European Journal of Cancer 159 (2021) 237–246

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Consistent survival benefit of enzalutamide plus androgen deprivation therapy in men with nonmetastatic castration-resistant prostate cancer: PROSPER subgroup analysis by age and region

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Received 4 June 2021; received in revised form 30 September 2021; accepted 7 October 2021
Available online 14 November 2021

KEYWORDS
Castration-resistant prostate cancer;
Prostate cancer;
Urological cancers;
Antiandrogen therapy;
Enzalutamide

Abstract ***Background:*** Enzalutamide combined with androgen deprivation therapy (ADT) significantly prolonged metastasis-free survival and overall survival (OS) versus ADT alone in patients with non-metastatic castration-resistant prostate cancer (nmCRPC) with rapidly rising prostate-specific antigen (PSA). The objective of this *post hoc* analysis of the PROSPER trial is to evaluate OS benefit and safety of enzalutamide in patients across age and regional subgroups. ***Patients and methods:*** Eligible men with nmCRPC, PSA doubling time ≤10 months and PSA ≥2 ng/mL with continued ADT use were randomised 2:1 to enzalutamide 160 mg or placebo.

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https://doi.org/10.1016/j.ejca.2021.10.015
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OS and safety were examined by age (<70 vs ≥70 years) and region (North America, Europe, Asia or the rest of the world). The impact of prior and subsequent therapy was also examined.
Results: In total, 1401 men were enrolled (median age, 74 years). Enzalutamide plus ADT reduced the risk of death, independent of age or region. Multivariate analyses identified Eastern Cooperative Oncology Group (ECOG) status ($P < 0.0001$), log (PSA; $P = 0.0002$) and subsequent therapy ($P < 0.0001$) as statistically significant factors impacting OS. Safety was consistent across age and regional subgroups. Any grade treatment-emergent adverse events were similar across age groups, were more common in the placebo group and had regional variation.
Conclusions: In men with nmCRPC and rapidly rising PSA, the benefit and safety of enzalutamide were consistent across age and regional subgroups. Variables impacting OS included ECOG status, log (PSA) and subsequent therapy.
ClinicalTrials.gov identifier: NCT02003924.
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1. Introduction

In men with non-metastatic castration-resistant prostate cancer (nmCRPC), the risk of progression to metastasis increases with a prostate-specific antigen (PSA) doubling time (PSADT) of ≤10 months [1,2]. Median survival for mCRPC is nearly three years [3], and delaying time to metastases may delay cancer-related morbidity and use of antineoplastic therapies and prolong overall survival (OS) [4,5]. Enzalutamide, an androgen receptor inhibitor, significantly improved metastasis-free survival (MFS) in men with nmCRPC (vs placebo) in the primary analysis of PROSPER (NCT02003924) trial [6] and was superior to bicalutamide in improving radiographic progression-free survival in the STRIVE (NCT01664923) study [7].

In the final analysis of the PROSPER study, treatment with enzalutamide plus androgen deprivation therapy (ADT) significantly improved OS in men with nmCRPC and rapidly rising PSA levels, in comparison with those who only received ADT [8]. Survival benefit with novel hormonal therapies (NHTs) in this patient population was also demonstrated more broadly in the final analyses of apalutamide [9,10] and darolutamide [11] in the SPARTAN (NCT01946204) and ARAMIS (NCT02200614) studies, respectively.

Variations in prostate cancer diagnosis, management and treatment exist across geographic regions and age groups, which may affect disease recurrence and patient outcomes [12–15]. The primary analysis of PROSPER [6] identified the need for more information on the efficacy and safety of NHTs across these groups to better inform patient-specific treatment decisions. The objective of our *post hoc* analysis of PROSPER was to evaluate OS and safety in subgroups of patients by age (<70 and ≥ 70 years) and geographic region (North America, Europe, Asia and the rest of the world [ROW]). International guidelines, used to distinguish prostate cancer management strategies for men aged <70 and ≥ 70 years [16], divided patients into these age subgroups. The impact of prior and subsequent therapy is also examined.

2. Methods

2.1. Study design

The PROSPER study design has been described previously [6]. Eligible men had pathologically confirmed prostate adenocarcinoma with rising PSA despite castrate serum levels of testosterone (≤50 ng/dL), baseline PSA ≥2 ng/mL and PSADT ≤10 months. Patients were assessed by soft tissue and whole-body radionuclide bone scanning, via computerised tomography or magnetic resonance imaging, to identify previous and/or concurrent metastatic disease. The patients were also stratified by PSADT (<6 months vs ≥6 months) and use of bone-targeting agents at baseline (yes vs no), and they were randomised 2:1 to receive enzalutamide 160 mg/day plus ADT or placebo plus ADT once daily until radiographic progression, death or unacceptable toxicity.

The primary end-point was MFS, defined as time from randomisation to radiographic progression or death; the secondary end-point was OS, defined as the time from randomisation to death from any cause. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee at each participating centre. All participants provided written informed consent before enrolment.

