Enzalutamide in Men With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC): Long-term Overall Survival and Safety Analyses of the Phase 3 PREVAIL Study

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BACKGROUND

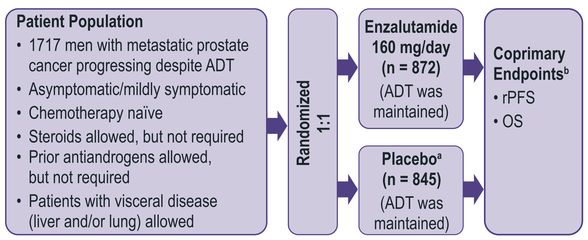
- The oral androgen receptor inhibitor enzalutamide reduced the risk of death and radiographic progression versus placebo in the PREVAIL study of patients with asymptomatic or minimally symptomatic chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC).[1]
- The magnitude of prostate-specific antigen (PSA) decline at 3 months was strongly associated with improved clinical and patient-reported outcomes in patients with mCRPC treated with enzalutamide in the PREVAIL study.[2]
- Overall survival (OS) benefit of enzalutamide in these patients was confirmed in an analysis of the PREVAIL study after an additional 9 months of follow-up.[3]
- A validated prognostic model incorporated variables routinely collected in PREVAIL patients with chemotherapy-naïve mCRPC treated with enzalutamide, identifying a subset of patients with widely different survival outcomes to help inform external validation, patient care, and clinical trial design.[4]
- Here we evaluated long-term OS and safety in patients from the PREVAIL study with > 5 years of follow-up.

METHODS

Study Design

- The PREVAIL study design is presented in **Figure 1**.
- PREVAIL was halted after a preplanned interim analysis revealed the superiority of enzalutamide compared with placebo.
- Eligible patients could cross over to enzalutamide (n = 234) in an open-label extension; these patients were included in the placebo group for the final analysis of OS after > 5 years of follow-up.

Figure 1. PREVAIL Study Design



[a]Patients were offered the opportunity to receive enzalutamide (crossover began January 1, 2014).
[b]Total alpha 0.05, 2-sided (OS allocation, 0.049; rPFS allocation, 0.001); target hazard ratio: OS, 0.82; rPFS, 0.57.
ClinicalTrials.gov identifier: NCT01212991.
Abbreviations: ADT, androgen deprivation therapy; OS, overall survival; rPFS, radiographic progression-free survival.

Statistical Analyses

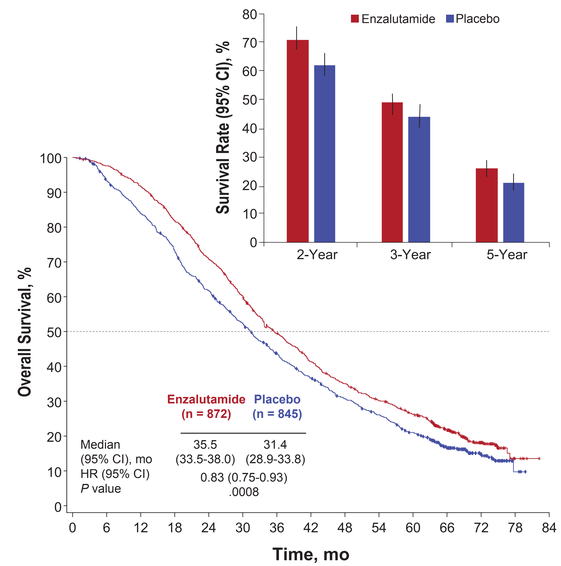
- This preplanned final OS analysis was performed in the intention-to-treat population.
- Comparisons were made between enzalutamide and placebo treatment arms.
- Hazard ratios (HRs) were based on Cox regression models, with treatment as the only covariate.

RESULTS

Baseline Characteristics

- 1717 men were randomized (1715 treated) to PREVAIL between September 2010 and September 2012.
- At the extended OS 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 (**Table 1**).
- Of these, 465 patients continued to receive enzalutamide in the open-label extension and 489 patients discontinued study drug but were monitored in the long-term follow-up.

Figure 2. Long-term Overall Survival From PREVAIL



CI, confidence interval; HR, hazard ratio.

Overall Survival

- At the 5-year OS analysis (data cutoff December 20, 2017; 5 years after the last patient was randomized), there were 1382 deaths (enzalutamide arm, n = 689; placebo arm, n = 693).
- Survival probabilities at 2, 3, and 5 years favored enzalutamide (**Figure 2**).
- At the 5-year OS analysis, enzalutamide reduced the risk of death by 17% (HR, 0.83; 95% confidence interval [CI], 0.75-0.93; *P* = .0008).
- At a median follow-up of 69 months, median OS was 35.5 months (95% CI, 33.5-38.0) in the enzalutamide arm versus 31.4 months (95% CI, 28.9-33.8) in the placebo arm.

Table 1. Patient Flow in the Long-term PREVAIL Study

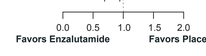
Patients, no. (%)	Enzalutamide (n = 872)	Placebo (n = 845)
Patients enrolled in OLE or in LTFU	520 (59.6)	435 (51.5)
Patients received study drug in OLE	231 (26.5)	234 (27.7)
Patients enrolled in OLE, but not dosed by data cutoff date	1 (0.1)	0
Patients in LTFU	288 (33.0)	201 (23.8)
Patients not enrolled in OLE	352 (40.4)	410 (48.5)
Patients died prior to OLE	342 (39.2)	395 (46.7)
Patients not transitioned to OLE	10 (1.1)	15 (1.8)
Patients only received study drug in blinded phase	10 (1.1)	15 (1.8)

Abbreviations: LTFU, long-term follow-up; OLE, open-label extension.

- The enzalutamide treatment effect was generally consistent across all baseline disease-specific subgroups (**Figure 3**).
  - In patients with liver metastasis at baseline, OS benefit was not observed with enzalutamide compared with placebo (HR = 1.12) but there were relatively few patients in this subgroup with a wide CI.

Figure 3. Long-term Overall Survival From PREVAIL by Subgroup

Subgroup	No. of Patients Enzalutamide / Placebo	Overall Survival Median, mo Enzalutamide / Placebo	Hazard Ratio for Death (95% CI)
All patients	872 / 845	35.5 / 31.4	0.83 (0.75-0.93)
ECOG performance status			
0	584 / 585	37.7 / 35.3	0.87 (0.77-0.99)
1	288 / 260	31.4 / 25.4	0.73 (0.61-0.88)
Age (years)			
< 75	555 / 553	36.5 / 34.7	0.88 (0.77-1.00)
≥ 75	317 / 292	33.5 / 24.5	0.74 (0.62-0.88)
Geographic region			
North America	218 / 208	37.3 / 34.7	0.85 (0.68-1.05)
Europe	465 / 446	34.2 / 29.9	0.85 (0.74-0.98)
Rest of the world	189 / 191	37.0 / 31.8	0.79 (0.63-0.99)
Total Gleason score at diagnosis			
≤ 7	414 / 385	37.7 / 32.4	0.84 (0.72-0.98)
≥ 8	424 / 423	33.7 / 30.4	0.86 (0.74-1.00)
Type of progression at study entry			
PSA progression only	375 / 369	43.3 / 36.4	0.77 (0.65-0.91)
Radiographic progression with or without PSA progression	475 / 451	31.4 / 27.5	0.87 (0.76-1.00)
Visceral disease at screening			
Node only	105 / 126	49.0 / 40.3	0.86 (0.63-1.17)
Bone only	387 / 358	39.8 / 32.8	0.76 (0.64-0.89)
Lung	64 / 75	35.6 / 25.2	0.77 (0.53-1.11)
Liver	40 / 34	19.2 / 14.8	1.12 (0.69-1.83)
Baseline PSA value (ng/mL)			
≤ median (49.60)	420 / 440	43.7 / 43.3	0.90 (0.77-1.06)
> median (49.60)	452 / 404	30.1 / 22.5	0.70 (0.61-0.81)
Baseline lactate dehydrogenase value (U/L)			
≤ median (185)	442 / 422	43.0 / 37.0	0.75 (0.65-0.88)
> median (185)	428 / 421	29.8 / 25.3	0.93 (0.80-1.07)
Baseline hemoglobin value (g/L)			
≤ median (130)	454 / 416	31.2 / 25.5	0.84 (0.72-0.97)
> median (130)	417 / 428	43.0 / 37.4	0.81 (0.69-0.94)



