EUROPEAN UROLOGY 70 (2016) 675–683

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

The PREVAIL Study: Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-treated Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer

Christopher P. Evans[a,*], *Celestia S. Higano*[b], *Thomas Keane*[c], *Gerald Andriole*[d], *Fred Saad*[e], *Peter Iversen*[f], *Kurt Miller*[g], *Choung-Soo Kim*[h], *Go Kimura*[i], *Andrew J. Armstrong*[j], *Cora N. Sternberg*[k], *Yohann Loriot*[l], *Johann de Bono*[m], *Sarah B. Noonberg*[n,†], *Hank Mansbach*[o,†], *Suman Bhattacharya*[p], *Frank Perabo*[q,‡], *Tomasz M. Beer*[r], *Bertrand Tombal*[s]

[a] *Department of Urology, UC Davis Comprehensive Cancer Center, Sacramento, CA, USA;* [b] *Medical Oncology Division, University of Washington/Seattle Cancer Care Alliance, Seattle, WA, USA;* [c] *Department of Urology, Medical University of South Carolina, Charleston, SC, USA;* [d] *Division of Urologic Surgery, Washington University School of Medicine, St. Louis, MO, USA;* [e] *Department of Surgery, University of Montreal Health Center, Montreal, Canada;* [f] *Copenhagen Prostate Cancer Center, Rigshospitalet, University of Copenhagen, Denmark;* [g] *Department of Urology, Charité-Universitätsmedizin Berlin, Berlin, Germany;* [h] *Department of Urology, Asan Medical Center, Seoul, South Korea;* [i] *Department of Urology, Nippon Medical School Hospital, Tokyo, Japan;* [j] *Division of Medical Oncology and Urology, Duke Cancer Institute, Durham, NC, USA;* [k] *Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy;* [l] *Department of Cancer Medicine, Institut Gustave-Roussy, Villejuif, France;* [m] *Drug Development Unit, Institute of Cancer Research, Royal Marsden Hospital, London, UK;* [n] *Department of Early Clinical Development, Medivation, Inc., San Francisco, CA, USA;* [o] *Department of Medical Affairs, Medivation, Inc., San Francisco, CA, USA;* [p] *Department of Biostatistics, Medivation, Inc., San Francisco, CA, USA;* [q] *Astellas Pharma, Inc., Northbrook, IL, USA;* [r] *Department of Hematology and Medical Oncology, OHSU Knight Cancer Institute, Portland, OR, USA;* [s] *Department of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

Article info

Article history:
Accepted March 4, 2016

Associate Editor:
James Catto

Keywords:
Androgen receptor
Castration-resistant prostatic cancer
Enzalutamide

Abstract

Background: Enzalutamide, an oral androgen receptor inhibitor, significantly improved overall survival (OS) and radiographic progression-free survival (rPFS) versus placebo in the PREVAIL trial of men with chemotherapy-naïve metastatic castration-resistant prostate cancer.
Objective: To assess the effects of enzalutamide versus placebo in patients from PREVAIL based on site and extent of baseline disease.
Design, setting, and participants: One thousand seven hundred and seventeen asymptomatic or minimally symptomatic patients were randomized to enzalutamide (n = 872) or placebo (n = 845). Subgroup analyses included nonvisceral (only bone and/or nodal; n = 1513), visceral (lung and/or liver; n = 204), low-volume bone disease (<4 bone metastases; n = 867), high-volume bone disease (≥4 bone metastases; n = 850), lymph node only disease (n = 195).
Intervention: Oral enzalutamide (160 mg) or placebo once daily while continuing androgen deprivation therapy.
Outcome measurements and statistical analysis: Coprimary endpoints (rPFS, OS) were prospectively evaluated in nonvisceral and visceral subgroups. All other efficacy analyses were post hoc.

† These authors were employees of Medivation, Inc.
‡ This author was an employee of Astellas Pharma, Inc.
* Corresponding author. Department of Urology, Urologic Surgical Oncology, University of California, Davis, School of Medicine, 4860 Y Street, Suite 3500, Sacramento, CA 95817, USA.
Tel. +1-916-734-7520; Fax: +1-916-734-8094.
E-mail address: cpevans@ucdavis.edu (C.P. Evans).

http://dx.doi.org/10.1016/j.eururo.2016.03.017

CrossMark

Results and limitations: Enzalutamide improved rPFS versus placebo in patients with nonvisceral disease (hazard ratio [HR], 0.18; 95% confidence interval [CI], 0.14–0.22), visceral disease (HR, 0.28; 95% CI, 0.16–0.49), low- or high-volume bone disease (HR, 0.16; 95% CI, 0.11–0.22; HR, 0.22; 95% CI, 0.16–0.29, respectively), and lymph node only disease (HR, 0.09; 95% CI, 0.04–0.19). For OS, HRs favored enzalutamide (<1) across all disease subgroups, although 95% CI was >1 in patients with visceral disease (HR, 0.82; 95% CI, 0.55–1.23). Enzalutamide was well tolerated in patients with or without visceral disease.
Conclusions: Enzalutamide provided clinically significant benefits in men with chemotherapy-naïve metastatic castration-resistant prostate cancer, with or without visceral disease, low- or high-volume bone disease, or lymph node only disease.
Patient summary: Patients with metastatic castration-resistant prostate cancer—including those with or without visceral disease or widespread bone disease—benefitted from enzalutamide, an active well-tolerated therapy.

1. Introduction

Prostate cancer is the second most common cancer in men, trailing only lung cancer in global incidence [1]. In 2012, approximately 1.1 million men worldwide were diagnosed with prostate cancer. In the USA, it is estimated that in 2015 there will be 220 080 new cases of prostate cancer and 27 540 deaths due to this disease, accounting for 5% of all US cancer deaths [2]. The majority of deaths occur due to metastatic castration-resistant prostate cancer (mCRPC), when disease progression occurs despite maintaining castrate levels of testosterone with medical or surgical castration. Bone and/or lymph node metastases are common in patients with mCRPC, with bone metastases contributing to skeletal-related complications that can reduce quality of life and increase the risk of death [3,4]. Visceral disease in the lung and/or liver occurs in about 20–30% of mCRPC patients and is associated with a particularly poor prognosis [5–10].