2.2. Statistical analysis

Efficacy and baseline characteristics were analysed in the intent-to-treat population defined as all patients randomised to study treatment. Safety end-points were

analysed in the safety population, based on the treatment received rather than assigned. The enzalutamide and placebo treatment groups were compared. Kaplan–Meier curves were provided for each subgroup, and a stratified Cox regression model was used to estimate hazard ratios (HR) with associated 95% confidence intervals (CIs). The Cox analysis stratification factors included Eastern Cooperative Oncology Group (ECOG) performance status (PS; 1 vs 0), log (PSA) levels, PSADT (<6 months vs ≥6 months) and subsequent therapy (yes vs no). Subsequent therapy was not a time-dependent variable. Common prognostic factors were selected and defined in the study protocol based on potential associations with OS, and the significance of these factors and patient subgroups (age and region) impacting OS was determined by multivariate Cox-proportional analysis. Exposure-adjusted adverse event rates per 100 patient-years were calculated as the number of events/total patient-years of exposure for the treatment group x100.

3. Results

3.1. Baseline patient characteristics

From 26th November 2013 to 28th June 2017, 1401 adult men with nmCRPC were randomised 2:1 to receive either 160 mg/day enzalutamide plus ADT (n = 933) or placebo plus ADT (n = 468) in the PROSPER study. Among the 1401 patients, the median age was 74 years (range, 50–95 years), 425 were aged <70 years (enzalutamide, n = 274; placebo, n = 151), and 970 were aged ≥70 years (enzalutamide, n = 656; placebo, n = 314). Six patients did not receive treatment

Table 1
Patient demographics by region.

	Europe, n = 690	North America, n = 204	Asia, n = 216	Rest of world, n = 291
Age category, no. (%)				
<70 years	217 (31.4)	67 (32.8)	65 (30.1)	78 (26.8)
≥70 years	473 (68.6)	137 (67.2)	151 (69.9)	213 (73.2)
Age, median, years	73.0	73.0	73.5	75.0
Race, no. (%)				
Asian	0 (0)	8 (3.9)	216 (100.0)	8 (2.7)
Black or African American	5 (0.7)	14 (6.9)	0 (0)	13 (4.5)
White	564 (81.7)	179 (87.7)	0 (0)	251 (86.3)
Other	6 (0.9)	2 (1.0)	0 (0)	19 (6.5)
Missing[a]	115 (16.7)	1 (0.5)	0 (0)	0 (0)
Weight, median, kg	84.5	88.4	68.0	83.0
BMI, median, kg/m^2	28.2	28.7	24.8	28.5
Baseline ECOG				
0	555 (80.4)	173 (84.8)	178 (82.4)	223 (76.6)
1	134 (19.4)	31 (15.2)	38 (17.6)	67 (23.0)
>1	0 (0)	0 (0)	0 (0)	0 (0)
Missing[b]	1 (0.1)	0 (0)	0 (0)	1 (0.3)
PSA doubling time				
<6 months	73.9%	76.0%	81.9%	80.1%
≥6 months	25.9%	24.0%	18.1%	19.9%
Median, months	3.9	3.7	3.1	3.8
Range	0.4–71.8	0.5–14.7	0.7–9.8	0.4–24.7
Serum PSA, ng/mL				
Median	11.4	9.6	8.0	12.4
Alkaline phosphatase, U/L				
Median	71.0	72.0	77.0	74.0
Range	27.0–257.0	24.0–149.0	35.0–153.0	21.0–156.0
Prior therapies received, no. (%)				
Bicalutamide	390 (56.9)	111 (54.4)	154 (71.3)	133 (45.9)
Flutamide	62 (9.1)	10 (4.9)	39 (18.1)	35 (12.1)
Other[c]	340 (49.6)	119 (58.3)	92 (42.6)	198 (68.3)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PSA, prostate specific antigen.
[a] Data were not collected in all countries.
[b] Data were not reported for one patient.
[c] 'Other' prior therapies included but not limited to the following: cyproterone; denosumab; dexamethasone; diethylstilbestrol; docetaxel and nilutamide. Data cutoff date was 15th October 2019.

Table 2
Patient demographics by age subgroup.

	<70 years		≥70 years	
	Enzalutamide, n = 275	Placebo, n = 53	Enzalutamide, n = 658	Placebo, n = 140
Age, years				
Median	65.0	64.0	77.7	76.5
Range	50.0–69.0	53.0–69.0	70.0–95.0	70.0–92.0
Race, no. (%)				
Asian	14.2	22.6	15.7	24.3
Black or African American	3.3	3.8	2.0	3.6
White	75.6	67.9	70.7	64.3
Other	0.7	0.0	1.1	1.4
Missing[a]	6.2	3.8	9.1	4.3
Weight, median, kg	87.2	85.5	81.0	81.0
BMI, median, kg/m^2	28.5	29.1	27.4	27.1
Baseline ECOG, (%)				
0	246 (89.5)	42 (79.2)	501 (76.1)	107 (76.4)
1	28 (10.2)	11 (20.8)	157 (23.9)	32 (22.9)
>1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing[b]	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)
Baseline use of bone-targeting agents, (%)				
No	242 (88.0)	50 (94.3)	583 (88.6)	127 (90.7)
Yes	32 (11.6)	3 (5.7)	73 (11.1)	13 (9.3)
PSA doubling time				
<6 months	224 (81.5%)	44 (83.0%)	490 (74.5%)	114 (81.4%)
≥6 months	51 (18.5%)	9 (17.0%)	167 (25.4%)	26 (18.6%)
Median, months	3.3	3.0	3.9	3.4
Range	0.7–28.9	0.6–9.6	0.4–37.4	0.5–14.7
Serum PSA, ng/mL				
Median	8.3	11.1	12.4	12.5
Alkaline phosphatase, U/L				
Median	76.0	75.0	72.0	74.0
Range	33.0–189.0	43.0–132.0	21.0–183.0	35.0–257.0

