Name of Sponsor/Company: Astellas Pharma Global Development, Inc		
Name of Finished Product: Xtandi		
Name of Active Ingredient: Enzalutamide		

SYNOPSIS

Title of Study: A Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC) – ARCHES

Investigators/Coordinating Investigator: [redacted] MD, Urological Oncologist, [redacted] Germany.

Study Center(s): This study was conducted at more than 200 clinical sites worldwide; 241 sites were activated, 211 sites screened patients and 204 sites randomized patients. Enrollment by site ranged from 1 to 40 patients.

Publication Based on the Study: None at the time of report

Study Period:

Study Initiation Date (First Informed Consent Signed): 09 Mar 2016

Study Completion Date (Data Cutoff Date): Ongoing; data cutoff date: 14 Oct 2018

Phase of Development: Phase 3

Objectives: The primary objective was to determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by radiographic progression-free survival (rPFS) based on independent central review (ICR). The key secondary objectives were to determine time to prostate-specific antigen (PSA) progression, time to start of new antineoplastic therapy, PSA undetectable rate, objective response rate (ORR), time to deterioration of urinary symptoms and overall survival (OS). The safety objective was to determine the safety of enzalutamide plus ADT as compared to placebo plus ADT.

Methodology: This was a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of enzalutamide plus ADT vs placebo plus ADT in patients with mHSPC. Approximately 1100 patients were planned to be randomized centrally 1:1. The randomization was stratified by volume of disease and prior docetaxel therapy for prostate cancer. The primary endpoint was rPFS.

Patients received treatment with enzalutamide 160 mg once daily or placebo matching enzalutamide, administered orally as 4 capsules or tablets. Treatment was continued as long as patients were tolerating enzalutamide and continued ADT until radiographic progression was documented or until the patients started an investigational agent or new therapy for treatment of prostate cancer or until any other discontinuation criterion was met.

Patients were to remain on study treatment until radiographic progression was confirmed by independent central imaging review. Patients who discontinued study treatment without radiographic progression continued to

follow the radiographic assessment schedule until radiographic progression event was confirmed by the central imaging independent reviewer or until the target number of progression events was reached as assessed by ICR. All patients are being followed for OS until the final OS analysis. At the time of primary endpoint analysis and recommendation of an independent Data Safety Monitoring Board (DSMB) on study continuation, patients were eligible to transition to an open-label extension portion of the current study. The DSMB monitored the safety data on an ongoing basis.

Patients had a safety follow-up visit 30 days after their last dose of study drug or prior to initiation of new antineoplastic therapy for prostate cancer, whichever occurred first. All patients were to be followed for survival until death, loss to follow-up, withdrawal of consent or study termination by the sponsor.

Number of Patients (Planned, Enrolled and Analyzed): Approximately 1100 patients (550 patients per treatment group) were planned to be randomized in the study. A total of 1150 patients were randomized (574 to enzalutamide plus ADT, 576 to placebo plus ADT) and analyzed for efficacy and 1146 patients were treated (572 with enzalutamide plus ADT, 574 with placebo plus ADT) and analyzed for safety.

Diagnosis and Main Criteria for Inclusion: A patient was eligible for the study if he was diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell or small cell histology; had metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on computed tomography or magnetic resonance imaging scan (for soft tissue). Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible. Once randomized at day 1, patients maintained ADT with a luteinizing hormone-releasing hormone agonist or antagonist during study treatment or had a history of bilateral orchiectomy (i.e., medical or surgical castration). Furthermore, eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening and an estimated life expectancy of ≥ 12 months as assessed by the investigator. Up to 6 prior cycles of docetaxel therapy were allowed, if completed at least 2 months before day 1.

The following medications were prohibited within 4 weeks of day 1 and during the study treatment period: 5-α reductase inhibitors (finasteride, dutasteride); estrogens; cyproterone acetate; biologic or other agents with antitumor activity against prostate cancer; systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone intended for the treatment of prostate cancer; herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels (i.e., saw palmetto); and androgens (e.g., testosterone, dihydroepiandrosterone).

Test Product, Dose and Mode of Administration, Batch Numbers: Test product was provided in bottles with child-resistant closures containing 124 capsules or tablets of enzalutamide 40-mg capsules, to be taken as 160 mg (4 capsules or tablets) orally once daily.

Batch numbers: capsules: P152089-0005L, P152089-0008L, P152089-0011L, P152089-0013L, P152089-0015L, 16048A, 16103E, 18062A; tablets P152089-0003L.

Duration of Treatment: Study drug was to be taken until disease progression, unacceptable toxicity or any other discontinuation criteria were met.

Reference Product (Placebo), Dose and Mode of Administration, Batch Numbers: Placebo was provided in bottles with child-resistant closures containing 124 capsules of enzalutamide-matching placebo capsules or tablets, to be taken as 4 capsules orally once daily.

Batch numbers: capsules P152089-0006L, P152089-0010L, P152089-0011L, P152089-0013L, P152089-0014L, P152089-0015L, 16047A, 16102C, 18061A; tablets P152089-0004L.

Criteria for Evaluation: The primary efficacy endpoint was rPFS (based on central review), where rPFS events were defined as objective evidence of rPD as assessed by ICR or death, as follows:

- Death from any cause within 24 weeks (2 scan cycles) from study drug discontinuation.
- rPD was defined by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) for soft tissue disease or the appearance of 2 or more new bone lesions on bone scan compared to baseline per PCWG2. Unconfirmed disease progression on bone scan at week 13 was not considered as event.

The key secondary efficacy endpoints were:

- Time to PSA progression calculated as the time from randomization to the date of first observation of PSA progression.
- Time to start of new antineoplastic therapy defined as the time from randomization to the date of first dose administration of the first antineoplastic therapy.
- PSA undetectable rate defined as the percentage of patients with detectable (≥ 0.2 ng/mL) PSA at baseline, which became undetectable (< 0.2 ng/mL) during study treatment.
- ORR, calculated as the percentage of intent-to-treat (ITT) patients with measureable disease at baseline who achieved a complete response (CR) or partial response (PR) (unconfirmed responses) in their soft tissue disease using the RECIST 1.1 criteria, i.e., with CR or PR as best RECIST overall response. The RECIST overall time point response was derived from radiographic data/images provided by the investigators, which were assessed by ICR.
- Time to deterioration in urinary symptoms using Quality of Life Questionnaire-Prostate 25 Module (QLQ-PR25) modified urinary symptom scale score.
- OS defined as the time from randomization to death from any cause.