Until recently, standard first-line therapy for patients progressing on androgen deprivation therapy (ADT) was docetaxel plus prednisone [5]. Over the last few years, several agents with distinct mechanisms of action have demonstrated benefit in phase 3 trials in men with asymptomatic or minimally symptomatic mCRPC who had not received previous chemotherapy. Sipuleucel-T, an autologous immunotherapy, prolonged survival but did not delay disease progression in this setting [11]. Abiraterone acetate, an androgen biosynthesis inhibitor, significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) [12]. Most recently, the oral androgen receptor inhibitor enzalutamide significantly prolonged OS and rPFS in the PREVAIL trial of men with chemotherapy-naïve mCRPC progressing despite ADT [13]. The benefit of enzalutamide was demonstrated for all prespecified secondary endpoints.

The primary findings of PREVAIL were reported previously [13]. The current analyses focus on the effect of enzalutamide versus placebo on clinical outcomes in PREVAIL patients based on the extent of bone and lymph node disease at baseline (including those with or without visceral disease), low- or high-volume bone disease, or lymph node only disease. Our analyses includes secondary outcomes in patients with only bone and or nodal soft-tissue disease, a patient population commonly treated by urologists and medical oncologists.

2. Materials and methods

2.1. Study population

Eligibility criteria for PREVAIL were described in detail previously [13]. Briefly, eligible patients had asymptomatic or minimally symptomatic mCRPC, an Eastern Cooperative Oncology Group Performance Status of 0–1, and had not previously received chemotherapy. PREVAIL allowed patients with visceral disease (metastases to the lung and/or liver).

2.2. Study design and treatment

PREVAIL was a phase 3, multinational, double-blind, randomized, placebo-controlled study (NCT01212991) comparing the efficacy of enzalutamide versus placebo in men with minimally symptomatic or asymptomatic metastatic prostate cancer who had not received chemotherapy. Patients were enrolled at 207 sites in 22 countries between September 2010 and September 2012. Patients were randomized 1:1 to receive either oral enzalutamide (160 mg) or placebo once daily, which they continued until confirmed radiographic disease progression and initiation of cytotoxic chemotherapy or an investigational agent for prostate cancer. Randomization was central and stratified by study site. Patients were required to continue ADT during the study. Patients were allowed to continue or initiate corticosteroids. Radiation therapy and initiation of bisphosphonates or other approved bone-targeting agents were permitted.

Study endpoints have been defined previously [13]. The coprimary endpoints were rPFS and OS. Secondary endpoints included time to first skeletal-related event, time to initiation of cytotoxic chemotherapy, best overall soft-tissue response, time to prostate-specific antigen (PSA) progression, and PSA response ≥50% from baseline. Prespecified exploratory endpoints included quality-of-life assessments using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) and PSA response ≥90% from baseline.

Our analyses were conducted in the following subgroups: (1) the nonvisceral subgroup (patients with only bone or nodal disease at screening), (2) the visceral subgroup (patients with lung and/or liver metastases), (3) the low- and high-volume bone disease subgroups (patients with <4 vs ≥4 bone metastases, respectively), and (4) the subgroup of patients with lymph node only disease. Patients in the visceral subgroup may have also had bone or nodal disease. The

coprimary endpoints of rPFS and OS were prospectively evaluated in the nonvisceral and visceral subgroups. All other efficacy analyses were post hoc. These included evaluation of secondary endpoints and an exploratory analysis of rPFS and OS in patients with three or fewer bone metastases at baseline and those with four or more bone metastases at baseline for all patients and separately for the nonvisceral and visceral subgroups. For this analysis, the cutoff (<4 vs ≥4 bone metastases) was selected based on the definition for high-volume disease used in the CHAARTED trial [14].

2.3. Statistical analysis

A two-sided, unstratified log-rank test was used to compare rPFS and OS between the enzalutamide and placebo groups. Estimates of medians and 95% confidence intervals (CIs) were determined using the Kaplan–Meier method. Hazard ratios (HRs) were determined using an unstratified Cox regression model (with treatment as the only covariate) and were relative to placebo, with <1 favoring enzalutamide. Similarly, time-to-cytotoxic chemotherapy, FACT-P total score decline, and PSA progression were analyzed using the Kaplan–Meier method and log-rank test Cox regression model. For PSA response, only patients who had both baseline and postbaseline PSA assessments were included in the analysis; 95% CIs were reported using the Clopper–Pearson method. The *p* values are not provided for the subgroup analyses as testing for statistical significance was not prespecified.

The data cutoff date for all analyses (overall study population and subgroup analyses) was September 16, 2013, except for rPFS, which had a cutoff date of May 6, 2012. Results from the overall study population have been previously reported.

3. Results

3.1. Patients and treatments

Of 1717 patients randomized to treatment in PREVAIL, 1513 (88%) presented at screening with only nonvisceral disease to the bone and/or nodal disease, and 204 (12%) presented with visceral disease to the lung and/or liver. In both the nonvisceral and visceral subgroups, patient demographics and disease characteristics were generally similar between treatment groups (Table 1). Patients without visceral disease had a lower baseline median PSA, better performance status, and less lymph node disease than patients with visceral disease, but similar rates of bone disease (Table 1).

The median treatment duration with enzalutamide was 16.8 mo (interquartile range [IQR], 10.9–21.3) and 13.9 mo (IQR, 5.5–19.0) in the nonvisceral and visceral subgroups, respectively, and 4.7 mo (IQR, 3.0–10.3) and 3.7 mo (IQR, 2.1–6.0), respectively, with placebo. In the nonvisceral subgroup, 69% of patients receiving enzalutamide versus 20% receiving placebo had at least 12 mo of treatment. In the visceral subgroup, these percentages were 58% and 6.6%, respectively. The median follow-up for survival in the nonvisceral subgroup was 22.1 mo (IQR, 18.5–26.5) in the enzalutamide group and 22.2 mo (IQR, 18.2–26.3) in the placebo group, and was 22.8 mo (IQR, 18.2–29.2) and 24.4 mo (IQR, 20.5–27.6), respectively, in the visceral subgroup.