[a] Data were not collected in all countries. [b] Data were not reported for one patient. Data cutoff date was 15th October 2019.
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PSA, prostate specific antigen.

and were not included in the *post hoc* multivariate analysis. Eighty-seven patients in placebo groups during the initial study period were subsequently treated with enzalutamide during the open-label extension (crossover population: <70 years, n = 28; ≥70 years, n = 59).

Patient demographics and disease characteristics, including age, age distribution and baseline ECOG status, were well balanced between treatment groups and regions (Table 1). Patients in Asia had lower average weight and body mass index compared with other regions (68 kg vs 83–88 kg and 25 kg/m^2 vs ~29 kg/m^2, respectively). Patients from the ROW were older (median age, 75 years) and presented with worse ECOG scores than other regions. Compared with younger men (<70 years), men aged ≥70 years presented more commonly with ECOG scores of ≥1 (22.9% vs 10.2%) and had higher median PSADT (3.9 months vs 3.0 months) (Table 2). Use of prior therapeutic medication ≤1 month before randomisation differed by regions, with prior bicalutamide use comparatively higher in Asia (71.3%) than in Europe and North America (56.9% and 54.4%, respectively) and comparatively lower in the ROW (45.9%). The use of flutamide was low, irrespective of regions (Table 1).

3.2. Multivariate analysis of overall survival by subgroups

The final analysis of PROSPER demonstrated improved survival with enzalutamide in the overall patient population (HR, 0.73; 95% CI 0.61–0.89; P = 0.001) [8]. In this *post hoc* analysis, the prognostic value of age, region and other baseline characteristics on OS was assessed with a multivariate analysis (Table 3). The benefit of enzalutamide on OS was not observed in patients aged ≥70 years versus <70 years (P = 0.063). Patients treated with enzalutamide received less subsequent therapies than those in the placebo group (34.2% vs 66.2%). OS decreased for those who received subsequent therapies versus those who did not (HR, 2.5; 95% CI 2.1–3.1; P < 0.0001), possibly owing to the presence of more aggressive disease requiring additional treatment. Similarly, reduced OS correlated with higher ECOG PS (HR, 1.728; 95% CI 1.402–2.130; P < 0.0001) and log (PSA) values (HR, 1.185; 95% CI 1.085–1.293;

Table 3
Multivariate Cox proportional analysis of overall survival.

	Placebo, n = 465	Enzalutamide, n = 929	HR (95% CI)	*P* value
Patients with an event, no. (%)	177 (38.1)	285 (30.7)		
Patient years at risk	1502.9	3208.8		
Baseline characteristic				
ECOG PS (1 vs 0)			**1.728 (1.402–2.130)**	**<.0001**
Prior bicalutamide use (yes vs no)			0.906 (0.705–1.095)	0.3065
Albumin			0.971 (0.936–1.007)	0.1152
Haemoglobin			0.995 (0.986–1.004)	0.2475
Log (PSA)			**1.185 (1.085–1.293)**	**0.0002**
PSA doubling time (≥6 months vs <6 months)			0.892 (0.711–1.118)	0.3209
Asia vs North America			1.164 (0.824–1.644)	0.3883
Europe vs North America			0.940 (0.712–1.241)	0.6617
ROW vs North America			1.114 (0.822–1.509)	0.4872
Age (≥70 years vs <70 years)			1.231 (0.989–1.533)	0.0633
Post-baseline characteristic				
Subsequent therapy (yes vs no)			**2.543 (2.087–3.098)**	**<.0001**

The P values noted in bold indicate influence on OS. Hazard ratios (95% CIs) are from a multivariate Cox proportional hazards model with the covariates above. Data cutoff date was 15th October 2019.
CI, confidence internal; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; ROW, rest of world.

P < 0.0001), but OS was not affected by prior use of bicalutamide, age, PSADT or region.

3.3. Subsequent therapy

To gain insight into factors driving outcomes across subgroups, trends in subsequent therapy use were examined in the safety population patients (n = 606) who discontinued study treatment. Younger patients (<70 years) more commonly used ≥1 subsequent therapy compared with older patients (≥70 years; 77.8% vs 57.0%) (Table 4). The most common treatments among younger and older age groups were next-generation antiandrogens (54.9% and 43.2%) and chemotherapy (63.6% and 32.0%), respectively (Supplemental Table 1).

