# Association of Baseline Corticosteroid With Outcomes in a Multivariate Analysis of the Phase 3 Affirm Study of Enzalutamide (ENZA), an Androgen Receptor Signaling Inhibitor (ARSI)

Abstract 899PD

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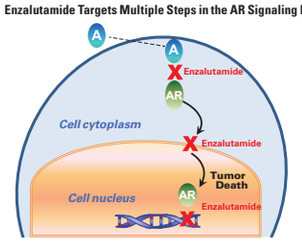
## Introduction and Background

- Prostate cancers that are progressing on androgen deprivation therapy are classified as castration-resistant, but tumors remain dependent on the androgen receptor (AR) and AR signaling for growth.
- Enzalutamide is a rationally designed oral androgen receptor inhibitor that targets multiple steps in the AR signaling pathway. It is approved by the US Food and Drug Administration for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who had previously received docetaxel, based on results from the phase 3 AFFIRM study.[1]
- In AFFIRM, enzalutamide increased median overall survival by 4.8 months ($P$<0.0001; hazard ratio [HR], 0.631) vs placebo.[1] Patients were allowed, but not required, to take corticosteroids.
- A growing body of evidence suggests that corticosteroids may stimulate prostate cancer growth by activating "promiscuous" ARs,[2-7] stimulating human sgk1 gene expression,[8-10] or by promoting downstream expression of heat shock protein 90 and interleukin 6.[11-14]
- This post hoc analysis evaluates the impact of baseline corticosteroid use on outcomes in the AFFIRM study, and tests the hypothesis that men with metastatic CRPC who take concomitant corticosteroids will have an inferior outcome in the post-docetaxel setting, but will still obtain benefit from enzalutamide therapy.

**Enzalutamide Targets Multiple Steps in the AR Signaling Pathway**




1. Competitively inhibits androgen binding to AR

***And Uniquely***

2. Inhibits AR nuclear translocation
3. Inhibits AR interaction with DNA

AR=androgen receptor.

## Study Design

- The AFFIRM trial was a randomized, double-blind, placebo-controlled, multinational phase 3 study conducted at 156 centers in 15 countries in North America, Europe, Australia, South America, and Africa.[1]
- Patients were randomized 2:1 to 160 mg of enzalutamide once a day or placebo.
- Patients were allowed, but not required, to take corticosteroids.
- Treatment could be continued until disease progression and initiation of new systemic antineoplastic therapy, unacceptable toxicity, or withdrawal.
- The primary endpoint was overall survival. Secondary endpoints included radiographic progression-free survival (rPFS), time to prostate-specific antigen (PSA) progression, and safety.

## Statistical Plan

- In this post hoc analysis, HRs for death were calculated after adjustment for prognostic factors.
- Treatment group, baseline oral corticosteroid use, and the prespecified prognostic factors listed below were entered into a Cox proportional-hazards model. A stepwise selection method eliminated nonsignificant ($P$≥0.25) factors at entry into the model. Additional factors were eliminated after contribution to model was assessed ($P$≥0.10):
  - Treatment arm
  - Baseline oral corticosteroid use (no vs yes)
  - Age (<65 years vs ≥65 years)
  - Region (North America vs rest of world)
  - Baseline Eastern Cooperative Oncology Group performance status (0–1 vs 2)
  - Baseline mean pain score (<4 vs ≥4)
  - Visceral disease (no vs yes)
  - Number of prior chemotherapy regimens (1 vs ≥2)
  - Type of progression at entry (PSA progression only vs radiographic progression)
  - Baseline serum lactate dehydrogenase level
  - Baseline serum PSA level
  - Baseline hemoglobin level
  - Baseline serum alkaline phosphatase level
- A logistic regression model was fit to investigate if baseline corticosteroid use (yes vs no) could be predicted from the other baseline prognostic factors included in the multivariate model.