Other secondary efficacy endpoints were:

- Time to first symptomatic skeletal event (SSE) defined as the time from randomization to the occurrence of the first SSE (i.e., radiation to bone, surgery to bone, clinically apparent pathological bone fracture or spinal cord compression) prior to the data analysis cutoff date.
- Time to castration resistance defined as the time from randomization to the first castration resistance event.
- Time to deterioration of quality of life (QoL) defined as the time from the date of randomization to the first date a decline from baseline of ≥ 10 points in the Functional Assessment of Cancer Therapy – Prostate (FACT-P) total score was recorded.
- Time to pain progression defined as time from randomization to the first pain progression event, which was an increase of ≥ 30% from baseline in the average Brief Pain Inventory-Short Form (BPI-SF) item scores.

Other efficacy endpoints included, amongst others, QoL as measured by QLQ-PR25, FACT-P and EuroQol Group-5 Dimensions-5 Levels health questionnaire (EQ-5D-5L).

Safety was assessed by evaluation of treatment-emergent adverse events (TEAEs; frequency, severity, seriousness and relationship to study drug), clinical laboratory variables (hematology, biochemistry including liver enzymes and total bilirubin, PSA and testosterone), vital signs (systolic and diastolic blood pressure, pulse rate, body temperature and weight) and 12-lead electrocardiogram (ECG).

Statistical Methods: The final analysis of the primary endpoint (rPFS) was to be conducted when a minimum of 262 progression events had occurred and was based on a target hazard ratio (HR) of 0.67. Analysis after the occurrence of 262 rPFS events provides 90% power to detect the target HR based on a 2-sided log-rank test and a significance level of 0.05. The study was also powered for OS. Specifically, 342 death events were required to provide 80% power to detect a target HR of 0.73 with a target difference in Kaplan-Meier estimated median of approximately 15 months (40 months for placebo plus ADT vs 55 months for enzalutamide plus ADT) at the 0.04 significance level under the assumption of an exponential distribution. This significance level was chosen to apply a parallel testing strategy between OS and some other secondary endpoints (with allocated type I error rate of 0.01).

The expected median rPFS for the placebo plus ADT group was 20 months as measured from the date of randomization. Under the assumption of an exponential distribution, a target HR of 0.67 corresponds to approximately 50% increase in median rPFS for the enzalutamide plus ADT group relative to the placebo plus ADT group (approximately 30 vs 20 months). The effect of enzalutamide plus ADT compared to placebo plus ADT was tested using a stratified log-rank test at the level of significance of 0.05 (2-sided). Stratification factors were the factors used at randomization, prior docetaxel use (yes vs no) and disease volume (low vs high).

Kaplan-Meier methods were used to estimate the distribution of rPFS events by treatment group. The median rPFS was estimated using the corresponding 50th percentile of Kaplan Meier estimates. A 2-sided 95% confidence interval (CI) was provided for this estimate by use of the Brookmeyer and Crowley method. A Kaplan-Meier plot by treatment group was presented. The estimates of the event free rate on a 3-monthly basis up to 1 year and every 6 months thereafter were summarized by treatment group, as long as at least 10 patients were at risk.

The benefit of enzalutamide plus ADT compared to placebo plus ADT was summarized by a HR with its 95% CI based on a Cox regression model stratified for the prior docetaxel use and disease volume. If the estimate of the HR (enzalutamide plus ADT/placebo plus ADT) < 1 and the results from the log-rank test led to the rejection of the null hypothesis in favor of its alternative, then it could be concluded that enzalutamide plus ADT prolonged rPFS compared to placebo plus ADT.

Sensitivity analyses were performed to evaluate the robustness of the rPFS results by investigating the extent to which the results and conclusions may be affected by various limitations of the data, assumptions and analytic approaches to data analysis. These sensitivity analyses were conducted on the ITT population using the same analysis methods as for the primary analysis. No adjustment was made for the multiple comparisons in the sensitivity analyses.

The study-specified definition of the rPFS endpoint was not followed in this report. The ICR mistakenly used the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria to evaluate progression on bone lesions, rather than comparing bone lesions to the best response on treatment for progression. The impact of this change is small, and reassessments are ongoing.

Subgroup analyses of rPFS were performed to determine whether the treatment effect was consistent among subgroups. To avoid possible issues related to small numbers of events, subgroup analyses were not adjusted for the stratification factors used at randomization.

All secondary endpoint analyses (including an interim analysis of OS) were performed at the time of the rPFS final analysis. If the primary endpoint statistical analysis test was statistically significant, the 6 key secondary endpoints were tested using a method to preserve the family-wise 2-sided type I error rate at 0.05. To maintain this rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.04) and the other 5 endpoints (with allocated type I error rate 0.01) was performed.

Summary of Results/Conclusions:

Study Population:

From 21 Mar 2016 to 14 Oct 2018 (the study data cutoff date), 1150 patients were randomly assigned at a 1:1 ratio to treatment with enzalutamide plus ADT (574 patients) or placebo plus ADT (576 patients); 1146 patients received at least 1 dose of enzalutamide plus ADT (572 patients) or placebo plus ADT (574 patients). A patient disposition flowchart is presented in [Figure 1].

As of data cutoff date, 769 (66.9%) patients remained on study drug (437 [76.1%] in the enzalutamide plus ADT group and 332 [57.6%] in the placebo plus ADT group), and 377 (32.8%) patients discontinued study drug (135 [23.5%] in the enzalutamide plus ADT group and 242 [42.0%] in the placebo plus ADT group). Overall, the primary reason for study drug discontinuation in both treatment groups was progressive disease.

Patient demographics and baseline characteristics for the ITT population are summarized in Table 1. The demographic and baseline characteristics were well balanced between the 2 treatment groups. The median age at randomization was 70.0 years in both treatment groups. Most (80.5%) patients in the total population were white. Baseline disease characteristics were well balanced between the 2 treatment groups [Table 2].