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

Subsequent Therapy

- At the data cutoff, 67% of patients in the enzalutamide arm and 82% in the placebo arm had received ≥ 1 postbaseline antineoplastic therapy (**Table 2**).
- The most common subsequent therapy was docetaxel (enzalutamide arm, 55%; placebo arm, 65%) followed by abiraterone acetate (enzalutamide arm, 42%; placebo arm, 54%).

Table 2. Selected Postbaseline Antineoplastic Therapies

Subsequent Therapy, no. (%)	Enzalutamide (n = 872)	Placebo (n = 845)
Patients taking ≥ 1 of the 6 subsequent therapies below	583 (66.9)	695 (82.2)
Abiraterone acetate[a]	362 (41.5)	456 (54.0)
Cabazitaxel	151 (17.3)	210 (24.9)
Docetaxel	481 (55.2)	546 (64.6)
Enzalutamide	53 (6.1)	364 (43.1)[b]
Radium-223	57 (6.5)	65 (7.7)
Sipuleucel-T	20 (2.3)	12 (1.4)

[a]Concomitant abiraterone acetate use was allowed before study drug discontinuation in patients with confirmed radiographic progression or a skeletal-related event. [b]Includes patients who received enzalutamide in the open-label extension (n = 234) and commercial enzalutamide (n = 130).

Safety

- Treatment-emergent adverse events (TEAEs) were reported as the primary reason for discontinuation in 9.1% of patients in the enzalutamide arm and 6.0% in the placebo arm (**Table 3**).
- TEAEs that led to death were observed in 6.9% of patients in the enzalutamide arm and 3.8% of patients in the placebo arm.

Table 3. Long-term Safety Summary

TEAE, no. (%)	Enzalutamide (n = 871)	Placebo (n = 844)
Overall TEAEs	857 (98.4)	791 (93.7)
Grade ≥ 3 TEAE	462 (53.0)	318 (37.7)
TEAE leading to death	60 (6.9)	32 (3.8)
Any serious TEAE	382 (43.9)	229 (27.1)
TEAE leading to treatment discontinuation	79 (9.1)	51 (6.0)
TEAE leading to study drug discontinuation	208 (23.9)	218 (25.8)
TEAEs of Special Interest, no. (%)		
Fatigue	454 (52.1)	299 (35.4)
Select gastrointestinal events[a]	424 (48.7)	354 (41.9)
Hypertension	154 (17.7)	41 (4.9)
Fractures	138 (15.8)	45 (5.3)
Hypersensitivity[b]	84 (9.6)	50 (5.9)
Select cardiovascular events[c]	66 (7.6)	17 (2.0)
Major adverse cardiovascular events[d]	48 (5.5)	17 (2.0)
Renal impairment[e]	39 (4.5)	38 (4.5)
Hepatic impairment[f]	34 (3.9)	23 (2.7)
Loss of consciousness	20 (2.3)	10 (1.2)
Venous thromboembolic events	17 (2.0)	17 (2.0)
Neutropenia	14 (1.6)	5 (0.6)
Seizures	2 (0.2)	1 (0.1)
Hallucinations	1 (0.1)	1 (0.1)
Mental impairment[g]	0	0

[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."
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA query; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- With > 5 years of follow-up, enzalutamide continued to demonstrate benefit compared with placebo in OS for patients with asymptomatic or mildly symptomatic mCRPC despite crossover in the placebo arm and multiple subsequent therapies.
- Enzalutamide OS benefit was observed across all patient subgroups studied, aside from the liver metastasis subgroup which had relatively few patients.
- The safety profile with enzalutamide was consistent with that reported previously.

REFERENCES

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