**Table 1. Baseline and Disease Characteristics**

| | Patients With Baseline Corticosteroid Use | | Patients With No Baseline Corticosteroid Use | |
|---|---|---|---|---|
| | Enzalutamide | Placebo | Enzalutamide | Placebo |
| | n=241 (30%)* | n=119 (30%)† | n=559 (70%)* | n=280 (70%)† |
| **Baseline characteristics** | | | | |
| Age | | | | |
| Median, y | 69 | 67 | 69 | 70 |
| Age ≥75 y, % | 26 | 20 | 25 | 29 |
| Median Gleason score | 8.0 | 8.0 | 7.0 | 7.5 |
| ECOG performance status = 2, % | 14.5 | 4.2 | 6.3 | 9.6 |
| BPI ≥4 on question 3, % | 31.5 | 36.1 | 26.8 | 25.7 |
| **Disease burden** | | | | |
| Median PSA, ng/mL | 199.7 | 174.5 | 89.1 | 111.5 |
| Median hemoglobin, g/L | 116.5 | 117.0 | 122.0 | 120.5 |
| % Abnormal (<125 g/L) | 68.3 | 61.3 | 57.1 | 57.5 |
| Median alkaline phosphatase, U/L | 145.0 | 122.0 | 137.5 | 107.0 |
| % Abnormal (>125 U/L) | 56.4 | 47.9 | 41.9 | 42.1 |
| Median LDH, U/L | 245.0 | 239.0 | 197.0 | 208.0 |
| % Abnormal (>234 U/L) | 53.1 | 52.5 | 31.3 | 35.5 |
| Visceral disease at screening, % | 29.0 | 18.5 | 22.5 | 21.4 |
| >20 Bone metastases at screening, % | 49.0 | 47.1 | 32.9 | 33.9 |
| Median time from initial diagnosis, mo | 66 | 56 | 75 | 76 |

BPI=Brief Pain Inventory; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; PSA=prostate-specific antigen.
*Percentage of all enzalutamide patients; †Percentage of all placebo patients

**Table 2. Oral Corticosteroids Used by ≥4% of Patients per Treatment Group at Baseline**

| Patients, % | Enzalutamide (n=800) | Placebo (n=399) |
|---|---|---|
| Any oral corticosteroid | 30.1 | 29.8 |
| Prednisone | 18.3 | 20.6 |
| Prednisolone | 6.8 | 5.3 |
| Dexamethasone | 4.0 | 4.0 |

**Table 3. Results of Stepwise Multivariate Analysis of Overall Survival***

| Variable | Parameter Estimates: Coefficient | Parameter Estimates: $P$ Value | HR for Death (95% CI) |
|---|---|---|---|
| Treatment (enzalutamide vs placebo) | −0.54±0.090 | <0.0001 | 0.58 (0.49–0.70) |
| Mean pain score: <4 vs ≥4 | −0.26±0.098 | 0.0091 | 0.78 (0.64–0.94) |
| Progression at study entry: | | | |
| PSA only vs radiographic | −0.35±0.094 | 0.0002 | 0.70 (0.59–0.85) |
| Visceral disease at screening (no vs yes) | −0.42±0.097 | <0.0001 | 0.66 (0.54–0.80) |
| Baseline hemoglobin result | −0.03±0.003 | <0.0001 | 0.97 (0.97–0.98) |
| Baseline lactate dehydrogenase result | 0.002±0 | <0.0001 | 1.002 (1.001–1.002) |
| Baseline corticosteroid use (no vs yes) | −0.62±0.091 | <0.0001 | 0.54 (0.45–0.64) |

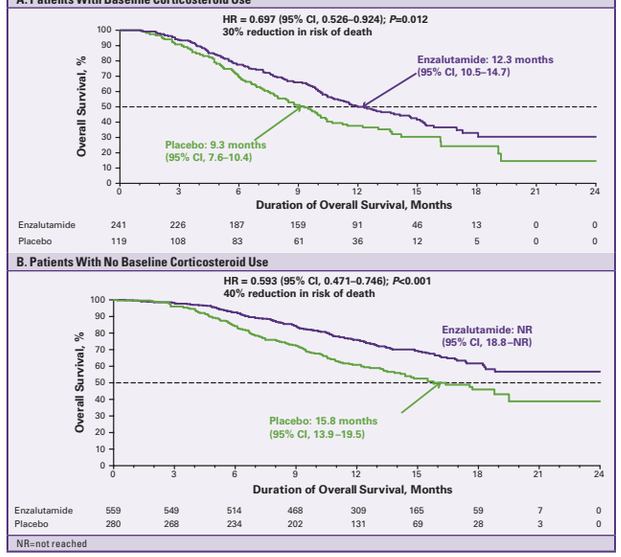
*Survival for patients who had not died by the time of analysis was censored at the date the patient was last known to be alive. Assumptions of proportional hazards were investigated and deemed appropriate for the model fit.