3.2. Efficacy

3.2.1. Primary endpoints

3.2.1.1. Prespecified analyses in patients with or without visceral disease. Consistent with results in the overall population, treatment with enzalutamide reduced the risk of radiographic progression or death in both the nonvisceral (82% risk reduction; HR, 0.18; 95% CI, 0.14–0.22) and visceral subgroups (72% risk reduction; HR, 0.28; 95% CI, 0.16–0.49; Fig. 1A). In the nonvisceral subgroup, median rPFS was 14.1 mo with enzalutamide and 4.0 mo with placebo. In the visceral subgroup, median rPFS was not yet reached with enzalutamide and 3.6 mo with placebo. A post-hoc test of the interaction between treatment and visceral status was not found ($p = 0.2$).

Table 1 – Baseline patient and disease characteristics

Baseline characteristics	Nonvisceral subgroup (*n* = 1513)		Visceral subgroup (*n* = 204)		Overall ITT population (*n* = 1717)	
	Enzalutamide (*n* = 774)	Placebo (*n* = 739)	Enzalutamide (*n* = 98)	Placebo (*n* = 106)	Enzalutamide (*n* = 872)	Placebo (*n* = 845)
Median age, yr (IQR)	71 (66–78)	71 (65–77)	73 (67–78)	71 (65–75)	72 (66–78)	71 (65–77)
Gleason score ≥8 at initial diagnosis, %	51	53	46	48	51	52
ECOG PS = 0, %	68	70	60	63	67	69
Baseline pain 0–1 on BPI-SF Q3, %	67	68	62	62	66	68
Baseline use of corticosteroids, %	3.7	4.3	6.1	3.8	4.0	4.3
Baseline use of bone targeting agents, %	25	27	28	26	26	27
Prior antiandrogen use, %	88	86	84	90	87	86
Prior radical prostatectomy, %	26	28	28	21	26	27
Median PSA, ng/ml (IQR)	51 (17–124)	42 (17–125)	80 (21–171)	70 (18–188)	54 (18–131)	44 (17–132)
Median LDH, IU/L (IQR)	184 (164–216)	184 (162–214)	188 (163–228)	201 (173–235)	185 (164–218)	185 (164–217)
Bone disease, %	85	82	82	79	85	82
Lymph node, %	49	51	59	57	50	51
Soft-tissue disease, %[a]	54	54	100	100	59	60

BPI-SF Q3 = Brief Pain Inventory Short Form Question 3; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; ITT = intent-to-treat; LDH = lactate dehydrogenase; PS = performance status; PSA = prostate-specific antigen.
[a] Lymph node, visceral, or other.