One-third of patients in both age groups received a single subsequent therapy (<70 years, 33.3% and ≥70 years, 33.8%), whereas use of a second subsequent therapy (Table 4) was nearly twice as common in younger patients (37.0%) than in older patients (20.0%). Regional trends were also observed in subsequent therapy use. More patients in Asia and ROW received a single subsequent therapy (38.4% and 43.6%, respectively) compared with patients in North America (27.0%) and Europe (28.0%) (Table 4). The proportion of patients receiving two subsequent therapies were similar across regions. Regardless of regions, the first and second most frequently used subsequent therapies were endocrine therapy and chemotherapy.

The proportion of placebo patients who crossed over to enzalutamide after study unblinding (n = 87) was similar across age and region (overall 18.7%; range 16.5%–23.9%). Cross-over patients were omitted from analyses of subsequent therapies when assessing age-related and regional variations in access to therapies other than enzalutamide.

3.4. Safety

In both age groups, patients treated with enzalutamide were on treatment for longer compared with those in the placebo group. Any-grade treatment-emergent adverse events (TEAEs) were similar across age groups, were more common in the placebo group than in the group treated with enzalutamide and had regional variation (Fig. 1A). Exposure-adjusted grade ≥3 TEAEs and serious TEAEs were more common among older patients than younger patients in both treatment groups (Fig. 1A). Older patients (aged ≥70 years) in both treatment groups also experienced 1) exposure-adjusted

Table 4
Trends in therapy use following study discontinuation.

	<70 years, n = 162	≥70 years, n = 444	Europe, n = 265	North America, n = 89	Asia, n = 112	ROW, n = 140
Patients taking ≥1 subsequent antineoplastic therapy, no. (%)	126 (77.8)	253 (57.0)	156 (58.9)	54 (60.7)	76 (67.9)	93 (66.4)
One type of therapy	54 (33.3)	150 (33.8)	76 (28.0)	24 (27.0)	43 (38.4)	61 (43.6)
Two types of therapies	60 (37.0)	89 (20.0)	71 (26.8)	21 (23.6)	27 (24.1)	30 (21.4)
Three types of therapies	8 (4.9)	9 (2.0)	7 (2.6)	8 (9.0)	1 (0.9)	1 (0.7)

ROW, rest of world.