**Table 4. Outcomes by Use of Corticosteroids Irrespective of Treatment Group**

| | Patients With Baseline Corticosteroid Use (n=360) | Patients With No Baseline Corticosteroid Use (n=839) |
|---|---|---|
| **Overall survival** | | |
| Median (95% CI), mo | 10.8 (10.0–12.5) | NR (18.3–NR) |
| $P$ value (stratified log rank) | <0.0001 | |
| Stratified hazard ratio (95% CI) | 0.470 (0.394–0.560) | |
| **Radiographic progression-free survival** | | |
| Median (95% CI), mo | 5.2 (4.0–5.5) | 8.0 (6.1–8.3) |
| $P$ value (stratified log rank) | <0.0001 | |
| Stratified hazard ratio (95% CI) | 0.670 (0.580–0.774) | |
| **Time to PSA progression** | | |
| Median (95% CI), mo | 4.6 (4.6–5.5) | 5.7 (5.6–8.3) |
| $P$ value (stratified log rank) | <0.0001 | |
| Stratified hazard ratio (95% CI) | 0.666 (0.553–0.801) | |

Stratification factors are baseline ECOG performance status (0 and 1 vs 2) and baseline mean pain score (<4 vs ≥4).

**Figure 1. Duration of Overall Survival**




NR=not reached

## Results

- 30% of the patients were taking corticosteroids at baseline.
- Baseline demographics and disease burden **(Table 1)** and corticosteroid use patterns **(Table 2)** were similar in the treatment groups.
- Baseline oral corticosteroid use was associated with an inferior overall survival **(Table 3)** independent of study treatment after adjusting for prognostic factors **(Table 4)**.
- Enzalutamide improved overall survival, rPFS, and time to PSA progression, regardless of baseline corticosteroid use **(Figures 1–3)**.
- Lactate dehydrogenase was the only statistically significant ($P$=0.02) prognostic factor associated with baseline corticosteroid use (yes vs no).

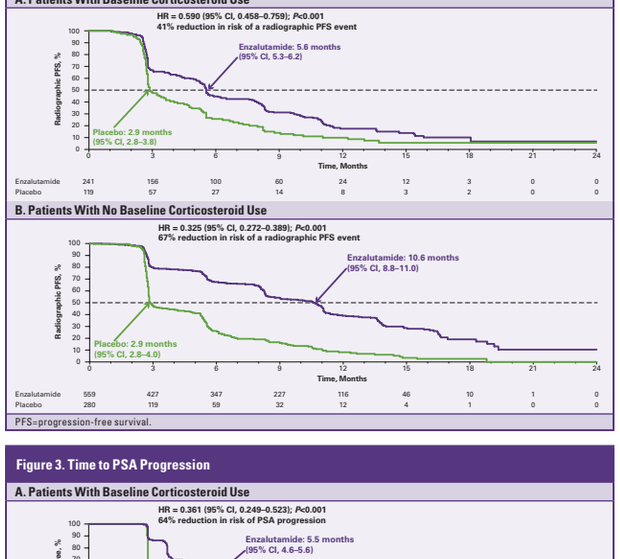
## Limitations of the Analysis

- AFFIRM was not designed to assess the effect of baseline corticosteroid use on efficacy.
- The multivariate analysis controlled for many but not all factors that could affect overall survival.
- In these post hoc analyses, corticosteroid use at baseline had a possible independent response, which could confound the results.
- These analyses do not distinguish whether the use of corticosteroids at baseline was an adverse factor for sensitivity to enzalutamide or an independent measure not related to study treatment.

## Conclusions

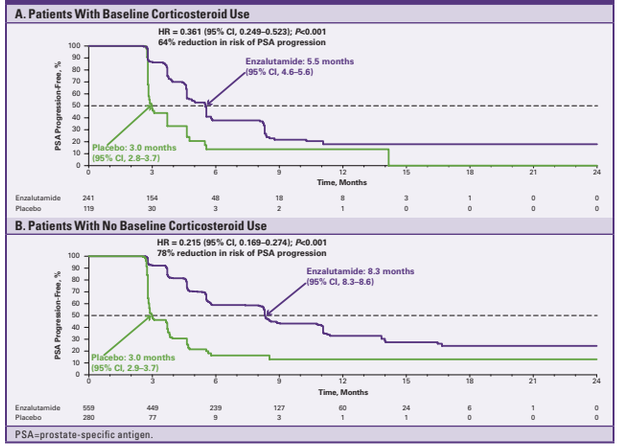
- Baseline corticosteroid use was associated with reduced survival even in multivariate analysis after accounting for other known prognostic factors in this post-docetaxel CRPC population.
- Although patients on corticosteroids had inferior outcomes, enzalutamide was consistently superior to placebo with respect to overall survival, rPFS, and time to PSA progression.
- The observed inferior clinical outcomes in patients receiving corticosteroids may be due to either unmeasured confounders or the biologic properties of corticosteroid use itself, such as stimulation of "promiscuous" ARs.

**Figure 2. Radiographic Progression-Free Survival**




PFS=progression-free survival.

**Figure 3. Time to PSA Progression**




PSA=prostate-specific antigen.

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All authors assume responsibility for this poster, and the completeness and integrity of the data.

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