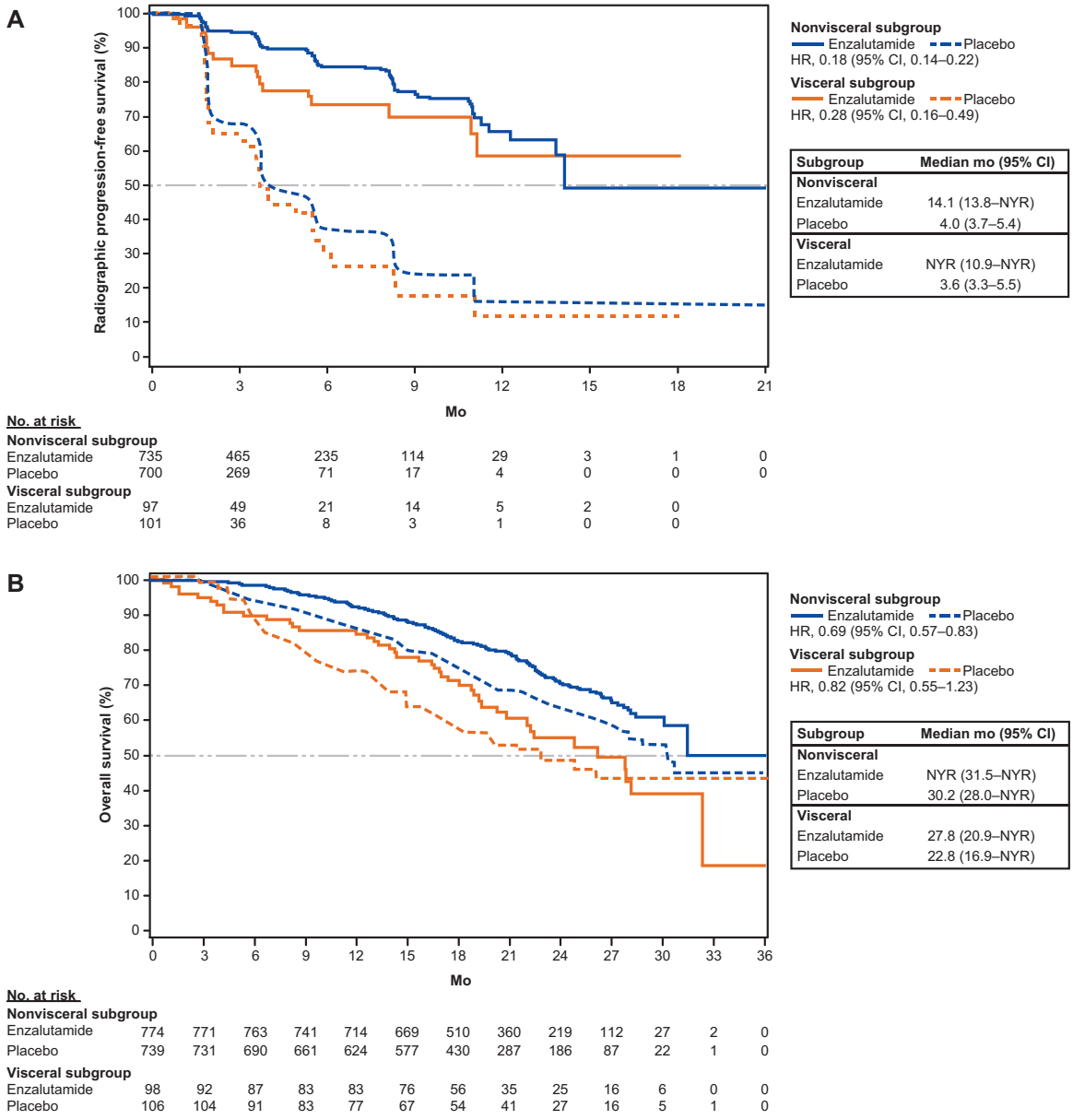

Fig. 1 – Kaplan–Meier estimates of (A) radiographic progression-free survival and (B) overall survival in the nonvisceral and visceral subgroups. CI = confidence interval; HR = hazard ratio; NYR = not yet reached.

Enzalutamide treatment also reduced the risk of death in both the nonvisceral (31% risk reduction; HR, 0.69; 95% CI, 0.57–0.83) and visceral subgroups (18% risk reduction; HR, 0.82; 95% CI, 0.55–1.23; Fig. 1B). In the nonvisceral subgroup, median OS was not yet reached in the enzalutamide group compared with 30.2 mo in the placebo group. In the visceral subgroup, median OS was 27.8 mo in the enzalutamide group and 22.8 mo in the placebo group. A post-hoc test of the interaction between treatment and visceral status was not found ($p = 0.5$).

3.2.1.2. Post-hoc analyses by extent of baseline disease. The beneficial treatment effect of enzalutamide on rPFS was observed in patients with low-volume (<4 metastases) or high-volume (≥4 metastases) bone disease (Fig. 2A), with HRs (HR, 0.16; 95% CI, 0.11–0.22 and HR, 0.22; 95% CI, 0.16–0.29, respectively) similar to those observed in the overall population. In both bone disease subsets, an rPFS benefit was observed in those with and those without visceral disease (Table 2; Supplementary Fig. 1). For OS, HRs favored enzalutamide in patients with low- or high-volume bone disease (HR, 0.62; 95% CI, 0.47–0.84 and HR, 0.75; 95% CI, 0.61–0.92, respectively; Fig. 2B). Of note, among patients with high-volume bone disease, those with nonvisceral only disease achieved a similar OS benefit with enzalutamide as those with less extensive bone disease (Table 2; Supplementary Fig. 2A), whereas those with visceral disease showed no OS benefit (HR, 1.13; 95% CI, 0.69–1.86; Table 2; Supplementary Fig. 2).

Among patients with lymph node only disease at baseline, enzalutamide reduced the risk of radiographic progression or death by 91% versus placebo (HR, 0.09;