Efficacy Results:

Enzalutamide plus ADT was demonstrated to be effective in the treatment of patients with mHSPC. A summary of the primary and secondary efficacy results is presented in [Table 3].

Primary Endpoint

Based on a total of 287 rPFS events assessed by ICR per PCWG2 criteria at the data cutoff date, treatment with enzalutamide plus ADT demonstrated a statistically significant 61% reduction in the risk of a patient experiencing an rPFS event compared with placebo plus ADT treatment (HR = 0.39, 95% CI: 0.30, 0.50; P < 0.0001) Table 4. The rPFS analysis is illustrated by a Kaplan-Meier plot in Figure 2. The HRs for all prespecified sensitivity analyses were consistent with the primary rPFS HRs (HRs ranging from 0.36 to 0.47), showing the rPFS results are robust.

The treatment effect on rPFS of enzalutamide plus ADT vs placebo plus ADT as measured by the estimated HR was consistently favorable across all prespecified subgroups, including age, geographic region, baseline ECOG performance status, Gleason score at initial diagnosis, disease location at baseline, baseline PSA, volume of disease at baseline, prior docetaxel use and prior use of ADT or orchiectomy (HRs ranging from 0.20 to 0.53).

Key Secondary Endpoints

A total of 45 (7.84%) patients in the enzalutamide plus ADT group and 189 (32.81%) patients in the placebo plus ADT group had PSA progression. Treatment with enzalutamide plus ADT was associated with a statistically significant 81.0% reduction in the risk of PSA progression compared with placebo plus ADT treatment (HR = 0.19, 95% CI: 0.13, 0.26; P < 0.0001).

Treatment with enzalutamide plus ADT was associated with a statistically significant 72% reduction in risk of start of a new antineoplastic therapy for prostate cancer compared with placebo plus ADT treatment (HR = 0.28, 95% CI: 0.20, 0.40; P < 0.0001).

Of the patients with a detectable PSA level at baseline, treatment with enzalutamide plus ADT significantly increased the chance of a PSA decline to an undetectable level (< 0.2 ng/mL) compared to treatment with placebo plus ADT. The absolute difference in the PSA undetectable rate between the treatment groups was 50.5% (95% CI: 45.3, 55.7; P < 0.0001).

The ORR as assessed by the ICR in patients with measurable disease was 83.1% (147/177) for patients in the enzalutamide plus ADT group and 63.7% (116/182) for patients in the placebo plus ADT group for an absolute difference of 19.3% (95% CI: 10.4, 28.2; P < 0.0001).

Treatment with enzalutamide plus ADT was not associated with a statistically significant difference in the time to deterioration in urinary symptoms compared with placebo plus ADT treatment (HR = 0.88, 95% CI: 0.72, 1.08; P = 0.2162).

With 24.6% of deaths required for the final analysis of OS, the data are considered to be immature at this interim analysis preventing a robust characterization of treatment effect on OS, although the HR = 0.81 favors the enzalutamide plus ADT group. There were 39 (6.8%) deaths in the enzalutamide plus ADT group and 45 (7.8%) deaths in the placebo plus ADT group (HR = 0.81, 95% CI: 0.53, 1.25; P = 0.3361). OS data collection is ongoing and will be analyzed as planned for the final analysis.

Other Secondary Endpoints

Treatment with enzalutamide plus ADT was associated with a 48% reduction in the risk of a patient experiencing an SSE compared with placebo plus ADT treatment (HR = 0.52, 95% CI: 0.33, 0.80; nominal P = 0.0026).

Treatment with enzalutamide plus ADT was associated with a 72% reduction in the risk of a patient experiencing a castration-resistance event compared with placebo plus ADT treatment (HR = 0.28, 95% CI: 0.22, 0.36; nominal P < 0.0001).

No change in the time to deterioration of QoL based on the FACT-P total score was observed for the enzalutamide plus ADT group compared to the placebo plus ADT group (HR = 0.96, 95% CI: 0.81, 1.14; nominal P = 0.6548).

No change in the time to pain progression was observed for the enzalutamide plus ADT group compared to the placebo plus ADT group (HR = 0.92, 95% CI: 0.78, 1.07; nominal P = 0.2715).

Other Patient-reported Outcomes Data

Other prespecified analyses of patient-reported outcomes data, including summary QoL data, are reported separately.

Safety Results:

As of the data cutoff date of 14 Oct 2018, the median duration of treatment was 12.8 months for the enzalutamide plus ADT group and 11.6 months for the placebo plus ADT group.

Treatment-emergent Adverse Events

An overview of TEAEs is presented in Table 5. The incidence of TEAEs was similar between the enzalutamide plus ADT group and the placebo plus ADT group (85.1% and 85.9%, respectively). The most frequently reported TEAEs (in at least 10% of patients in either treatment group) were hot flush (27.1% and 22.3%, respectively), fatigue (19.6% and 15.3%, respectively), arthralgia (12.2% and 10.6%, respectively) and back pain (7.5% and 10.8%, respectively) [Table 6].

In the enzalutamide plus ADT and placebo plus ADT treatment groups, the incidence of patients with grade 3 or 4 TEAEs (23.6% and 24.7%, respectively), serious TEAEs (18.2% and 19.5%, respectively), TEAEs leading to permanent discontinuation of study drug (7.2% and 5.2%, respectively) and the TEAEs leading to death (2.4% and 1.7%, respectively) were similar between the 2 groups.

Serious TEAEs reported in at least 0.5% of patients in either treatment group are displayed in Table 7. Serious TEAEs were considered drug-related by the investigator in 22 (3.8%) patients in the enzalutamide plus ADT group and 16 (2.8%) patients in the placebo plus ADT group. Serious drug-related TEAEs reported in at least 2 patients in the enzalutamide plus ADT group were ALT increased, AST increased, seizure, spinal cord compression, syncope and fatigue; serious drug-related TEAEs reported in at least 2 patients in the placebo plus ADT group were myocardial infarction and general physical health deterioration.

None of the fatal TEAEs reported for patients receiving enzalutamide plus ADT were assessed by the investigator as related to study drug.

The TEAEs of special interest most frequently reported in the enzalutamide plus ADT group were musculoskeletal events (26.4%), fatigue (24.1%), hypertension (8.6%) and fractures (6.5%) Table 8. The incidence of TEAEs of special interest was generally similar between treatment groups. The categories of TEAEs of special interest with an at least 2% difference between treatment groups were fatigue, cognitive/memory impairment, hypertension and fractures.

In summary, the AE profile of enzalutamide plus ADT appears to be broadly consistent with the known safety profile of enzalutamide.

Other Observations Related to Safety

No clinically significant differences between treatment groups were noted in hematology parameters.

Overall, no clinically significant differences between treatment groups were noted in serum chemistry parameters. The results for potentially clinically significant values in liver enzymes and total bilirubin were generally similar between the treatment groups. None of the patients were confirmed as a Hy's law case.

No clinically significant differences between treatment groups were noted in testosterone levels, ECG abnormalities or ECOG performance status.

For blood pressure, clinically significant changes were observed in both treatment groups but consistent with the known safety profiles of both drugs. No clinically significant changes or findings were noted from the other vital sign measurements including pulse rate, body temperature and weight.

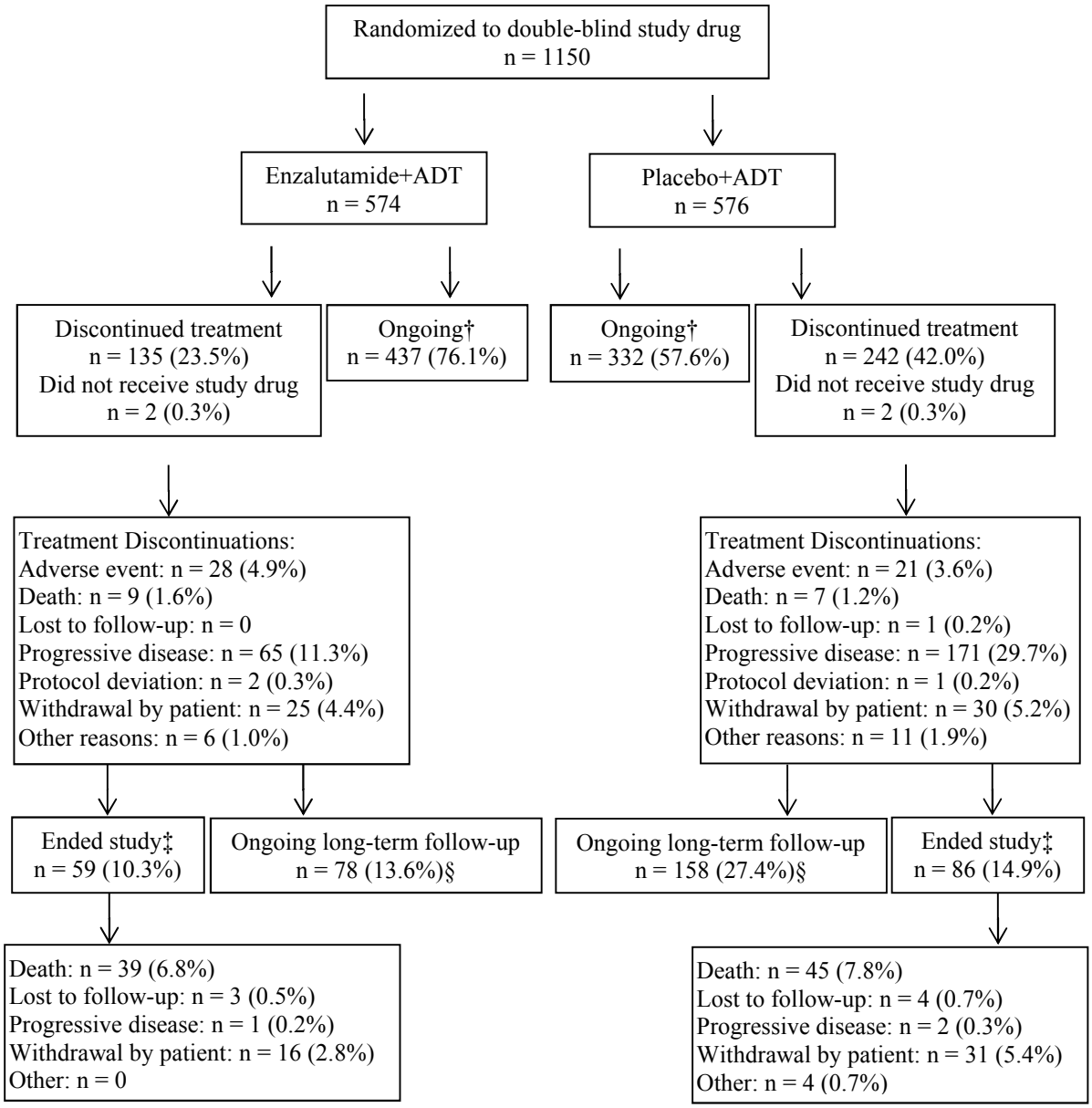
Overall Conclusions:

ARCHES (Study 9785-CL-0335) demonstrated a substantial clinical benefit for enzalutamide plus ADT compared with placebo plus ADT in patients with mHSPC. The demonstrated benefits as seen with rPFS were clinically meaningful, statistically significant, robust and supported by consistent results from most secondary efficacy endpoints.

The overall safety profile of enzalutamide in this study appears to be generally consistent with the safety profile of enzalutamide in previous clinical studies in patients with CRPC.

Date of Report: 31 May 2019

Figure 1 Disposition of Patients



Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy.

† Patients were still on-treatment by the cutoff date (or no documentation of treatment discontinuation was received).

‡ Includes patients who did not complete any long-term follow-up visits or ended their participation in the long-term follow-up.

§ Patients in long-term follow-up after treatment discontinuation

Source: End-of-Text Tables 12.1.1.3 and 12.1.1.5

Table 1 Demographic Characteristics (ITT Population)

Parameter Statistics/Criteria	Enzalutamide+ADT (n = 574)	Placebo+ADT (n = 576)	Total (n = 1150)
Age Category (years), n (%)			
< 65	148 (25.8)	152 (26.4)	300 (26.1)
65 to < 75	256 (44.6)	255 (44.3)	511 (44.4)
≥ 75	170 (29.6)	169 (29.3)	339 (29.5)
Age (years)			
Mean (SD)	69.5 (8.0)	69.5 (8.4)	69.5 (8.2)
Median (min, max)	70.0 (46, 92)	70.0 (42, 92)	70.0 (42, 92)
Race†, n (%)			
White	466 (81.2)	460 (79.9)	926 (80.5)
Black or African American	8 (1.4)	8 (1.4)	16 (1.4)
Asian	75 (13.1)	80 (13.9)	155 (13.5)
Other	2 (0.3)	3 (0.5)	5 (0.4)
Missing	23 (4.0)	25 (4.3)	48 (4.2)
Ethnicity†, n (%)			
Hispanic or Latino	46 (8.0)	37 (6.4)	83 (7.2)
Not Hispanic or Latino	504 (87.8)	514 (89.2)	1018 (88.5)
Missing	24 (4.2)	25 (4.3)	49 (4.3)
Geographic Region‡, n (%)			
Asia-Pacific	104 (18.1)	113 (19.6)	217 (18.9)
Europe	341 (59.4)	344 (59.7)	685 (59.6)
North America	86 (15.0)	77 (13.4)	163 (14.2)
South America	32 (5.6)	30 (5.2)	62 (5.4)
Other	11 (1.9)	12 (2.1)	23 (2.0)
Weight (kg)			
n	573	575	1148
Mean (SD)	81.25 (16.17)	81.26 (16.22)	81.26 (16.19)
Median (min, max)	80.00 (42.7, 163.0)	80.00 (39.1, 157.5)	80.00 (39.1, 163.0)
Body Mass Index (kg/m^2)			
n	567	570	1137
Mean (SD)	27.20 (4.44)	27.21 (4.61)	27.20 (4.53)
Median (min, max)	26.65 (16.7, 45.2)	26.91 (16.4, 48.8)	26.81 (16.4, 48.8)

Data cutoff date: 14 Oct 2018

All patients who were randomized in this study (ITT population).

ITT: intent-to-treat

† Race/Ethnicity was not collected in France, by country regulations.

‡ Europe includes: Russian Federation, Slovakia, Italy, Denmark, Romania, Spain, the Netherlands, Poland, France, Finland, Belgium, Sweden, Germany and the United Kingdom. North America includes the United States and Canada. South America includes Chile and Argentina. Asia-Pacific includes Japan, Taiwan, Republic of Korea, Australia and New Zealand. Other is Israel.

Source: End-of-Text Table 12.1.2.1

Table 2 Prostate Cancer Disease History (ITT Population)

Parameter Statistics/Criteria	Enzalutamide+ADT (n = 574)	Placebo+ADT (n = 576)	Total (n = 1150)
ECOG Performance Status† on Day 1, n (%)			
0	448 (78.0)	443 (76.9)	891 (77.5)
1	125 (21.8)	133 (23.1)	258 (22.4)
Baseline Serum PSA (ng/mL)‡			
n	572	574	1146
Mean (SD)	75.37 (356.36)	104.78 (834.48)	90.10 (641.90)
Median (min, max)	5.36 (0.0, 4823.5)	5.07 (0.0, 19000.0)	5.21 (0.0, 19000.0)
Total Gleason Score at Initial Diagnosis, n (%)			
< 8	171 (29.8)	187 (32.5)	358 (31.1)
≥ 8	386 (67.2)	373 (64.8)	759 (66.0)
Volume of Disease§, n (%)			
Low	220 (38.3)	203 (35.2)	423 (36.8)
High	354 (61.7)	373 (64.8)	727 (63.2)
Prior Docetaxel Therapy Use§, n (%)			
None	471 (82.1)	474 (82.3)	945 (82.2)
1 to 5 cycles	14 (2.4)	11 (1.9)	25 (2.2)
6 cycles	89 (15.5)	91 (15.8)	180 (15.7)
Previous Use of ADT, n (%)			
None	39 (6.8)	61 (10.6)	100 (8.7)
≤ 3 months	414 (72.1)	394 (68.4)	808 (70.3)
> 3 months	121 (21.1)	120 (20.8)	241 (21.0)
Unknown¶	0	1 (0.2)	1 (0.1)
Duration of prostate cancer (months)††			
n	572	575	1147
Mean (SD)	17.56 (37.47)	19.99 (41.40)	18.78 (39.49)
Median (min, max)	3.47 (0.26, 267.89)	3.38 (0.39, 259.09)	3.45 (0.26, 267.89)
Duration of metastatic disease (months)‡‡			
n	562	571	1133
Mean (SD)	3.40 (6.66)	3.77 (8.34)	3.59 (7.55)
Median (min, max)	2.07 (0.20, 82.83)	2.07 (0.03, 141.21)	2.07 (0.03, 141.21)
Metastasis based on ICR§§, n (%)			
Yes	536 (93.4)	531 (92.2)	1067 (92.8)
No	34 (5.9)	45 (7.8)	79 (6.9)
Unknown	4 (0.7)	0	4 (0.3)
Location of metastasis based on ICR, n (%)			
Bone only	268 (46.7)	245 (42.5)	513 (44.6)
Soft tissue only	51 (8.9)	45 (7.8)	96 (8.3)
Bone and soft tissue	217 (37.8)	241 (41.8)	458 (39.8)
Location of metastasis based on investigator assessment, n (%)			
Bone only	249 (43.4)	241 (41.8)	490 (42.6)
Soft tissue only	64 (11.1)	72 (12.5)	136 (11.8)
Bone and soft tissue	254 (44.3)	258 (44.8)	512 (44.5)
Total number of bone lesions based on ICR, n (%)			
1	83 (14.5)	70 (12.2)	153 (13.3)
2 to 4	151 (26.3)	142 (24.7)	293 (25.5)
5 to 9	95 (16.6)	106 (18.4)	201 (17.5)
10 to 19	111 (19.3)	114 (19.8)	225 (19.6)
≥ 20 (including TNC)	45 (7.8)	54 (9.4)	99 (8.6)

Table continued on next page

Parameter Statistics/Criteria	Enzalutamide+ADT (n = 574)	Placebo+ADT (n = 576)	Total (n = 1150)
Total number of bone lesions based on investigator assessment, n (%)			
1	72 (12.5)	59 (10.2)	131 (11.4)
2 to 4	124 (21.6)	126 (21.9)	250 (21.7)
5 to 9	77 (13.4)	74 (12.8)	151 (13.1)
10 to 19	26 (4.5)	28 (4.9)	54 (4.7)
≥ 20	23 (4.0)	23 (4.0)	46 (4.0)
TNC¶¶	181 (31.5)	189 (32.8)	370 (32.2)

Data cutoff date: 14 Oct 2018

All patients who were randomized in this study (ITT population).

ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; ICR: independent central review; ITT: intent-to-treat; max: maximum; min: minimum; PSA: prostate-specific antigen; TNC: too numerous to count.

† Grade 0: Fully active, able to carry on all predisease performance without restriction. Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

‡ PSA levels of 0 were observed, which could have been due to prior treatment with docetaxel and/or use of ADT within 3 months of study start. One patient receiving placebo plus ADT had a baseline PSA level of > 19000 ng/mL, which impacts the calculation of mean baseline PSA for this group.

§ Volume of disease and prior docetaxel therapy were stratification factors at randomization.

¶ The patient had prior ADT; however, the duration of ADT use is unknown.

†† Duration of prostate cancer (months) = [(date of randomization - date of initial diagnosis) + 1]/(365.25/12)

‡‡ Duration of metastatic disease (months) =
[(date of randomization - date of metastatic disease) + 1]/(365.25/12)

§§ Enrollment was based on investigator assessment of metastatic disease; ICR confirmation of this assessment was not required prior to entry into the study.

¶¶ The instructions to the investigators allowed the selection of “too numerous to count” as an alternative to an exact bone lesion count.

Source: End-of-Text Tables 12.1.2.2, 12.1.2.4 and 12.1.2.5

Table 3 Summary of Primary and Secondary Efficacy Results (ITT Population)

	Enzalutamide +ADT (n = 574)	Placebo +ADT (n = 576)	Hazard Ratio (95% CI) or Difference in Response Rates (95% CI)†	P value†
Primary Efficacy Endpoint				
Radiographic Progression-free Survival‡				
Number of events, n (%)	89 (15.51)	198 (34.38)	0.39 (0.30, 0.50)	< 0.0001
Median (95% CI) (months)	NR	19.4 (16.59, NR)		
Key Secondary Efficacy Endpoints				
Time to PSA Progression¶				
Number of events, n (%)	45 (7.84)	189 (32.81)	0.19 (0.13, 0.26)	< 0.0001
Median (95% CI) (months)	NR	NR (16.59, NR)		
Time to Start of New Antineoplastic Therapy††				
Number of events, n (%)	46 (8.01)	133 (23.09)	0.28 (0.20, 0.40)	< 0.0001
Median (95% CI) (months)	30.2 (NR, NR)	NR (21.06, NR)		
PSA Undetectable Rate (Decline to < 0.2 ng/mL)				
Patients with detectable PSA at baseline, n	511	506	50.5% (45.3, 55.7)	< 0.0001 §§§
Undetectable rate, n (%)	348 (68.1)	89 (17.6)		
Objective Response Rate Based on ICR‡‡				
Patients with measurable disease, n	177	182	19.3% (10.4, 28.2)	< 0.0001 §§§
Objective response, n (%)	147 (83.1)	116 (63.7)		
Time to Deterioration of Urinary Symptoms				
Number of events, n (%)	184 (32.06)	201 (34.90)	0.88 (0.72, 1.08)	0.2162
Median (95% CI) (months)	NR (19.35, NR)	16.8 (14.06, NR)		
Overall Survival (Interim Analysis)§				
Number of events, n (%)	39 (6.79)	45 (7.81)	0.81 (0.53, 1.25)	0.3361
Median (95% CI) (months)	NR	NR		
Other Secondary Efficacy Endpoints				
Time to First Symptomatic Skeletal Event§§				
Number of events, n (%)	31 (5.40)	56 (9.72)	0.52 (0.33, 0.80)	0.0026 ¶¶¶
Median (95% CI) (months)	NR	NR		
Time to Castration Resistance¶¶				
Number of events, n (%)	90 (15.68)	257 (44.62)	0.28 (0.22, 0.36)	< 0.0001 ¶¶¶
Median (95% CI) (months)	NR	13.9 (11.40, 17.18)		
Time to Deterioration of Quality of Life (FACT-P)†††				
Number of events, n (%)	280 (48.78)	274 (47.57)	0.96 (0.81, 1.14)	0.6548 ¶¶¶
Median (95% CI) (months)	11.3 (11.04, 13.83)	11.1 (8.48, 13.83)		
Time to Pain Progression (BPI-SF)‡‡‡				
Number of events, n (%)	324 (56.45)	329 (57.12)	0.92 (0.78, 1.07)	0.2715 ¶¶¶
Median (95% CI) (months)	8.3 (8.25, 10.91)	8.3 (5.65, 8.38)		

Footnotes appear on next page

Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CR: complete response; FACT-P: Functional Assessment of Cancer Therapy – Prostate; ICR: independent central review; ITT: intent-to-treat; NR: not reached; ORR: objective response rate; PR: partial response; PSA: prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumours; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1.

† Hazard ratio and its 95% CI were based on a Cox regression model stratified by prior docetaxel use and disease volume. Difference in rate (95% CI) for PSA undetectable rate and ORR was computed using Clopper-Pearson method based on exact binomial distribution. P value (2-sided) from stratified log-rank test, unless indicated otherwise.

‡ Time from randomization to the first objective evidence of radiographic disease progression as assessed by central review, or death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurred first.

§ Number of patients known to have died as of the analysis data cutoff date. Analysis was performed at a level of significance of 0.0000054.

¶ PSA progression date was defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir, which was confirmed by a second consecutive value at least 3 weeks later. In patients with PSA progression, the time to PSA progression was calculated as the time from randomization to the date of first observation of PSA progression.

†† Based on the first postbaseline use of antineoplastic therapy for prostate cancer.

‡‡ The objective response rate was calculated as the percentage of patients with measureable disease at baseline who achieved a CR or PR in their soft tissue disease using the RECIST 1.1 criteria; that is with CR or PR as best RECIST overall response.

§§ A symptomatic skeletal event was defined as radiation to bone, surgery to bone, a clinically apparent pathological bone fracture or a spinal cord compression.

¶¶ A castration resistance event was defined as any of the following in the presence of castrate levels of testosterone (< 50 ng/dL): radiographic disease progression, PSA progression or a symptomatic skeletal event, whichever occurred first.

††† A deterioration of quality of life was defined as a decrease of at least 10 points in the FACT-P total score from baseline.

‡‡‡ Pain progression was defined as an increase of ≥ 30% from baseline in the average BPI-SF item scores.

§§§ Cochran-Mantel-Haenszel score test, stratified by volume of disease and previous docetaxel use.

¶¶¶ Nominal P values.

Source: End-of-Text Tables 12.3.1.1.1, 12.3.3.1.1, 12.3.4.1.1, 12.3.5.1.1, 12.3.6.1.1, 12.3.7.1.1, 12.3.7.2.1, 12.3.8.1.1, 12.3.8.2.3, 12.3.8.3.1 and 12.3.9.1

Table 4 rPFS - Primary Efficacy Analysis Based on ICR Assessment (ITT Population)

Category **Parameter/Statistics**	**Enzalutamide+ADT (n = 574)**	**Placebo+ADT (n = 576)**
Events†, n (%)	89 (15.51)	198 (34.38)
Kaplan-Meier estimates (months)		
25th percentile	NR	8.5
Median (95% CI)‡	NR	19.4 (16.59, NR)
75th percentile	NR	NR
Kaplan-Meier events free rate estimate at 12 months	84.45%	63.71%
Treatment comparison: enzalutamide+ADT vs placebo+ADT		
Cox HR (95% CI)§	0.39 (0.30, 0.50)	
Log-rank P value§	< 0.0001	
Individual components in rPFS events¶, n (%)		
rPD	77 (13.41)	185 (32.12)
Death within 24 weeks after treatment discontinuation	12 (2.09)	13 (2.26)
Censoring†, n (%)		
Censored	485 (84.49)	378 (65.63)
First censored reason		
No baseline assessment	4 (0.82)	0
No postbaseline assessment	9 (1.86)	16 (4.23)
All postbaseline assessments were “Not evaluable”	24 (4.95)	14 (3.70)
No rPFS event before the data cutoff date	448 (92.37)	348 (92.06)

Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ICR: independent central review; ITT: intent-to-treat; NR: not reached; rPD: radiographic disease progression; rPFS: radiographic progression-free survival.

† A progression event was defined as objective evidence of radiographic disease progression based on the assessments by ICR or death by any cause within 24 weeks from study drug discontinuation, whichever occurred first. The time to event was calculated from the date of randomization to the date of occurrence of the first progression event. For patients with no documented progression event, rPFS was censored on the date of the last radiologic assessment performed before the cutoff date.

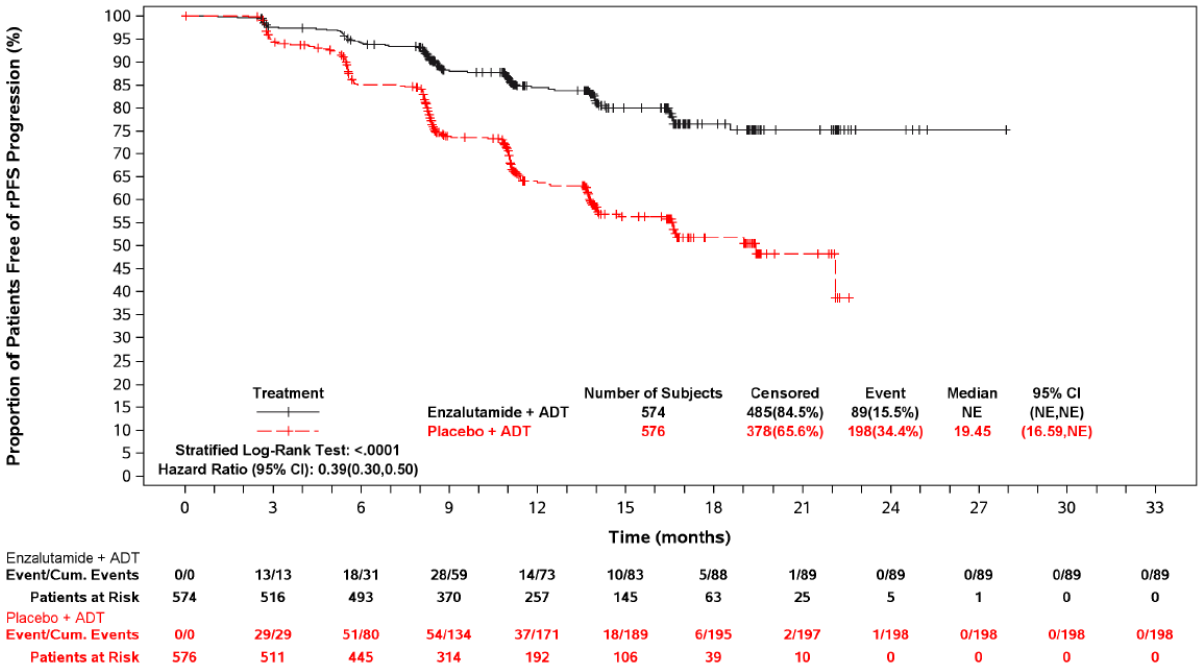
‡ Calculated by Brookmeyer and Crowley method

§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)

¶ Calculated as a percentage of the total number of randomized patients

Source: End-of-Text Tables 12.3.1.1.1, 12.3.1.1.2 and 12.3.1.1.3

Figure 2 Kaplan-Meier Plot of rPFS Based on ICR Assessment (ITT Population)



Enzalutamide + ADT												
Event/Cum. Events	0/0	13/13	18/31	28/59	14/73	10/83	5/88	1/89	0/89	0/89	0/89	0/89
Patients at Risk	574	516	493	370	257	145	63	25	5	1	0	0
Placebo + ADT												
Event/Cum. Events	0/0	29/29	51/80	54/134	37/171	18/189	6/195	2/197	1/198	0/198	0/198	0/198
Patients at Risk	576	511	445	314	192	106	39	10	0	0	0	0

Data cutoff date: 14 Oct 2018

A progression event was defined as objective evidence of radiographic disease progression based on the assessments by ICR or death by any cause within 24 weeks from study drug discontinuation, whichever occurred first. The time to event was calculated from the date of randomization to the date of occurrence of the first progression event. For patients with no documented progression event, rPFS was censored on the date of the last radiologic assessment performed before the cutoff date.

