 12 / 107 (11.21%) | |
| occurrences (all) | 0 | 14 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 55 (10.91%) | 8 / 107 (7.48%) | |
| occurrences (all) | 6 | 11 | |
| Cough | | | |
| subjects affected / exposed | 6 / 55 (10.91%) | 12 / 107 (11.21%) | |
| occurrences (all) | 6 | 14 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 7 / 55 (12.73%) | 13 / 107 (12.15%) | |
| occurrences (all) | 7 | 14 | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 9 / 55 (16.36%) | 16 / 107 (14.95%) | |
| occurrences (all) | 10 | 23 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 7 / 55 (12.73%) | 8 / 107 (7.48%) | |
| occurrences (all) | 10 | 8 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 5 / 107 (4.67%) | |
| occurrences (all) | 4 | 5 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 6 / 107 (5.61%) | |
| occurrences (all) | 2 | 9 | |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 15 / 107 (14.02%) | |
| occurrences (all) | 6 | 17 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 0 / 107 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 4 / 107 (3.74%) | |
| occurrences (all) | 7 | 7 | |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 55 (7.27%) | 7 / 107 (6.54%) | |
| occurrences (all) | 4 | 9 | |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 2 / 107 (1.87%) | |
| occurrences (all) | 5 | 2 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 55 (12.73%) | 12 / 107 (11.21%) | |
| occurrences (all) | 8 | 17 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 2 / 107 (1.87%) | |
| occurrences (all) | 3 | 2 | |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 6 / 107 (5.61%) | |
| occurrences (all) | 6 | 6 | |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 55 (14.55%) | 15 / 107 (14.02%) | |
| occurrences (all) | 9 | 24 | |
| Ascites | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 11 / 107 (10.28%) | |
| occurrences (all) | 2 | 16 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 9 / 55 (16.36%) | 7 / 107 (6.54%) | |
| occurrences (all) | 9 | 10 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 15 / 107 (14.02%) | |
| occurrences (all) | 5 | 18 | |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 55 (23.64%) | 13 / 107 (12.15%) | |
| occurrences (all) | 22 | 17 | |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 55 (10.91%) | 9 / 107 (8.41%) | |
| occurrences (all) | 6 | 13 | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 55 (10.91%) | 29 / 107 (27.10%) | |
| occurrences (all) | 6 | 33 | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 11 / 107 (10.28%) | |
| occurrences (all) | 5 | 13 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 13 / 107 (12.15%) | |
| occurrences (all) | 4 | 14 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 4 / 107 (3.74%) | |
| occurrences (all) | 3 | 5 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 10 / 107 (9.35%) | |
| occurrences (all) | 3 | 13 | |
| Bone pain | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 2 / 107 (1.87%) | |
| occurrences (all) | 3 | 2 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 6 / 107 (5.61%) | |
| occurrences (all) | 8 | 6 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 3 / 107 (2.80%) | |
| occurrences (all) | 4 | 3 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 12 / 55 (21.82%) | 33 / 107 (30.84%) | |
| occurrences (all) | 13 | 40 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 2 / 107 (1.87%) | |
| occurrences (all) | 5 | 3 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 September 2015 | The changes included ● The TTP endpoint was changed from a secondary endpoint to an exploratory endpoint, because TTP is not an established endpoint in this study population. ● Study procedures related to testing on eligibility tissue samples were updated. ● In order to be consistent with the enzalutamide US label, the concomitant medications were modified to clarify advice regarding coadministration with cytochrome P450 (CYP)2C8 inhibitors and warfarin (CYP2C9 substrate). ● The definition of the full analysis set (FAS) was changed from "all randomized patients who receive at least 1 dose of study drug" to "all randomized patients." |
| 29 March 2016 | The changes included ● Advanced HCC was clarified as unresectable and/or metastatic and that the additional line of systemic therapy could have been given before or after sorafenib/anti-VEGF therapy. ● The number of unstained serial tissue slides requirement was removed from Inclusion Criterion 10. ● Clarified Exclusion Criterion 8 to state that transfusions/infusions to meet eligibility criteria were not allowed. ● Clarified Exclusion Criterion 10 to state that only bleeding esophageal varices were exclusionary. ● Added dosing information for clarity and completeness and to align with the Enzalutamide IB and US Package Insert. ● Clarified the values and dose modifications for clinically significant study drug-related liver toxicities. ● Added guidance that the investigator should consult with medical monitor if initiation of antiviral therapy was deemed necessary during the study. ● Included a pharmacodynamic analysis set (PDAS) and removed the per-protocol set (PPS). The efficacy analysis would be conducted on the FAS and would not include the PPS. ● Replaced AEs with treatment-emergent AEs (TEAEs). All analyses would be done on TEAEs only. |
| 10 August 2016 | The changes included ● Added language to allow patients previously using spironolactone (an AR signal inhibitor) to be enrolled in the study, and allowed spironolactone to be initiated during the study after consultation with the medical monitor. ● Nonsubstantial change: Updated data cutoff and increased the number of patients to be treated with enzalutamide. |
| 08 March 2018 | The changes included ● Added open-label period to allow patients to continue on enzalutamide after the doubleblind period. ● Nonsubstantial change: Updated clinical research contact details. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported