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Platinum Priority – Prostate Cancer

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Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial

Andrew J. Armstrong[a,*], *Ping Lin*[b], *Bertrand Tombal*[c], *Fred Saad*[d], *Celestia S. Higano*[e], *Anthony M. Joshua*[f,†], *Teresa Parli*[g], *Brad Rosbrook*[h], *Steve van Os*[i], *Tomasz M. Beer*[j]

[a] *Division of Medical Oncology and Urology, Duke Cancer Institute, Duke University, Durham, NC, USA;* [b] *Biostatistics, Pfizer Inc., San Francisco, CA, USA;* [c] *Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium;* [d] *Division of Urology and Urologic Oncology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada;* [e] *Medical Oncology, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA;* [f] *Department of Medical Oncology, Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, New South Wales, Australia;* [g] *Clinical Development, Pfizer Inc., San Francisco, CA, USA;* [h] *Biostatistics, Pfizer Inc., San Diego, CA, USA;* [i] *Biostatistics, Astellas Pharma Europe BV, Leiden, The Netherlands;* [j] *Hematology/Medical Oncology, OHSU Knight Cancer Institute Oregon Health & Science University, Portland, OR, USA*

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Abstract

Background: In the PREVAIL study, enzalutamide significantly improved clinical outcomes versus placebo in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC).
Objective: To evaluate long-term benefits and risks of enzalutamide in the final prespecified PREVAIL analysis.
Design, setting, and participants: We conducted a final 5-yr survival analysis of PREVAIL in men with chemotherapy-naïve mCRPC from the enzalutamide ($n = 689$) and placebo ($n = 693$) arms.
Outcome measurements and statistical analysis: Predictors of the primary outcome of overall survival were estimated using the Kaplan-Meier method. Long-term adverse events over time were analyzed.
Results and limitations: At the 5-yr data cutoff, 1382 of 1717 (80%) men had died. Enzalutamide reduced the hazard of death by 17% (hazard ratio 0.83; 95% confidence interval [CI] 0.75–0.93; $p < 0.001$), despite 65%, 54%, and 43% of placebo-treated patients receiving subsequent docetaxel, abiraterone, and enzalutamide, respectively. Median overall survival was 36 mo (95% CI 34–38) in the enzalutamide arm versus 31 mo (95% CI 29–34) in the placebo arm, with a median follow-up of 69 mo. Prognostic modeling showed 5-yr survival rates of 42%, 24%, and 5% for low-, intermediate-, and high-risk groups, respectively. Greater degrees of confirmed prostate-specific antigen declines (≤3 mo) were associated with greater 5-yr survival. A higher incidence of fatal treatment-emergent adverse events was observed with enzalutamide (6.9% vs 3.8%), with an increase in fatal cardiovascular events (1.6% vs 0.4%).

† Prior affiliation: Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, Canada.
* Corresponding author. Division of Medical Oncology and Urology, Duke Cancer Institute, Duke University, DUMC Box 103861, Durham, NC 27710, USA. Tel.: +1-(919) 668-8797; Fax: +1-(919) 660-0178.
E-mail address: andrew.armstrong@duke.edu (A.J. Armstrong).

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Conclusions: With >5 yr of follow-up, enzalutamide continued to demonstrate improved survival in patients with mCRPC despite crossover and multiple subsequent effective therapies, balanced against a slightly higher rate of fatal cardiovascular events.

PREVAIL is registered on ClinicalTrials.gov as NCT01212991.

Patient summary: We report a maintained long-term survival benefit with enzalutamide and risks with >5 yr of enzalutamide treatment and follow-up in men with metastatic prostate cancer, and identify groups of men with widely different outcomes based on clinical factors.

1. Introduction

Long-term survival of men with metastatic castration-resistant prostate cancer (mCRPC) beyond 5 yr was previously very rare. In the pivotal TAX327 docetaxel trial, <5% of men lived beyond 5 yr [1–3]. Various prognostic models have been developed to estimate long-term survival using common clinical factors such as prostate-specific antigen (PSA) level, hemoglobin, alkaline phosphatase, pain, pattern of spread, lactate dehydrogenase (LDH), and other factors [1,4,5], but 5-yr survival predictability has been limited by a lack of long-term follow-up. Previously, risk groups were developed in the setting of chemotherapy that predicted 5-yr overall survival (OS) [1,2]; however, recent studies have demonstrated improved OS with potent androgen receptor inhibition in chemotherapy-naïve men with mCRPC [6,7]. Thus, updated models are needed.

We published an internally validated PREVAIL prognostic model that stratifies men with mCRPC into three risk groups with widely differing clinical outcomes and survival times [4]. Enzalutamide reduced the risk of death and radiographic progression-free survival in men in high-, intermediate-, or low-risk groups [6,8]. This model identified 11 key independent OS prognostic factors, and included a nomogram and a risk group calculator for predicting 1-, 2-, and 3-yr survival probabilities. We also confirmed the prognostic value of post-treatment PSA declines with enzalutamide for predicting OS in PREVAIL, validating work in other mCRPC settings [9–12]. The purpose of this final PREVAIL analysis is to provide long-term safety and efficacy of enzalutamide and 5-yr survival estimates based on pretreatment prognostic factors and risk groups, as well as post-treatment PSA declines.

2. Patients and methods

PREVAIL (NCT01212991), an international, randomized, double-blind, placebo-controlled, phase 3 study was reported previously [6]. Patients were randomized 1:1 to receive oral enzalutamide 160 mg or placebo once daily until intolerance, confirmed radiographic disease progression, or initiation of another therapy for prostate cancer. PREVAIL was stopped after a preplanned interim analysis revealed enzalutamide superiority compared with placebo. Eligible placebo patients could cross over to enzalutamide (n = 234) in an open-label extension. The crossover began on January 1, 2014. These patients were included in the placebo group for the final analysis of OS after >5 yr of follow-up.

2.1. Data sets

The primary endpoint of OS and safety analyses were updated after 1382 deaths (80%). Updated OS results utilized the full analysis set and included data based on randomized treatment assignment (ie, the placebo arm included data following the crossover). Safety analyses included data from patients who received at least one dose of study treatment, and were reported overall and in 1-yr intervals from randomization among evaluable patients. For the updated nomogram, the data set was used as defined previously, with patients from both the enzalutamide and the placebo arm of PREVAIL divided randomly 2:1 into training and testing sets [4]. Patient characteristics and outcomes were well balanced between the training and test sets.

2.1.1. Model update

Modeling was conducted as described [4]. A multivariate Cox proportional hazard model to predict OS was developed using the training set. The hazard ratio (HR) and 95% confidence interval (CI) were computed for each potentially prognostic variable. A risk score was developed using the test and training set. Based on risk scores, the entire data set was divided at the median cut-point (high- and low-risk groups) and by tertiles (high-, intermediate-, and low-risk groups) to provide OS rates . Outcomes were reported according to the number of risk factors (point system; zero to three risk factors: low risk; four to seven risk factors: intermediate risk; and eight to 10 risk factors: high risk, not including enzalutamide treatment). OS was analyzed using Kaplan-Meier methodology. Analyses used SAS software (version 9.4; SAS Institute, Cary, NC, USA) and R glmnet and R survAUC packages (R version 3.2.2) [13].

2.2. Analysis of PSA decline

A 13-wk PSA landmark analysis was conducted to determine prognostic association with OS, excluding patients who died or were censored prior to week 13. As in a previous post hoc analysis [12], the PREVAIL enzalutamide arm was grouped as per the confirmed maximal 3-mo PSA decline from baseline: (1) no decline/<30% decline; (2) ≥30% confirmed decline; (3) ≥50% confirmed decline; (4) ≥90% confirmed decline; and (5) maximal PSA decline (<0.2 ng/ml).

2.3. Statistical analysis of the final OS analysis

This preplanned final OS analysis was performed in the intent-to-treat population. Comparisons were made between the enzalutamide and placebo treatment arms. HRs were based on Cox regression models, with treatment being the only covariate.

3. Results

3.1. Patient disposition

Patients (N = 1717; 1715 treated) were randomized between September 2010 and September 2012. At the extended overall analysis data cutoff (September 30, 2017), 955 patients (520 from the original enzalutamide arm and 435 from the placebo arm) had entered the open-label extension or were in long-term follow-up (Supplementary

Table S1). Of these, 465 patients continued to receive enzalutamide in the open-label extension, including 234 patients who crossed over from placebo to enzalutamide and 231 patients on the enzalutamide arm who continued treatment, and 489 patients across both arms discontinued the study drug but were monitored in the long-term follow-up.

3.2. Overall survival

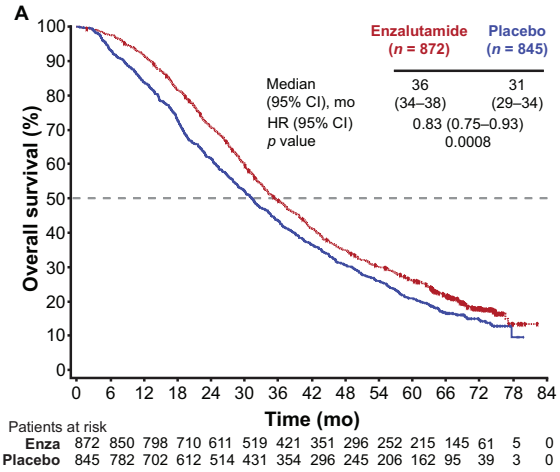
At the 5-yr OS analysis, there were 1382 deaths (enzalutamide, $n = 689$; placebo, $n = 693$). Enzalutamide reduced the hazard of death by 17% (HR 0.83; 95% CI 0.75–0.93; $p < 0.001$; Fig. 1A). At a median follow-up of 69 mo (67 mo without event), median OS was 36 mo (95% CI 34–38) in the enzalutamide arm versus 31 mo (95% CI 29–34) in the placebo arm. The 2-, 3-, and 5-yr survival rates were 71%, 49%, and 26% with enzalutamide versus 62%, 44%, and 21% with placebo (absolute risk reductions of 9%, 5%, and 5%), respectively (Supplementary Fig. S1). The enzalutamide treatment effect was generally consistent across all baseline disease-specific subgroups (Fig. 1B). In patients with baseline liver metastasis, OS benefit was not observed with enzalutamide versus placebo, but there were relatively few patients ($n = 74$) with a wide CI (HR 1.12; 95% CI 0.69–1.83).

3.3. Subsequent therapy

At the data cutoff, 70% of patients in the enzalutamide arm and 85.8% in placebo arm had received one or more postbaseline antineoplastic therapies. Of patients in the enzalutamide and placebo arms, 67% and 82%, respectively, had received one of the following subsequent therapies: abiraterone acetate, cabazitaxel, docetaxel, enzalutamide, radium-223, or sipuleucel-T (Supplementary Table S2). Within this group, the most common subsequent therapy was docetaxel (enzalutamide arm, 55%; placebo arm, 65%), and the second and third most common subsequent therapies were abiraterone acetate (enzalutamide arm, 42%; placebo arm, 54%), and enzalutamide (enzalutamide arm, 6.1%; placebo arm, 43%). In the placebo arm, 68% of men received at least subsequent abiraterone or enzalutamide.

3.4. Multivariable model for predicting OS

An updated nomogram based on 5-yr OS data used 11 prognostic factors, including treatment with enzalutamide or placebo (Fig. 2). The updated model using the full data set showed a significant separation between low-risk (HR 0.25; 95% CI 0.21–0.28) and intermediate-risk (HR 0.41; 95% CI 0.36–0.46; both $p < 0.0001$) patients versus high-risk patients (Fig. 3A and Table 1). Low- and intermediate-risk patients were more likely to receive crossover treatment (Supplementary Table S3). Nomogram factors to determine predictors of survival are shown in Supplementary Table S4. Survival rates at 5 yr were 42%, 24%, and 5% for the low-, intermediate-, and high-risk groups, respectively. Numerically based risk group stratification based on baseline risk variables also provided a significant separation of OS between low-risk (zero to three risk variables) and intermediate-risk (four to seven risk variables) patients versus high-risk (eight to 10 risk variables) patients (Fig. 3B), which also provided strong discrimination of 5-yr survival rates ranging



B

Subgroup	No. of patients Enzalutamide / Placebo	Overall survival Median (mo) Enzalutamide / Placebo	Hazard ratio for death (95% CI)	P value for interaction*
All patients	872/845	36/31	0.83 (0.75–0.93)	
ECOG performance status				
0	584/585	38/35	0.87 (0.77–0.99)	
1	288/260	31/25	0.73 (0.61–0.88)	0.0875
Age (years)				
<75	555/553	37 / 35	0.88 (0.77–1.00)	
≥75	317/292	34/25	0.74 (0.62–0.88)	0.1071
Geographic region				
North America	218/208	37/35	0.85 (0.68–1.05)	
Europe	465/446	34/30	0.85 (0.74–0.98)	
Rest of the world	189/191	37/32	0.79 (0.63–0.99)	0.8041
Total Gleason score at diagnosis				
≤7	414/385	38/32	0.84 (0.72–0.98)	
≥8	424/423	34/30	0.86 (0.74–1.00)	0.8304
Type of progression at study entry				
PSA progression only	375/369	43/36	0.77 (0.65–0.91)	
Radiographic progression with or without PSA progression	475/451	31/28	0.87 (0.76–1.00)	0.4204
Visceral disease at screening				
Node only	105/126	49/40	0.86 (0.63–1.17)	0.7718
Bone only	387/358	40/33	0.76 (0.64–0.89)	0.1137
Lung	64/75	36/25	0.77 (0.53–1.11)	0.5218
Liver	40/34	19/15	1.12 (0.69–1.83)	0.1295
Baseline PSA value (ng/ml)				
≤median (49.60)	420/440	44/43	0.90 (0.77–1.06)	
>median (49.60)	452/404	30/23	0.70 (0.61–0.81)	0.0114
Baseline lactate dehydrogenase value (U/l)				
≤median (185)	442/422	43/37	0.75 (0.65–0.88)	
>median (185)	428/421	30/25	0.93 (0.80–1.07)	0.0757
Baseline hemoglobin value (g/l)				
≤median (130)	454/416	31/26	0.84 (0.72–0.97)	
>median (130)	417/428	43/37	0.81 (0.69–0.94)	0.8560

Fig. 1 – Long-term OS from PREVAIL. (A) Kaplan-Meier estimates of overall survival and (B) long-term survival by subgroup. Using a Bonferroni adjustment to control for multiple comparisons, $p < 0.0042$ would be considered to be statistically significant. CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; enza = enzalutamide; OS = overall survival; PSA = prostate-specific antigen. * Treatment by subgroup interaction p value.

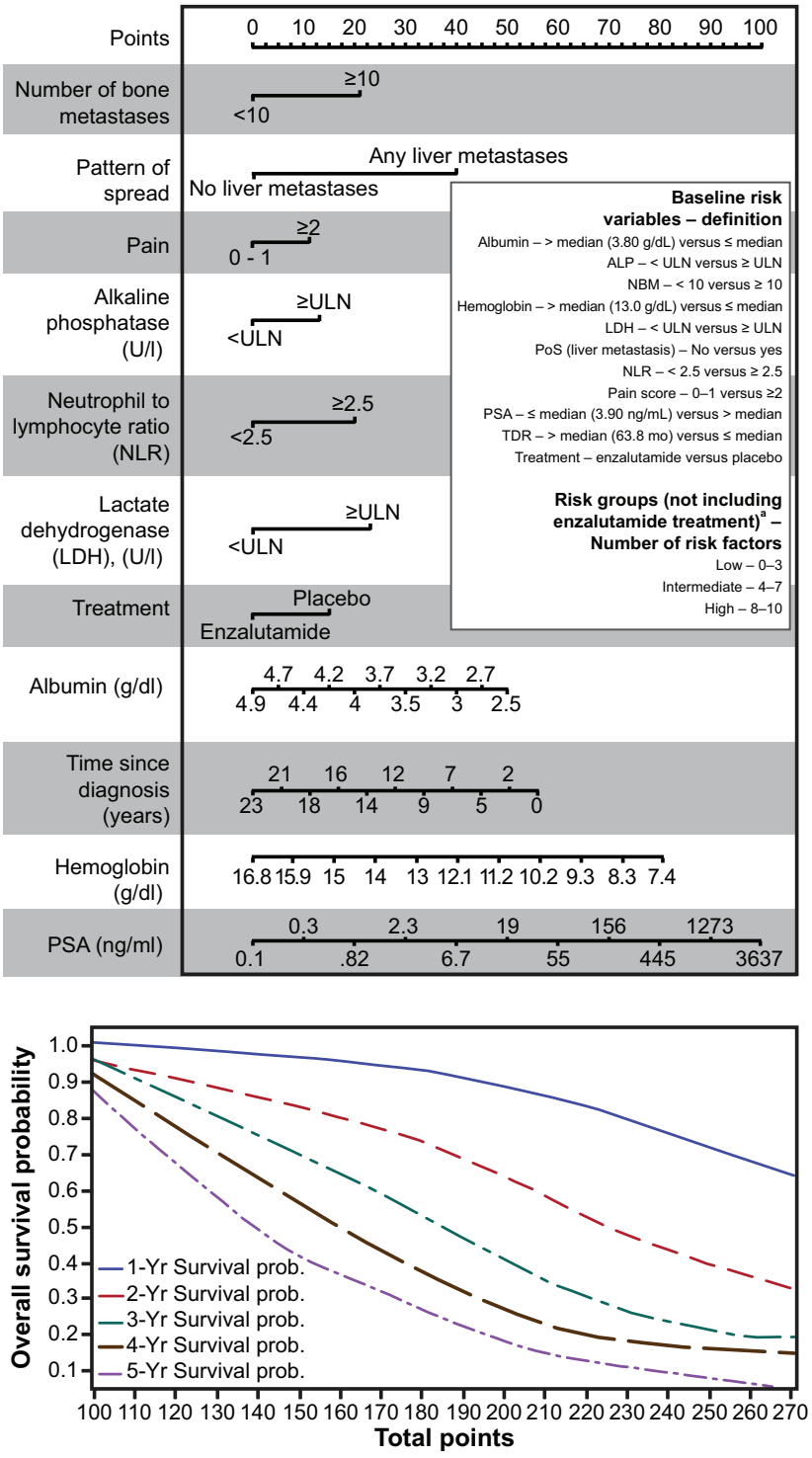


Fig. 2 – Survival probability estimates. Updated nomogram to estimate survival probability. A nomogram is used to assign each of 11 prognostic factors with a point (ranging from 0 to 100) in a graphic interface, based on the estimated regression coefficients from the final multivariable Cox proportional hazard model predicting OS. The nomogram results match with the algorithm. The 1-, 2-, 3-, 4-, and 5-yr survival probability versus total points were also generated to allow the clinical partition to predict OS. The nomogram was developed using SAS enterprise and is based on the article available as http://support.sas.com/resources/papers/proceedings13/264-2013.pdf. Instructions to physicians: all the 11 prognostic factors should be available before using this model. Start from the second top axis by identifying the number of bone metastases. Draw a vertical line to the point's axis (top line) to represent the number of prognostic points that patients will receive for the number of bone metastases. Do the same for the other prognostic variables. Once all prognostic points for the predictors have been determined, add up the prognostic points for each prognostic variable. On the basis of the total points, one can determine the 1-yr survival probability by drawing a vertical line from the total points (*x*-axis) to the survival probability. The same process can be performed to estimate the 2-, 3-, 4-, and 5-yr survival probability. ALP = alkaline phosphatase; LDH = lactate dehydrogenase; NBM = number of bone metastases; NLR = neutrophil to lymphocyte ratio; OS = overall survival; prob. = probability; PoS = pattern of spread; PSA = prostate-specific antigen; TDR = time from diagnosis to randomization; ULN = upper limit of normal. [a] Equation for risk score calculation: $-0.344Albumin + 0.235ALP - 0.166Hemoglobin + 0.408LDH + 0.378NLR + 0.381NBM + 0.262Pain$ score $+ 0.707PoS\ (liver\ metastasis) + 0.204\log_e PSA - 0.003TDR + 0.389Treatment$.

Table 1 – Survival rates based on stratification by low-, intermediate-, and high-risk tertiles.

Patients	HR (95% CI)	Survival rates, % (95% CI) *		
		1 yr	3 yr	5 yr
Overall				
Low risk	0.25 (0.21–0.28)	96 (95–98)	69 (65–73)	42 (38–46)
Intermediate risk	0.41 (0.36–0.46)	93 (91–95)	51 (46–55)	24 (21–28)
High risk	REF	74 (70–77)	19 (16–23)	5 (3–7)
Enzalutamide arm				
Low risk	0.24 (0.20–0.29)	97 (94–98)	70 (65–75)	44 (38–49)
Intermediate risk	0.43 (0.35–0.51)	95 (92–97)	50 (44–56)	23 (18–29)
High risk	REF	81 (75–85)	20 (16–26)	5 (3–9)
Placebo arm				
Low risk	0.26 (0.21–0.32)	96 (92–98)	68 (62–74)	40 (33–46)
Intermediate risk	0.39 (0.33–0.47)	91 (88–94)	51 (46–57)	25 (20–30)
High risk	REF	68 (63–73)	18 (14–23)	4 (2–7)

CI = confidence interval; HR = hazard ratio; REF = reference.
* Absolute risk reduction with treatment: Low risk: 1 yr, 1%; 3 yr, 2%; 5 yr, 4%. Intermediate risk: 1 yr, 4%; 3 yr, no reduction; 5 yr, no reduction. High risk: 1 yr, 13%; 3 yr, 2%; 5 yr, 1%.

Table 2 – Survival rates based on stratification by high (eight to 10 baseline risk variables), intermediate (four to seven baseline risk variables), and low (zero to three baseline risk variables) risks.

Patients	HR (95% CI)	Survival rates, % (95% CI)*		
		1 yr	3 yr	5 yr
Overall				
Low risk	0.17 (0.14–0.22)	95 (93–96)	64 (61–67)	37 (33–40)
Intermediate risk	0.40 (0.31–0.51)	84 (81–86)	31 (28–34)	11 (9–14)
High risk	REF	49 (37–59)	7 (2–14)	1 (0–6)
Enzalutamide arm				
Low risk	0.13 (0.10–0.18)	96 (94–98)	67 (63–72)	40 (36–45)
Intermediate risk	0.29 (0.21–0.40)	91 (88–94)	36 (31–40)	14 (11–18)
High risk	REF	54 (39–67)	4 (1–13)	0 (0–0)
Placebo arm				
Low risk	0.24 (0.16–0.36)	94 (91–96)	61 (56–65)	33 (28–38)
Intermediate risk	0.57 (0.38–0.86)	76 (71–80)	26 (21–30)	8 (6–12)
High risk	REF	38 (20–56)	12 (3–27)	4 (0–16)

CI = confidence interval; HR = hazard ratio; REF = reference.
* Absolute risk reduction with treatment: Low risk: 1 yr, 2%; 3 yr, 6%; 5 yr, 7%. Intermediate risk: 1 yr, 15%; 3 yr, 10%; 5 yr, 6%. High risk: 1 yr, 16%; 3 yr, no reduction; 5 yr, no reduction.

from 1% to 37% (Table 2). Stratification by median risk score also showed a separation between low- and high-risk patients (HR 0.37; 95% CI 0.33–0.41; $p < 0.0001$; Fig. 3C and Table 3). Median values for baseline prognostic variables are shown in Fig. 2. Adjustment of the original 11-variable model with dichotomous values of neutrophil to lymphocyte ratio (NLR), LDH, alkaline phosphatase, and bone metastases (incremental area under the curve [iAUC] = 0.7836) to categorical variables led to slight AUC improvement (iAUC = 0.7866); further adjustment to a continuous variable for NLR led to a very slight AUC improvement (iAUC = 0.7872; Supplementary Table S5).

3.5. *Prognostic association of PSA decline with OS (13-wk landmark analysis)*

The HRs for OS were 0.42 (95% CI 0.34–0.53), 0.40 (95% CI 0.32–0.50), and 0.32 (95% CI 0.25–0.41) for confirmed 3-mo enzalutamide-treatment PSA declines of ≥30%, ≥50%, and ≥90%, respectively, versus no decline or <30% decline (Fig. 3D) as the reference group. The HR for OS was 0.12 (95% CI 0.07–0.22) for men with PSA < 0.2 ng/ml. The 5-yr OS rates were 9%, 30%, 31%, 37%, and 67% for men with no PSA decline to <30% PSA decline ($n = 94$), ≥30% decline ($n = 701$), ≥50% PSA decline ($n = 639$), ≥90% PSA decline ($n = 307$), and PSA < 0.2 ng/ml ($n = 37$), respectively (Table 4).

3.6. *Safety*

Treatment-emergent adverse events (TEAEs) were reported as the primary reason for discontinuation in 9.1% of enzalutamide and 6.0% of placebo patients (Table 5). The median duration of therapy and adverse event reporting was 17.7 mo for the enzalutamide (range, 0.2–78.5) and 4.6 mo for the placebo (range, 0.1–34.5) group. The most frequently reported TEAEs in the enzalutamide arm were fatigue, select gastrointestinal events, hypertension, and fractures. Reported incidences for fatigue in the enzalutamide arm were highest during the 1st year (44%) and then generally decreased at 1–<2 (15.1%), 2–<3 (11.9%), 3–<4

Table 3 – Survival rates based on stratification by median risk score.

Patients	HR (95% CI)	Survival rates, % (95% CI)*		
		1 yr	3 yr	5 yr
Overall				
Low risk	0.37 (0.33–0.41)	96 (95–97)	67 (63–70)	38 (35–42)
High risk	REF	79 (77–82)	26 (24–30)	9 (7–11)
Enzalutamide arm				
Low risk	0.36 (0.31–0.42)	97 (95–98)	67 (62–71)	39 (35–44)
High risk	REF	85 (81–88)	27 (22–31)	9 (6–12)
Placebo arm				
Low risk	0.38 (0.33–0.45)	96 (93–97)	66 (61–71)	36 (31–42)
High risk	REF	75 (71–79)	26 (22–30)	9 (7–12)

CI = confidence interval; HR = hazard ratio; REF = reference.
* Absolute risk reduction with treatment: Low risk: 1 yr, 1%; 3 yr, 1%, 5 yr, 3%. High risk: 1 yr, 10%; 3 yr, 1%; 5 yr, no reduction.

Table 4 – Survival rates based on the degree of confirmed PSA decline at week 13 and best overall PSA decline.

Patients [a]	*n*	Survival rates, % (95% CI)		
		1 yr	3 yr	5 yr
PSA <0.2 ng/ml	37	97 (82–100)	84 (67–92)	67 (49–80)
PSA ≥90% confirmed decline	307	98 (95–99)	66 (60–71)	37 (32–43)
PSA ≥50% confirmed decline	639	96 (94–97)	58 (54–62)	31 (28–35)
PSA ≥30% confirmed decline	701	96 (94–97)	56 (52–59)	30 (27–33)
No PSA decline to <30% confirmed decline	94	82 (73–88)	25 (17–35)	9 (5–17)
All enzalutamide patients	819	94 (92–95)	51 (48–55)	27 (24–30)
Best overall PSA decline				
PSA <0.2 ng/ml	100	99 (93–100)	91 (83–95)	71 (61–79)
PSA ≥90% confirmed decline	376	98 (96–99)	69 (64–73)	42 (37–47)
PSA ≥50% confirmed decline	636	96 (95–98)	58 (54–62)	31 (28–35)
PSA ≥30% confirmed decline	691	96 (94–97)	56 (52–59)	30 (26–33)
No PSA decline to <30% confirmed decline	30	80 (61–90)	32 (17–49)	11 (3–25)
All enzalutamide patients	872	92 (90–93)	49 (46–53)	26 (23–29)

CI = confidence interval; PSA = prostate-specific antigen.
[a] Patients who died or were censored prior to week 13 were excluded.

(9.7%), 4–<5 (8.7%), and ≥5 (2.3%) yr (Fig. 4 and Supplementary Table S6). Fracture incidences were 4.7%, 5.7%, 5.4%, 5.6%, 4.3%, and 2.3% in these time frames, respectively. The incidence of other TEAEs was highest at <1 yr, and decreased or remained stable for subsequent yearly rates. For the most commonly reported TEAEs, a lower incidence was generally observed in the placebo group versus the enzalutamide group, and mostly reported in the first couple of years. Seizures were rare in both groups (<1%) over time (Fig. 4 and Supplementary Table S6).

Data on cardiovascular events in this extended follow-up period suggested that men treated with enzalutamide may be at an increased risk of cardiovascular events compared with the placebo group (Supplementary Table S7). Cardiovascular events (grade ≥3) were higher in men ≥75 yr of age treated with enzalutamide versus placebo (8.8% vs 2.4%) versus younger men (4.3% vs 2.0%) and were higher in men with and without established cardiovascular risk factors. The presence of known baseline cardiovascular risk factors was associated with an increased risk of cardiovascular events in the placebo group (2.6% vs 1.1%) and in placebo patients who received subsequent enzalutamide (7.2% vs 3.0%). Cardiovascular TEAEs resulting in death were higher with enzalutamide (*n* = 14, 1.6%) versus placebo (*n* = 3, 0.4%; Supplementary Table S8). Cardiovascular TEAEs resulting in enzalutamide-related death were observed in two patients (cardiac failure, *n* = 1; congestive cardiac failure, *n* = 1) and placebo-related death in one patient (pulmonary hemorrhage and tumor embolism; Supplementary Table S9).

4. Discussion

In this long-term PREVAIL analysis, enzalutamide maintained a long-term survival advantage over placebo despite the majority of placebo-treated men (68%) receiving subsequent enzalutamide or abiraterone. We provide rates of 5-yr survival according to treatment as well as according to pretreatment patient characteristics and post-treatment confirmed PSA declines. Such data provide clinical utility by establishing realistic and updated expectations for patients and providers around prognosis based on individual patient-specific factors and response to therapy. Men treated with enzalutamide had widely variable 5-yr survival rates. Using the risk score model, low-risk patients with mCRPC treated with enzalutamide had 5-yr survival of 40%, while high-risk patients with mCRPC treated with enzalutamide had 5-yr survival of 0%. Following treatment, prognosis can be updated based on an individual patient's

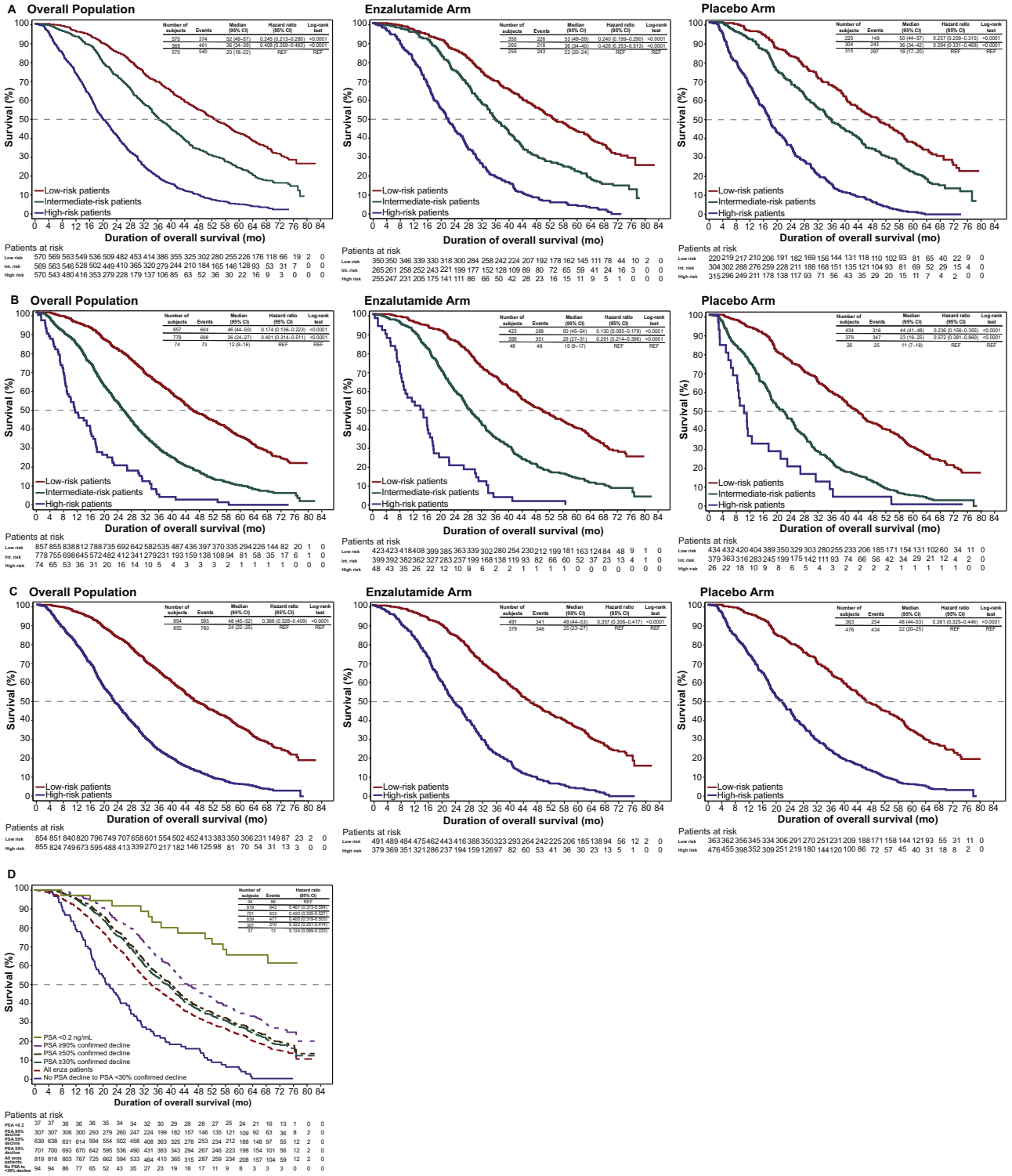


Fig. 3 – Analysis of OS based on the 11-variable model stratified by low-, intermediate-, and high-risk score tertiles: (A) analysis of OS based on the 11-variable model stratified by low-, intermediate-, and high-risk tertiles; (B) analysis of OS in patients stratified by high (eight to 10 baseline risk variables), intermediate (four to seven risk variables), and low (zero to three risk variables) risks based on the number of risk variables present at baseline; (C) analysis of overall survival based on the 11-variable model stratified by median risk score; and (D) Kaplan-Meier plot of overall survival by level of greatest confirmed PSA decline from baseline within the first 3 mo of treatment with enzalutamide (excluding patients who died or were censored prior to week 13). Survival plots are shown without making comparisons between treatment groups but for purposes of providing prognostic information. CI = confidence interval; enza = enzalutamide; Int. = intermediate; OS = overall survival; PSA = prostate-specific antigen; REF = reference.

Table 5 – Long-term safety summary.

	Enzalutamide (n = 871)				Placebo (n = 844)			
TEAEs, *n* (%)								
Overall TEAEs	857 (98)				791 (94)			
Grade ≥3 TEAEs	462 (53)				318 (38)			
TEAEs leading to death	60 (6.9)				32 (3.8)			
Any serious TEAEs	382 (44)				229 (27)			
TEAEs leading to treatment discontinuation	79 (9.1)				51 (6.0)			
TEAEs leading to study drug discontinuation	208 (24)				218 (26)			
Fatal CV TEAEs	14 (1.6)				3 (0.4)			
Drug-related fatal CV AEs	2 (0.2)				0			
	Grade 1/2	Grade 3/4	Grade 5	All	Grade 1/2	Grade 3/4	Grade 5	All
TEAEs of special interest, *n* (%)								
Fatigue	418 (48)	36 (4.1)	0	454 (52)	274 (32)	25 (3.0)	0	299 (35)
Select gastrointestinal events [a]	404 (46)	20 (2.3)	0	424 (49)	342 (41)	12 (1.4)	0	354 (42)
Hypertension	78 (9.0)	76 (8.7)	0	154 (18)	18 (2.1)	23 (2.7)	0	41 (4.9)
Fall	122 (14)	20 (2.3)	0	142 (16)	39 (4.6)	6 (0.7)	0	45 (5.1)
Fractures	96 (11)	42 (4.8)	0	138 (16)	28 (3.3)	17 (2.0)	0	45 (5.3)
Hypersensitivity [b]	79 (9.1)	4 (0.5)	1 (0.1)	84 (9.6)	48 (5.7)	2 (0.2)	0	50 (5.9)
Select CV events [c]	28 (3.2)	32 (3.7)	6 (0.7)	66 (7.6)	12 (1.4)	4 (0.5)	1 (0.1)	17 (2.0)
Major CV events [d]	12 (1.4)	31 (3.6)	5 (0.6)	48 (5.5)	9 (1.1)	7 (0.8)	1 (0.1)	17 (2.0)
Renal impairment [e]	24 (2.8)	15 (1.7)	0	39 (4.5)	26 (3.1)	10 (1.2)	2 (0.2)	38 (4.5)
Hepatic impairment [f]	21 (2.4)	12 (1.4)	1 (0.1)	34 (3.9)	18 (2.1)	4 (0.5)	1 (0.1)	23 (2.7)
Loss of consciousness	0	20 (2.3)	0	20 (2.3)	1 (0.1)	9 (1.1)	0	10 (1.2)
Venous thromboembolic events	9 (1.0)	7 (0.8)	1 (0.1)	17 (2.0)	8 (0.9)	9 (1.1)	0	17 (2.0)
Neutropenia	9 (1.0)	5 (0.6)	0	14 (1.6)	2 (0.2)	3 (0.4)	0	5 (0.6)
Seizures	0	2 (0.2)	0	2 (0.2)	1 (0.1)	0	0	1 (0.1)
Hallucinations	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0	0	1 (0.1)
Mental impairment [g]	0	0	0	0	0	0	0	0

AE = adverse event; CV = cardiovascular; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.
[a] Includes constipation, diarrhea, nausea, and vomiting.
[b] Includes prespecified narrow SMQ of "hypersensitivity."
[c] Includes prespecified narrow SMQs of "myocardial infarction" and "other ischemic heart disease."
[d] Includes narrow SMQs of "myocardial infarction," "hemorrhagic cerebrovascular conditions," and "ischemic cerebrovascular conditions."
[e] Includes broad SMQ of "acute renal failure."
[f] Includes narrow SMQ of "drug-related hepatic disorders comprehensive search."
[g] Includes all preferred terms under the MedDRA High Level Group Term "mental impairment disorders."

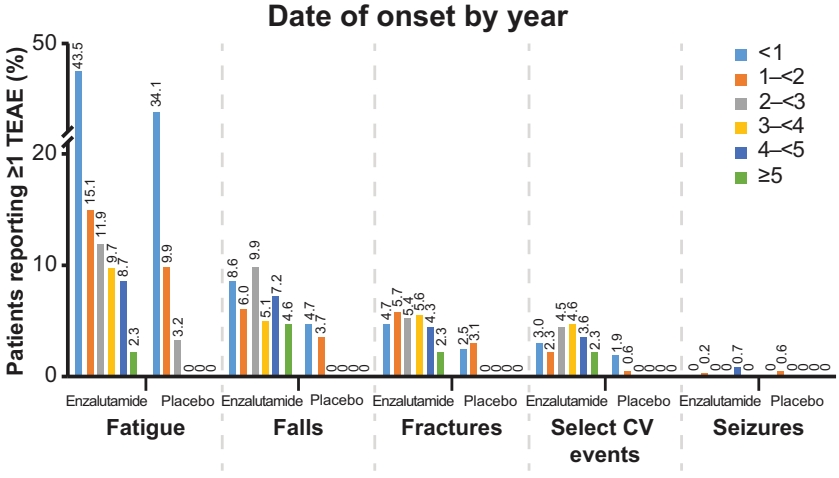


Fig. 4 – TEAEs of special interest by date of onset by year. CV = cardiovascular; TEAE = treatment-emergent adverse event.

sensitivity to enzalutamide therapy, with 5-yr survival rates ranging from 9% to 67%. These data, in the form of an online calculator (see https://www.mdcalc.com/prevail-model-prostate-cancer-survival) can provide valuable patient-specific information to guide communications and goals for care.

Enzalutamide maintained a survival advantage despite crossover of the majority of patients to life-prolonging

therapies, including abiraterone, docetaxel, and enzalutamide. This suggests that early use of potent androgen receptor inhibition may be beneficial to some men in this setting by delaying further metastatic spread. In the non-mCRPC setting, potent androgen receptor inhibition has also delayed metastatic spread, with the possibility of improved survival, pending long-term follow-up [14,15].

Enzalutamide was found to be safe and effective overall, with manageable long-term toxicities. We found a higher rate of treatment-related deaths, particularly cardiovascular deaths, with enzalutamide versus placebo and a higher rate of clinically significant fractures, falls, fatigue, cardiovascular events, and hypertension, which may lead to increases in mortality and morbidity over time. Based on these findings, we recommend cardiovascular risk assessment prior to starting hormonal therapy and over time, and for providers, to address known heart disease risk factors. We further recommend that risk factors such as these be evaluated at baseline and over time in future androgen receptor inhibition clinical trials. Exercise may be the most critical area for intervention because of its benefits in supporting heart health, maintaining a healthy body weight, reducing the risk of sarcopenia and metabolic syndrome, reducing hot flashes, improving bone health, and preventing fractures [16–18]. We have shown [19] that a proactive diet and exercise program may reduce many of these adverse events in men treated with androgen deprivation therapy with or without enzalutamide, and that an individualized exercise training program may be a low-cost and effective therapy to mitigate many adverse effects of hormonal therapies [20,21]. The use of denosumab or zoledronic acid is another important consideration in this setting to ensure bone health and for fracture prevention, as demonstrated in the PEACE III trial [22].

One limitation is the lack of integrated biomarker data for the development of a clinical-genomic risk group system. Certain biomarkers, such as AR-V7, TP53 alterations and RB1 loss, DNA repair alterations, androgen receptor gain and genomic structural rearrangements, enumeration of circulating tumor cells, circulating androgen levels, ctDNA quantification, and other molecular drivers of aggressive disease biology, were not assessed in the PREVAIL study [23–28]. Future analyses from independent data sets should examine these clinical prognostic models in the context of mutational information. Additionally, when this study was carried out, upfront docetaxel or potent androgen receptor inhibition was not used as the standard of care in de novo metastatic hormone-sensitive disease. It remains unclear whether models described herein can be applied to patients with metastatic hormone-sensitive prostate cancer when progressing to mCRPC.

5. Conclusions

These data provide important prognostic information to healthcare providers who commonly use androgen receptor inhibitors, such as enzalutamide, for the treatment of patients with chemotherapy-naïve mCRPC. With >5 yr of follow-up, enzalutamide continued to demonstrate OS benefit versus placebo in patients with asymptomatic or mildly symptomatic mCRPC, despite placebo crossover and multiple subsequent therapies. Survival benefits were observed across all patient subgroups with no treatment-risk group interactions noted. Five-year survival benchmarks for this disease state and therapy based on patient characteristics and response to enzalutamide therapy were established. We hope that this information will be useful for providers and patients (see Supplementary Fig. S2 for summary infographic). There is a need to study patients with mCRPC with multiple high-risk features including liver metastases in future clinical trials, as they continue to experience poor 5-yr survival rates regardless of therapy.

A portion of these data were presented at the 34th Annual European Association of Urology (EAU) Congress; March 15-19, 2019; Barcelona, Spain.

Author contributions: Andrew J. Armstrong 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: Armstrong, Tombal, Higano, Beer.
Acquisition, of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Armstrong.
Critical revision of the manuscript for important intellectual content: All authors.
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***Data Sharing Statement*:** Upon 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 USA and/or EU or (2) in programs that have been terminated (ie, 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 mo 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.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.04.061.

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