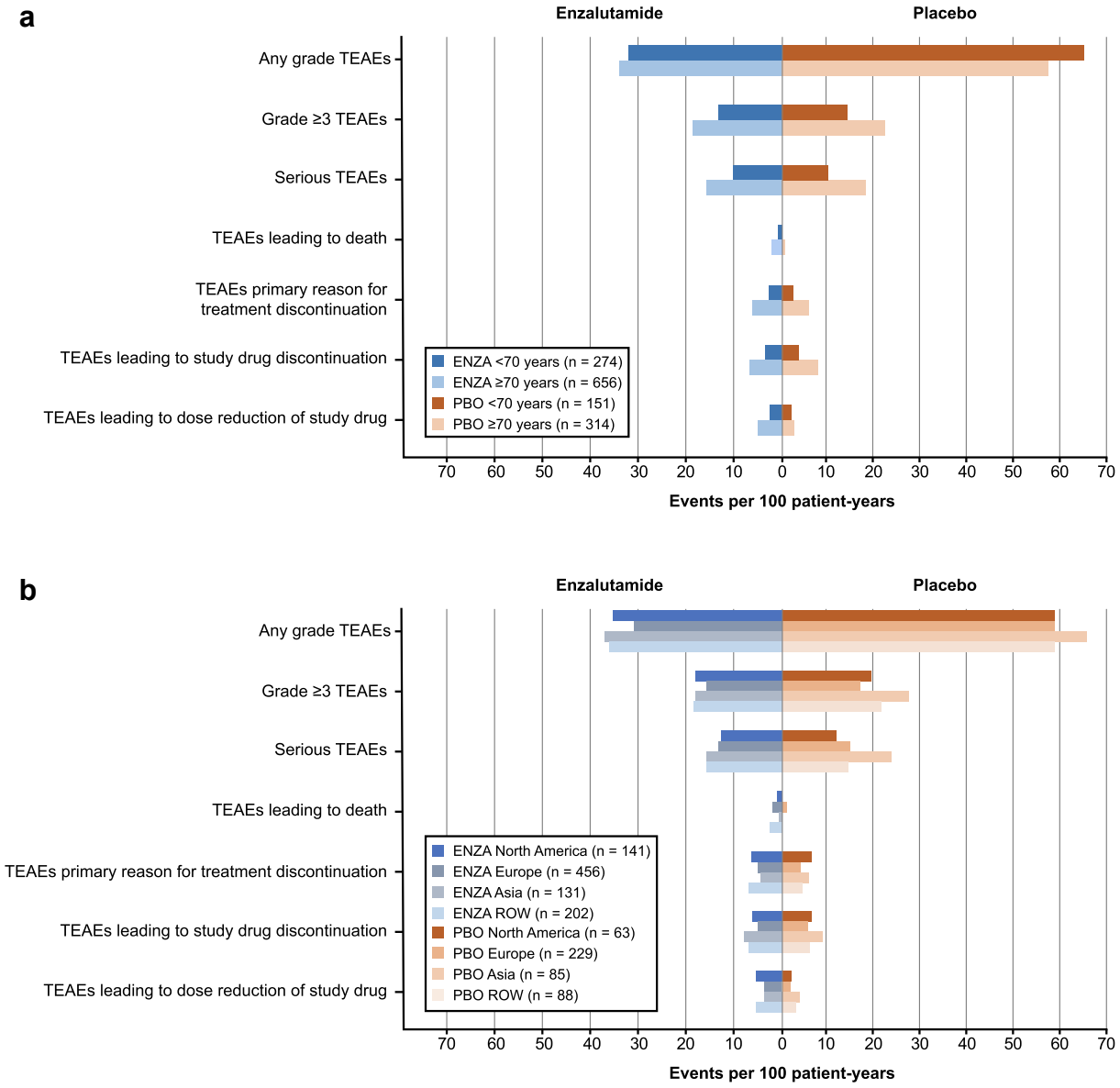

Fig. 1. **Exposure-adjusted AEs by subgroup. (a) Age (< 70 years vs ≥70 years) and (b) region (North America, Europe, Asia and ROW).** AE, adverse event; ENZA, enzalutamide; PBO, placebo; ROW, rest of world; TEAE, treatment-emergent adverse event.

TEAEs as the primary reason for treatment discontinuation, 2) TEAEs leading to study drug dose reduction, 3) exposure-adjusted TEAEs leading to study drug discontinuation and 4) exposure-adjusted TEAEs leading to death. Overall, exposure-adjusted TEAEs reported across regions were similar in both treatment groups (Fig. 1B). Exposure-adjusted grade ≥3 TEAEs and serious TEAEs in the placebo group were more common in Asia than in other regions. These differences were not observed in the enzalutamide group (Fig. 1B).

Patients treated with enzalutamide aged ≥70 years experienced more exposure-adjusted falls per 100 patient-years (100PYs; 7.2 vs 3.8) and fractures (7.2 vs 4.3) than placebo. These differences were decreased among the <70 years enzalutamide and placebo groups (falls: 4.1 vs 4.2; fractures: 4.6 vs 5.3) (Fig. 2A). Patients treated with enzalutamide reported higher rates of exposure-adjusted cognitive impairments than those in the placebo group, in both the older (2.6 vs 2.0) and younger patients (3.3 vs 0.5). Regional variations in exposure-adjusted TEAEs were also observed. Patients in North America exhibited higher rates of falls and musculoskeletal events in both study groups than other regions (Fig. 2B). Increases in hypertension among patients treated with enzalutamide in Asia versus those in the placebo group (5.4 vs 0.0 per 100PYs) were also observed.