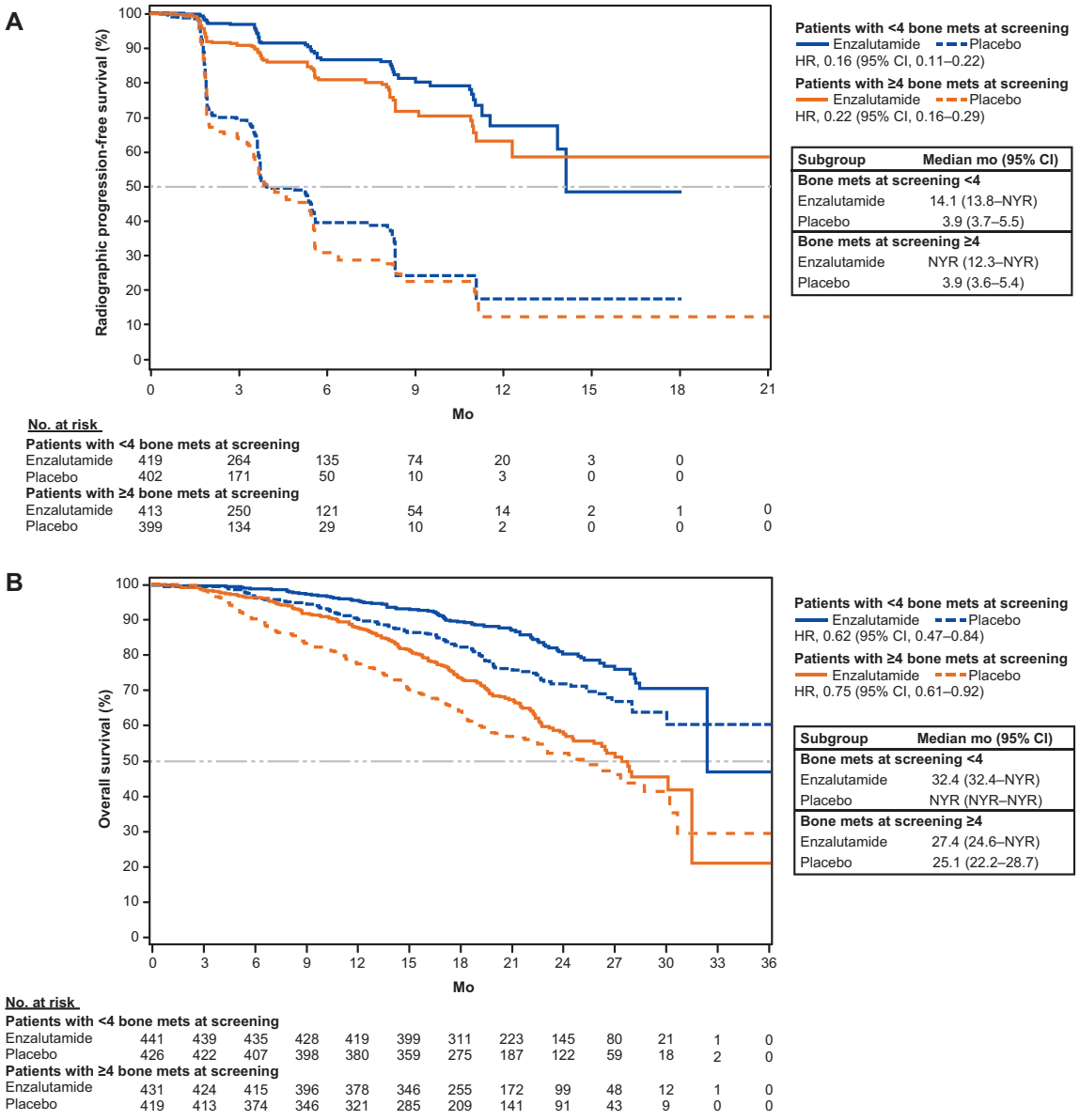

Fig. 2 – Kaplan–Meier estimates of (A) radiographic progression-free survival and (B) overall survival by number of bone metastases at screening (<4 vs ≥4).
CI = confidence interval; HR = hazard ratio; mets = metastases; NYR = not yet reached.

95% CI, 0.04–0.19; Table 2; Fig. 3A). Median OS in patients with lymph node only disease was not reached with either treatment (HR, 0.68; 95% CI, 0.35–1.32; Fig. 3B).

3.2.2. *Additional analyses for the nonvisceral subgroup*

3.2.2.1. Subsequent antineoplastic therapy. In the nonvisceral subgroup, fewer patients in the enzalutamide group than in the placebo group (40% vs 70%) received subsequent treatment with antineoplastic agents that have previously demonstrated a survival benefit in metastatic prostate cancer. The two most common therapies used by patients after discontinuing study drug were docetaxel (received by 33% and 56% of patients in the enzalutamide and placebo groups, respectively) and abiraterone (20% and 46%, respectively).

3.2.2.2. Secondary and exploratory endpoints. Post-hoc analyses included evaluation of secondary and exploratory endpoints in the nonvisceral subgroup (Table 3). Enzalutamide was associated with clinically significant delays for all progression endpoints, including a 16.8-mo delay (28.4 vs 11.6 mo) in median time to initiation of cytotoxic chemotherapy (HR, 0.36; 95% CI, 0.31–0.42; Table 3). Median time-to-PSA progression was 11.3 mo with enzalutamide versus 2.8 mo with placebo, a median difference of 8.5 mo (HR, 0.17; 95% CI, 0.15–0.20). Median time to deterioration in quality of life, as measured by a decline in FACT-P total score, was 11.2 mo with enzalutamide versus 5.6 mo with placebo (HR, 0.63; 95% CI, 0.54–0.73).

Confirmed PSA responses (≥50% PSA decline relative to baseline) were achieved by 78% of patients receiving

Table 2 – Radiographic progression-free survival and overall survival by extent and location of disease at baseline

	<4 bone metastases				≥4 bone metastases				Lymph node only		All patients	
	Nonvisceral		Visceral		Nonvisceral		Visceral					
	ENZA (n = 393)	PBO (n = 377)	ENZA (n = 48)	PBO (n = 49)	ENZA (n = 381)	PBO (n = 362)	ENZA (n = 50)	PBO (n = 57)	ENZA (n = 87)	PBO (n = 108)	ENZA (n = 872)	PBO (n = 845)
Median OS, mo	NYR	NYR	32.4	NYR	28.0	26.0	18.9	18.3	NYR	NYR	32.4	30.2
	HR, 0.64 (95% CI, 0.47–0.89)		HR, 0.52 (95% CI, 0.25–1.07)		HR, 0.70 (95% CI, 0.55–0.88)		HR, 1.13 (95% CI, 0.69–1.86)		HR, 0.68 (95% CI, 0.35–1.32)		HR, 0.71 (95% CI, 0.60–0.84) $p < 0.0001$	
Median rPFS, mo	14.1	5.2	NYR	3.6	NYR	4.0	10.9	3.9	14.1	3.7	NYR	3.9
	HR, 0.16 (95% CI, 0.11–0.23)		HR, 0.13 (95% CI, 0.05–0.35)		HR, 0.19 (95% CI, 0.13–0.26)		HR, 0.48 (95% CI, 0.24–0.95)		HR, 0.09 (95% CI, 0.04–0.19)		HR, 0.19 (95% CI, 0.15–0.23) $p < 0.0001$	

CI = confidence interval; ENZA = enzalutamide; HR = hazard ratio; NYR = not yet reached; PBO = placebo.

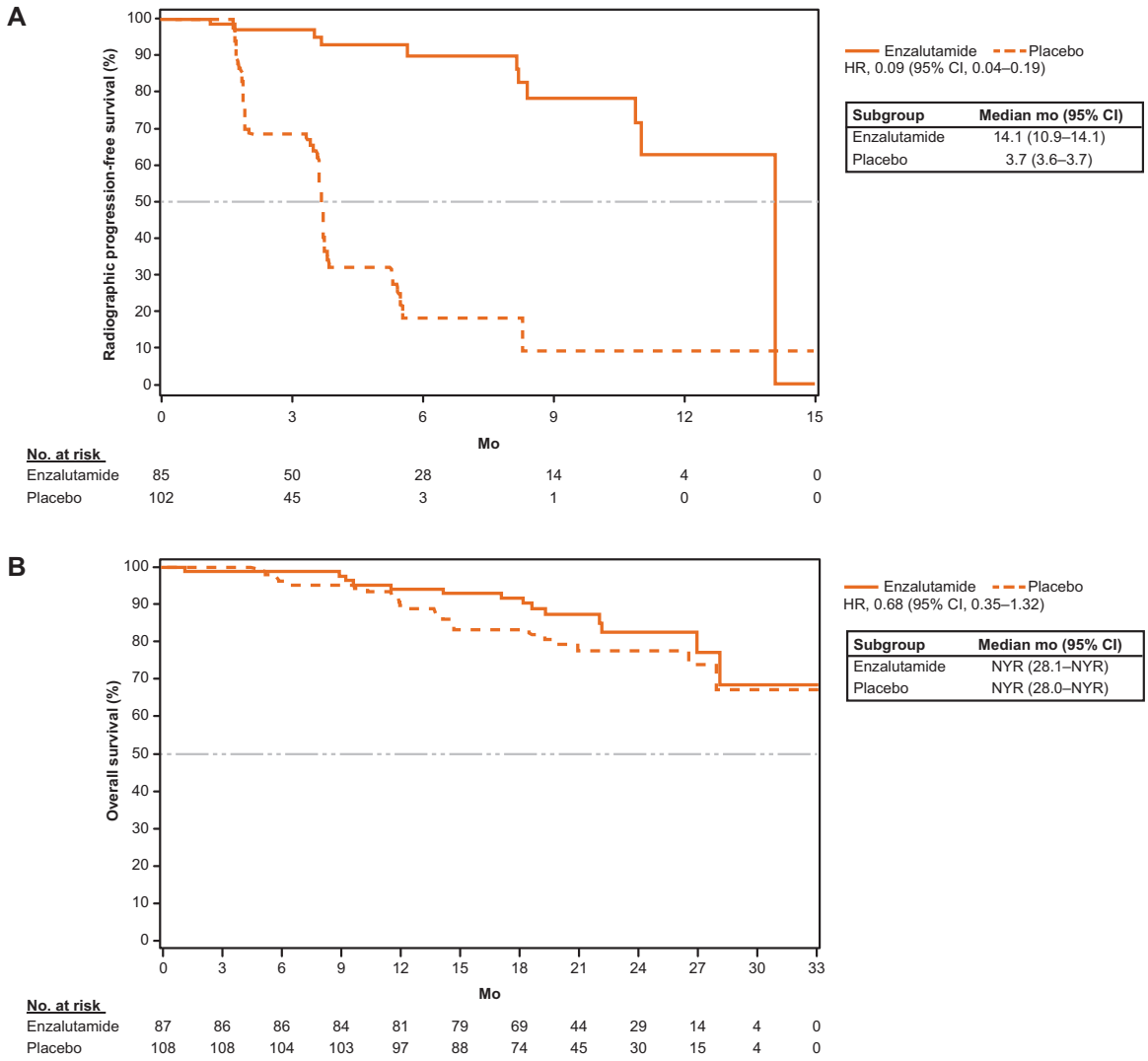

Fig. 3 – Kaplan–Meier estimates of (A) radiographic progression-free survival and (B) overall survival in the subgroup of patients with lymph node only disease.
CI = confidence interval; HR = hazard ratio; NYR = not yet reached.

Table 3 – Secondary efficacy outcomes in the nonvisceral subgroup

Endpoint	Enzalutamide (*n* = 774)	Placebo (*n* = 739)	HR (95% CI)
Median time to initiation of cytotoxic chemotherapy, mo (95% CI)	28.4 (25.8–NYR)	11.6 (10.0–13.1)	0.36 (0.31–0.42)
Median time to PSA progression, mo (95% CI)[a]	11.3 (11.1–13.8)	2.8 (2.8–2.9)	0.17 (0.15–0.20)
Median time to decline in the FACT-P total score, mo (95% CI)[b]	11.2 (11.1–13.9)	5.6 (5.3–5.6)	0.63 (0.54–0.73)
Confirmed change in PSA			
Patients with ≥1 postbaseline PSA assessment, *n* (%)	765 (99)	684 (93)	
PSA decline of ≥50% from baseline, *n*/total *N* (%)	597/765 (78)	25/684 (3.7)	
PSA decline of ≥90% from baseline, *n*/total *N* (%)	362/765 (47)	8/684 (1.2)	

CI = confidence interval; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HR = hazard ratio; NYR = not yet reached; PCWG2 = Prostate Cancer Clinical Trials Working Group; PSA = prostate-specific antigen.
[a] PSA progression defined by PCWG2 criteria [16].
[b] FACT-P decline defined as ≥10-point decrease in total score [17].

enzalutamide versus 3.7% of patients receiving placebo. Confirmed PSA responses ≥90% were achieved by 47% of patients receiving enzalutamide versus 1.2% of patients receiving placebo.

3.3. *Safety*

Nearly all patients with or without visceral disease reported at least one adverse event (AE) regardless of grade or causality. In the nonvisceral and visceral subgroups, the incidence of common AEs and specific AEs was similar to that observed in the full safety population (Table 4).

As in the full safety population, patients with nonvisceral or visceral disease receiving enzalutamide had a higher incidence of Grade 3 or higher events than those receiving placebo (42% vs 37%, nonvisceral subgroup, and 48% vs 36%, visceral subgroup); however, median exposure to study drug was much longer in the enzalutamide group than the placebo group (median difference in length of time on enzalutamide relative to placebo of 12.1 mo in the nonvisceral subgroup and 10.2 mo in the visceral subgroup). In the nonvisceral subgroup, incidence of AEs leading to treatment discontinuation (5.6% enzalutamide vs 5.3% placebo) or death (3.5% vs 3.7%, respectively) was comparable between groups and consistent with that observed in the full population.

4. Discussion

Enzalutamide added to ADT at the time of progression provided clinically significant benefit in men with chemotherapy-naïve metastatic prostate cancer, either with or without visceral disease, low- or high-volume bone disease, or lymph node only disease. Our results suggest that enzalutamide is an active treatment in this prostate cancer population, irrespective of the location and extent of baseline disease.

Table 4 – Most common and specific adverse events

Adverse events	Nonvisceral subgroup (*n* = 1511)		Visceral subgroup (*n* = 204)		Overall safety population (*n* = 1715)	
	Enzalutamide (*n* = 773)	Placebo (*n* = 738)	Enzalutamide (*n* = 98)	Placebo (*n* = 106)	Enzalutamide (*n* = 871)	Placebo (*n* = 844)
Any adverse event, *n* (%)	750 (97)	689 (93.4)	94 (96)	98 (93)	844 (97)	787 (93)
Any adverse event leading to treatment discontinuation, *n* (%)	43 (5.6)	39 (5.3)	6 (6.1)	12 (11)	49 (5.6)	51 (6.0)
Most common adverse events, *n* (%)[a]						
Fatigue	282 (37)	192 (26)	28 (29)	26 (25)	310 (36)	218 (26)
Back pain	210 (27)	163 (22)	25 (26)	24 (23)	235 (27)	187 (22)
Constipation	167 (22)	125 (17)	26 (27)	20 (19)	193 (22)	145 (17)
Arthralgia	160 (21)	123 (17)	17 (17)	12 (11)	177 (20)	135 (16)
Specific adverse events, *n* (%)						
Hypertension	106 (14)	31 (4.2)	11 (11)	4 (3.8)	117 (13)	35 (4.1)
Any cardiac adverse event	76 (9.8)	59 (8.0)	12 (12)	7 (6.6)	88 (10)	66 (7.8)
ALT increased	6 (0.8)	3 (0.4)	2 (2.0)	2 (1.9)	8 (0.9)	5 (0.6)
Seizure	1 (0.1)[b]	0	0	1 (0.9)	1 (0.1)[b]	1 (0.1)

ALT = alanine aminotransferase.
[a] Included in this category are adverse events that were reported in the overall safety population in ≥10% of patients in the enzalutamide group at a rate that was ≥2% higher than that in the placebo group.
[b] This seizure occurred after the data cutoff date.

On all primary and secondary outcomes, enzalutamide demonstrated clinically significant benefit in patients with nonvisceral disease, who represent both the majority of patients in PREVAIL (88%) and a population of patients commonly treated by urologists and medical oncologists. Nearly half of the nonvisceral subgroup had lymph node disease at study entry and 85% had bone metastases (a rate similar to that of the visceral disease subgroup). The extended duration of therapy (16.8 mo) and rPFS (14.1 mo) in patients receiving enzalutamide in the nonvisceral disease subgroup suggests long-term disease control in patients without visceral disease. In the subset of patients with lymph node only disease (13% of patients, nonvisceral subgroup), median rPFS was 10.4 mo longer with enzalutamide than with placebo. Another clinically important finding in patients with nonvisceral only disease was the 16.8-mo delay in median time to initiation of cytotoxic chemotherapy, although the study did not specify when chemotherapy was to be initiated; thus, this finding represents the collective decisions of patients and their treating physicians. The decrease in risk of PSA progression and improvement in radiographic response with enzalutamide provide additional evidence of clinical benefit. Furthermore, the benefit on time to degradation of FACT-P scores suggests that enzalutamide treatment may prolong quality of life.

Although patients with more extensive baseline bone metastases generally had shorter rPFS and OS, patients with nonvisceral disease who also had extensive bone disease achieved a similar rPFS and OS benefit with enzalutamide as those with less extensive disease. A consistent rPFS and OS benefit was observed in patients with visceral disease who had three or fewer bone metastases, whereas patients with visceral disease who had four or more bone metastases had improved rPFS but not OS. It is well established that patients with mCRPC display a high risk for bone metastases, which contribute significantly to reduced quality of life and shorter survival due to bone-related complications [4]. Our results suggest that enzalutamide provides meaningful benefit to patients with mCRPC who present with either limited or widespread bone disease.

We observed that a higher proportion of patients in the placebo than enzalutamide arm in the nonvisceral subgroup was treated with chemotherapy after progression on study, showing that use of a placebo control arm in PREVAIL did not prevent subsequent treatment with chemotherapy. The reason for the discrepancy between rates of uptake of subsequent antineoplastic therapy in the enzalutamide and placebo groups is unlikely due to treatment assignment unblinding upon progression, as this process only occurred in very few patients (20/1717; 1.1%) prior to database lock.

Enzalutamide demonstrated a favorable safety profile that was similar between patients with or without visceral disease and similar to that reported previously for the full safety population [13]. The most common AEs included fatigue, back pain, constipation, and arthralgia. Incidence of AEs leading to discontinuation of enzalutamide was low (6%) in both visceral and nonvisceral disease subgroups, suggesting good tolerability over an extended treatment duration. The incidence of hypertension was higher with enzalutamide than with placebo in both the nonvisceral (14% vs 4%) and visceral (11% vs 4%) subgroups. As described previously [13], hypertension in this study was most often reported in patients with a prior history of hypertension and was generally managed with standard therapies. Enzalutamide was not associated with a higher incidence of seizure in this study (one patient [0.1%] in each treatment group). In an earlier phase 3 study (AFFIRM) of enzalutamide in men with mCRPC who had previously received chemotherapy, 0.6% of enzalutamide-treated patients experienced a seizure [15].

5. Conclusions

In our study, enzalutamide provided meaningful clinical benefit to men with chemotherapy-naïve mCRPC, with or without visceral disease, low- or high-volume bone disease, or lymph node only disease. Patients without visceral disease particularly benefitted from enzalutamide, an active therapy with good tolerability that allowed for a long duration of treatment. A similar benefit was observed for patients with visceral disease who also had low-volume metastases to bone.