ADT: androgen deprivation therapy; CI: confidence interval; Cum.: cumulative; ICR: independent central review; ITT: intent-to-treat; NE: not estimable; rPFS: radiographic progression-free survival.

Source: End-of-Text Figure 12.3.1.1

Table 5 Overview of Treatment-emergent Adverse Events and Deaths (Safety Population)

	Enzalutamide+ADT (n = 572)		Placebo+ADT (n = 574)	
	n (%)	**#E**	**n (%)**	**#E**
Any TEAE	487 (85.1)	2475	493 (85.9)	2221
NCI-CTC Grade 3 and 4 TEAEs	135 (23.6)	231	142 (24.7)	225
Drug-related† TEAEs	303 (53.0)	856	268 (46.7)	624
Serious TEAEs‡	104 (18.2)	189	112 (19.5)	185
Drug-related† Serious TEAEs‡	22 (3.8)	34	16 (2.8)	23
TEAEs Leading to Death	14 (2.4)	18	10 (1.7)	11
Drug-related† TEAEs Leading to Death	0	0	1 (0.2)	1
TEAEs Leading to Permanent Discontinuation of Study Drug	41 (7.2)	50	30 (5.2)	37
Drug-related† TEAEs Leading to Permanent Discontinuation of Study Drug	16 (2.8)	19	12 (2.1)	15
TEAEs Leading to Dose Reduction	25 (4.4)	38	11 (1.9)	13
Deaths§	39 (6.8)	NA	45 (7.8)	NA

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

A TEAE was defined as an AE that occurred or worsened at any time from the first study drug intake up to the date of end of treatment plus 30 days, study discontinuation or the start of new antineoplastic therapy, whichever occurred first. AE grading was based on NCI-CTCAE v4.03.

ADT: androgen deprivation therapy; AE: adverse event; #E: number of events; NA: not applicable; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

† Possible or probable, as assessed by the investigator, or records where relationship was missing.

‡ Included SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.

§ All reported deaths after the first study drug administration.

Source: End-of-Text Table 12.6.1.1

Table 6 Treatment-emergent Adverse Events Reported in at Least 5% of Patients in Either Treatment Group (Safety Population)

MedDRA v21.0 Preferred Term	Overall Incidence, n (%)	
	Enzalutamide+ADT (n = 572)	Placebo+ADT (n = 574)
Overall	**487 (85.1)**	**493 (85.9)**
Hot flush	155 (27.1)	128 (22.3)
Fatigue	112 (19.6)	88 (15.3)
Arthralgia	70 (12.2)	61 (10.6)
Back pain	43 (7.5)	62 (10.8)
Weight increased	35 (6.1)	44 (7.7)
Hypertension	46 (8.0)	32 (5.6)
Diarrhoea	34 (5.9)	33 (5.7)
Oedema peripheral	29 (5.1)	38 (6.6)
Nausea	37 (6.5)	29 (5.1)
Asthenia	31 (5.4)	28 (4.9)
Constipation	28 (4.9)	31 (5.4)
Musculoskeletal pain	36 (6.3)	23 (4.0)
Dizziness	29 (5.1)	20 (3.5)

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

ADT: androgen deprivation therapy.

Source: End-of-Text Table 12.6.1.16

Table 7 Serious Treatment-emergent Adverse Events Reported in at Least 0.5% of Patients in Either Treatment Group (Safety Population)

MedDRA v21.0 Preferred Term	Overall Incidence, n (%)	
	Enzalutamide+ADT (n = 572)	Placebo+ADT (n = 574)
Overall	**104 (18.2)**	**112 (19.5)**
Anaemia	4 (0.7)	3 (0.5)
Atrial fibrillation	2 (0.3)	4 (0.7)
Sepsis	3 (0.5)	3 (0.5)
Fall	3 (0.5)	2 (0.3)
Malignant neoplasm progression	6 (1.0)	3 (0.5)
Basal cell carcinoma	4 (0.7)	4 (0.7)
Spinal cord compression	3 (0.5)	6 (1.0)
Syncope	3 (0.5)	0
Hydronephrosis	4 (0.7)	3 (0.5)
Urinary retention	3 (0.5)	4 (0.7)
Haematuria	4 (0.7)	2 (0.3)
Pulmonary embolism	3 (0.5)	3 (0.5)

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

Sorting order: ascending order by system organ class code and descending by the number of patients of total group by preferred term. In case of ties ascending order by preferred term code is applied.

ADT: androgen deprivation therapy.

Source: End-of-Text Table 12.6.1.7

Table 8 Overview of Treatment-emergent Adverse Events of Special Interest (Safety Population)

MedDRA v21.0 Category	Enzalutamide+ADT (n = 572)	Placebo+ADT (n = 574)
	n (%)	n (%)
Convulsion	2 (0.3)	2 (0.3)
Hypertension	49 (8.6)	36 (6.3)
Neutrophil count decreased	5 (0.9)	4 (0.7)
Cognitive/memory impairment	26 (4.5)	12 (2.1)
Ischemic heart disease	10 (1.7)	8 (1.4)
Other selected cardiovascular events	13 (2.3)	9 (1.6)
Posterior reversible encephalopathy syndrome	0	0
Fatigue	138 (24.1)	112 (19.5)
Fall	21 (3.7)	15 (2.6)
Fractures	37 (6.5)	24 (4.2)
Loss of consciousness	9 (1.6)	1 (0.2)
Thrombocytopenia	3 (0.5)	3 (0.5)
Musculoskeletal events	151 (26.4)	159 (27.7)
Severe cutaneous adverse reactions	0	1 (0.2)
Angioedema	7 (1.2)	1 (0.2)
Rash	15 (2.6)	9 (1.6)
Second primary malignancies	11 (1.9)	11 (1.9)

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

All second primary malignancies recorded after the study treatment start are reported, including those recorded after the treatment-emergent period.

ADT: androgen deprivation therapy.

Source: End-of-Text Table 12.6.1.20