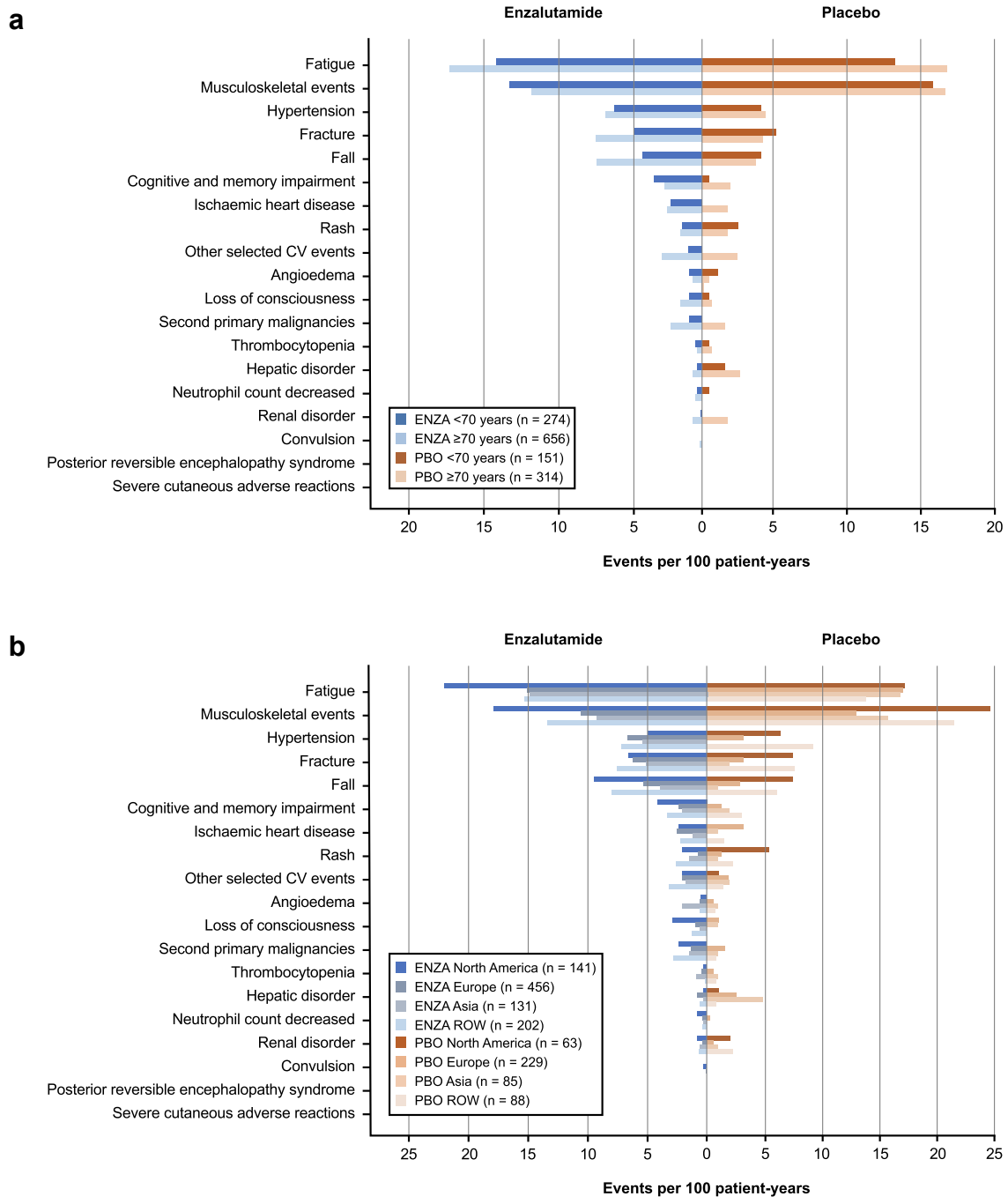

Fig. 2. **Exposure-adjusted AEs of interest by subgroup. (a) Age (< 70 years vs ≥70 years) and (b) region (North America, Europe, Asia, and ROW).** AE, adverse event; CV, cardiovascular; ENZA, enzalutamide; PBO, placebo; ROW, rest of world.

4. Discussion

This *post hoc* subgroup analysis of PROSPER examined the impact of age and region on the OS benefits and safety of enzalutamide treatment in men with nmCRPC and rapidly rising PSA, to better understand the role of demographics on outcomes of enzalutamide treatment. OS benefit of enzalutamide was not impacted by age, region, prior bicalutamide treatment or PSADT but was sensitive to ECOG PS, log (PSA) and subsequent therapy use.

Patient characteristics were similar across subgroups. Demographic differences included lower median weight and body mass index among patients from Asia versus other regions and higher ECOG PS in patients aged ≥70 years and patients from ROW (Table 1, Table 2). Black men accounted for 4.5% of patients enrolled in the PROSPER study. Potential reasons for low enrolment into this and other clinical trials may include a lack of awareness, socioeconomic and cultural factors. In the multivariate analysis, ECOG PS, log (PSA) and

subsequent therapy emerged as factors significantly impacting OS. The influence of subsequent therapy on OS observed here may represent variations in treatment strategies used with patients from different demographic groups. For example, reduced use of subsequent therapy among older patients may reflect a reduced tolerance for additional treatment regimens among ageing populations (Table 4) [15,17,18]. The influence of ECOG PS, log (PSA) and subsequent therapy as prognostic factors may produce shifts in OS observable on a larger scale. Here, the small decrease in the effect of enzalutamide on OS observed in the ROW population (Supplemental Fig. 1) may be explained by a combination of the less favourable ECOG PS scores and a higher rate of subsequent therapy use recorded for men from that region (Table 1).

Safety data from age and regional subgroups were consistent with previous reports [19,20]. In both treatment groups, older patients experienced more TEAEs, including exposure-adjusted grade ≥3 TEAEs, serious TEAEs, fatigue and select cardiovascular events, compared with younger patients. In addition, fractures, falls and cognitive impairments were more common in the older population and are recognised health concerns for the elderly [21]. The increased rate of falls with enzalutamide among older patients observed here and previously [22] suggests that enzalutamide may compound existing risk. However, outcome benefits of enzalutamide for older patients are clear [22,23], and strategies for reducing falls, including assessments of bone health and fall risk factors, lifestyle and nutritional recommendations by specialists, could minimise the risk of fall injury. In addition, better, earlier use of bone-targeting agents may minimise the risk of skeletal complications in men with CRPC [24]. Analysis of safety signals revealed that patients in the placebo group experienced more exposure-adjusted TEAEs than patients treated with enzalutamide, regardless of location (Fig. 2B). Similar trends were observed in rates of grade ≥3 and serious TEAEs: the higher rates of TEAEs in the placebo group (Fig. 1) raise the possibility that effects attributed to treatment are in fact disease comorbidities improving after exposure to enzalutamide.