Author contributions: Christopher P. Evans had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Evans, Higano, Keane, Andriole, Saad, Iversen, Miller, Kim, Kimura, Armstrong, Sternberg, Loriot, de Bono, Noonberg, Mansbach, Bhattacharya, Perabo, Beer, Tombal.
Acquisition of data: Evans, Higano, Keane, Andriole, Saad, Iversen, Miller, Kim, Kimura, Armstrong, Sternberg, Loriot, de Bono, Beer, Tombal.
Analysis and interpretation of the data: Evans, Higano, Keane, Andriole, Saad, Iversen, Miller, Kim, Kimura, Armstrong, Sternberg, Loriot, de Bono, Noonberg, Mansbach, Bhattacharya, Perabo, Beer, Tombal.
Drafting of the manuscript: Evans, Higano, Keane, Andriole, Saad, Iversen, Miller, Kim, Kimura, Armstrong, Sternberg, Loriot, de Bono, Noonberg, Mansbach, Bhattacharya, Perabo, Beer, Tombal.
Critical revision of the article for important intellectual content: Evans, Higano, Keane, Andriole, Saad, Iversen, Miller, Kim, Kimura, Armstrong, Sternberg, Loriot, de Bono, Noonberg, Mansbach, Bhattacharya, Perabo, Beer, Tombal.
Statistical analysis: Bhattacharya.
Obtaining funding: Evans, Higano, Keane, Andriole, Saad, Iversen, Miller, Kim, Kimura, Armstrong, Sternberg, Loriot, de Bono, Noonberg, Mansbach, Bhattacharya, Perabo, Beer, Tombal.
Administrative, technical, or material support: Evans, Higano, Keane, Andriole, Saad, Iversen, Miller, Kim, Kimura, Armstrong, Sternberg, Loriot, de Bono, Noonberg, Mansbach, Bhattacharya, Perabo, Beer, Tombal.
Supervision: Evans, Beer, Tombal.

Financial disclosures: Christopher P. Evans certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Evans has served as a consultant for and received research funding from Medivation, Astellas, Sanofi, and Janssen. Higano has served as a

consultant for Astellas, Bayer, Dendreon, Johnson & Johnson, and Medivation, and has received research funding from Algeta, Aragon, Astellas, Dendreon, Medivation, and Sanofi. Keane has received fees from Algeta, Dendreon, Ferring, Janssen, and Medivation. Andriole has served as a consultant for Augmenix, Bayer, Genomic Health, GlaxoSmithKline, and Myriad Genetics, and as an investigator for Johnson & Johnson, Medivation, and Wilex. Saad has served as a consultant for and received research funding from Astellas, Janssen, Bayer, Sanofi, Amgen, and Takeda. Iversen has served as a consultant for Astellas, Ferring, Janssen, and Medivation, and has received research funding from Astellas, Bavarian Nordic, and Medivation. Miller has served as a consultant and/or on speaker's bureaus for Astellas, Amgen, Janssen-Cilag, Medivation, Novartis, Pierre-Fabre, and Roche. Kimura has received honoraria and/or clinical study fees from Astellas, Bayer, GlaxoSmithKline, Novartis, Ono Pharmaceutical, Pfizer, Janssen, and Takeda. Armstrong has served as a consultant for and his institution has received research support from Astellas, Bayer, Dendreon, Janssen, Medivation, and Sanofi Aventis; he has served on a speaker's bureau for Dendreon and on advisory boards for Janssen, Medivation/Astellas, Bayer. Sternberg has served as a consultant for and her institution has received research support from Astellas, Bayer, Ipsen, Janssen, Sanofi Aventis, and Millennium. Loriot has received research funding from Astellas and Sanofi, and personal fees from Astellas, Bayer, Celgene, Janssen, and Sanofi. de Bono has served as a consultant for Astellas, AstraZeneca, Johnson & Johnson, Medivation, and Sanofi. Noonberg, Mansbach, and Bhattacharya are employees of Medivation. Perabo was an employee of Astellas at time of study design, conduct, and analysis. Beer has served as a consultant for Astellas and Janssen Japan, and has received research funding from Astellas, Janssen, and Medivation. Tombal has served as a consultant and/or on boards and speaker's bureaus for Amgen, Astellas, Bayer, Ferring, Medivation, and Sanofi, and has received research funding from Astellas.

Funding/Support and role of the sponsor: This study was supported by Medivation, Inc., and Astellas Pharma, Inc. The manuscript was reviewed and comments were provided to the authors by Medivation, Inc., and Astellas Pharma, Inc. Medical writing and editorial support was funded by Medivation, Inc. and Astellas Pharma, Inc., and provided by Tim Lohret, PhD, and Shannon Davis of Infusion Communications.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.03.017.

References

[1] International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality, and Prevalence Worldwide in 2012. GLOBOCAN Web site. http://globocan.iarc.fr.

[2] National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. SEER Web site. http://seer.cancer.gov.

[3] Sathiakumar N, Delzell E, Morrisey MA, et al. Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US Medicare beneficiaries, 1999–2006. Prostate Cancer Prostatic Dis 2011;14:177–83.

[4] Zustovich F, Fabiani F. Therapeutic opportunities for castration-resistant prostate cancer patients with bone metastases. Crit Rev Oncol Hematol 2014;91:197–209.

[5] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.

[6] Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008;26:242–5.

[7] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomized open-label trial. Lancet 2010;376:1147–54.

[8] Armstrong AJ, Garrett-Mayer E, de WR, Tannock I, Eisenberger M. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clin Cancer Res 2010;16:203–11.

[9] Goodman Jr OB, Flaig TW, Molina A, et al. Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 2014;17:34–9.

[10] Pond GR, Sonpavde G, de Wit R, Eisenberger MA, Tannock IF, Armstrong AJ. The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. Eur Urol 2014;65:3–6.

[11] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

[12] Ryan C, Smith M, Fizazi K, et al. Final overall survival analysis of COU-AA-302, a randomized phase 3 study of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy. Presented at European Society for Medical Oncology 2014 Congress; September 28, 2014; Madrid, Spain. Abstract 753O.

[13] Beer TM, Armstrong A, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.

[14] Sweeney C, Chen Y-H, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial. J Clin Oncol 2014;32(Suppl 5):abstr LBA2.

[15] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.

[16] Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148–59.

[17] Cella D, Ivanescu C, Holmstrom S, Bui CN, Spalding J, Fizazi K. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized clinical trial. Ann Oncol 2015;26:179–85.