The primary analysis of PROSPER demonstrated prolonged MFS, PSA progression and use of subsequent therapy in men with nmCRPC and rapidly rising PSA when being treated with enzalutamide versus placebo. Another recent analysis has documented a significant OS increase from 56.3 months to 67.0 months with enzalutamide treatment [8]. Here, enzalutamide treatment has been associated with reduced risk of metastasis or death across age and regional subgroups. The safety profile reported in the primary analysis of PROSPER was consistent with other studies and included higher frequency of hypertension, myocardial infarction, fatigue, falls and fractures with enzalutamide plus ADT versus placebo [6]. However, after adjustment for exposure, the rates of TEAEs per 100PYs were similar in the two treatment groups, with increased frequency of falls and fractures in the enzalutamide group (Fig. 1). This *post hoc* analysis extends the findings of PROSPER by demonstrating a reduced risk of death with enzalutamide treatment irrespective of age or geographic region. However, as the analysis presented here is *post hoc* in nature, the results are exploratory and should be interpreted with caution. A visual abstract (Supplementary Fig. 2) and summary video of the analysis have been included.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.ejca.2021.10.015

In conclusion, enzalutamide significantly extended OS in men with nmCRPC, irrespective of age and region. Significant impacts on OS were exerted by ECOG status, log (PSA) and subsequent therapy use. Patients aged ≥70 years treated with enzalutamide were subject to increased risk of exposure-adjusted falls and fractures in comparison with those in the placebo group and younger patients, whereas safety across regions was generally consistent.

Contributors

Ugo De Giorgi: conceptualisation, methodology, investigation, writing – reviewing and editing, visualisation, supervision. **Maha Hussain**: investigation, writing – original draft, writing – reviewing and editing, visualisation. **Neal Shore**: investigation, writing – original draft, writing – reviewing and editing, visualisation. **Karim Fizazi**: investigation, writing – reviewing and editing, visualisation. **Bertrand Tombal**: investigation, writing – original draft, writing – reviewing and editing, visualisation. **David Penson**: investigation, writing – original draft, writing – reviewing and editing, visualisation. **Fred Saad**: investigation, writing – original draft, writing – reviewing and editing, visualisation. **Eleni Efstathiou**: investigation, writing – reviewing and editing, visualisation. **Katarzyna Madziarska**: investigation, writing – original draft, writing – reviewing and editing, visualisation. **Joyce Steinberg**: investigation, writing – reviewing and editing, visualisation. **Jennifer Sugg**: investigation, writing – reviewing and editing, visualisation. **Xun Lin**: software, validation, formal analysis, investigation, data curation, writing – reviewing and editing, visualisation. **Qi Shen**: investigation, writing – original draft, writing – reviewing and editing, visualisation. **Cora N. Sternberg**: conceptualisation, methodology, investigation, writing – original draft, writing – reviewing and editing, visualisation, supervision. **Raj Patel**: resources, project administration, funding acquisition.

Role of the funding source

This study was sponsored by Pfizer and Astellas Pharma, Inc.

Data sharing statement

On request and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Cora N. Sternberg** served as a consultant for Janssen-Cilag, Astellas Pharma Inc., Sanofi–Genzyme, Novartis, Bayer, Pfizer Inc., Merck, MSD, AstraZeneca, Immunomedics (now Gilead), Janssen, Foundation Medicine, UroToday and Medscape and has received prior institutional funding from Cougar Biotechnology (now Janssen), Medivation (now Pfizer), Clovis Oncology and Roche-Genentech.**Ugo De Giorgi** served as a consultant for Janssen, Astellas Pharma Inc., Sanofi, Bayer, Pfizer Inc., BMS, Novartis, Ipsen and Merck. **Neal D. Shore** served as a consultant for Abbvie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Boston Scientific, Clovis Oncology, Cold Genesys, Dendreon, Exact Imaging, Exact Sciences, FerGene, Foundation Medicine, Genesis Care, Invitae, Janssen, MDxhealth, Merck, Myovant, Myriad, Nymox, Pacific Edge, Pfizer Inc., Phosphorous, Propella, PreView, Sanofi Genzyme, Speciality Networks, Sesen Bio, Tolmar and Urogen. **Karim Fizazi** served as a consultant for Janssen Oncology, Bayer, Astellas Pharma Inc., Sanofi, Orion Pharma GmbH, Curevac, AstraZeneca, ESSA Pharmaceuticals, Roche/Genentech, Clovis Oncology and Amgen, received money for travel/accommodation expenses from Amgen and has received honoraria from Janssen, Sanofi, Astellas Pharma Inc. and Merck. **Bertrand Tombal** received personal fees and non-financial support from Amgen, Astellas Pharma Inc., Bayer, Ferring, Janssen and Sanofi; personal fees from Pfizer, Steba Biotech and Takeda and grants from Ferring. **David Penson** reported no conflict of interest. **Fred Saad** served as a consultant for Astellas Pharma Inc., Janssen Oncology, Sanofi and AstraZeneca/MedImmune, received honoraria from Astellas Pharma Inc., Janssen Oncology, Sanofi, Bayer and AstraZeneca, received institutional funding from Astellas Pharma Inc., Bayer, Janssen Oncology, Sanofi, Myovant Sciences and AstraZeneca. **Eleni Efstathiou** received honoraria from Janssen-Cilag, Sanofi and Takeda, served as a consultant for Janssen-Cilag, Sanofi, Astellas Pharma Inc., Bayer, AstraZeneca, Merck Sharp & Dohme, Innocrin Pharma, Takeda and Tolmar, member of the Speakers Bureau for Janssen-Cilag; received research funding from Janssen-Cilag, Sanofi and Astellas Pharma Inc. **Katarzyna Madziarska** reported no conflict of interest. **Joyce Steinberg**: employee of Astellas Pharma, Inc. and has an immediate family member with stock ownership in Amgen. **Jennifer Sugg**: employee of Astellas Pharma, Inc., with stock ownership in AstraZeneca. **Xun Lin and Qi Shen**: employees and stockholders of Pfizer Inc. **Maha Hussain** served as a consultant or in an advisory role for AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi Sankyo Company, Genentech, Janssen and Pfizer Inc., received honoraria and/or travel expenses for educational functions/lectures from Astellas Pharma Inc., AstraZeneca Pharma, Bayer, Genentech/Roche, MLI PeerView, OncLive, Physicians' Education Resource LLC, Phillips Gilmore Oncology, projects in Knowledge, Research to Practice, Sanofi-Genzyme, UroToday and Precisca, and received institutional research funding from AstraZeneca, Bayer, Genentech, Prostate Cancer Clinical Trials Consortium (PCCTC), Pfizer Inc. and Arvinas.

Acknowledgements

The PROSPER trial and analyses presented were sponsored by Pfizer Inc. (New York, NY, USA) and Astellas Pharma, Inc. (Northbrook, IL, USA), the co-developers of enzalutamide. Medical writing and editorial support funded by the sponsors were provided by Ira Mills, PhD, Stephanie Vadasz, PhD, Sarah Marshall, Dena McWain of Ashfield Healthcare Communications and Lauren Rainer, BSc, of Onyx (a Prime Global agency).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.10.015.

References

[1] Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, et al. Denosumab and bone metastasis-free survival in men with non-metastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 2013;31:3800–6.

[2] Mateo J, Fizazi K, Gillessen S, Heidenreich A, Perez-Lopez R, Oyen WJG, et al. Managing nonmetastatic castration-resistant prostate cancer. Eur Urol 2019;75:285–93.

[3] Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. Eur Urol 2017;71:151–4.

[4] Xie W, Regan MM, Buyse M, Halabi S, Kantoff PW, Sartor O, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. J Clin Oncol 2017;35:3097–104.

[5] Frees S, Akamatsu S, Bidnur S, Khalaf D, Chavez-Munoz C, Struss W, et al. The impact of time to metastasis on overall survival in patients with prostate cancer. World J Urol 2018;36:1039–46.

[6] Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465–74.

[7] Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 2016;34:2098–106.

[8] Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020;382:2197–206.

[9] Small EJ, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. Ann Oncol 2019;30:1813–20.

[10] Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide and overall survival in prostate cancer. Eur Urol 2021;79:150–8.

[11] Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. N Engl J Med 2020;383:1040–9.

[12] Gallina A, Chun FK, Suardi N, Eastham JA, Perrotte P, Graefen M, et al. Comparison of stage migration patterns between Europe and the USA: an analysis of 11 350 men treated with radical prostatectomy for prostate cancer. BJU Int 2008;101:1513–8.

[13] Gillessen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A, et al. Management of patients with advanced prostate cancer: report of the advanced prostate cancer consensus conference 2019. Eur Urol 2020;77:508–47.

[14] Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1119–34.

[15] Sternberg CN, de Bono JS, Chi KN, Fizazi K, Mulders P, Cerbone L, et al. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. Ann Oncol 2014;25:429–34.

[16] Boyle HJ, Alibhai S, Decoster L, Efstathiou E, Fizazi K, Mottet N, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. Eur J Cancer 2019;116:116–36.

[17] Italiano A, Ortholan C, Oudard S, Pouessel D, Gravis G, Beuzeboc P, et al. Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration-resistant prostate cancer. Eur Urol 2009;55:1368–75.

[18] Mulders PF, Molina A, Marberger M, Saad F, Higano CS, Chi KN, et al. Efficacy and safety of abiraterone acetate in an elderly patient subgroup (aged 75 and older) with metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy. Eur Urol 2014;65:875–83.

[19] Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.

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

[21] Stenhagen M, Ekstrom H, Nordell E, Elmstahl S. Falls in the general elderly population: a 3- and 6- year prospective study of risk factors using data from the longitudinal population study 'Good ageing in Skane. BMC Geriatr 2013;13:81.

[22] Graff JN, Baciarello G, Armstrong AJ, Higano CS, Iversen P, Flaig TW, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castration-resistant prostate cancer: results from PREVAIL. Ann Oncol 2016;27:286–94.

[23] Vinh-Hung V, Natchagande G, Joachim C, Gorobets O, Drame M, Bougas S, et al. Low-dose enzalutamide in late-elderly patients (≥ 75 Years old) presenting with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2020;18:e660–8.

[24] Smith MR, Coleman RE, Klotz L, Pittman K, Milecki P, Ng S, et al. Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events. Ann Oncol 2015;26:368–74.