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 sites 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 (mCRPC) who had previously received docetaxel, based on results from the phase 3 AFFIRM study.

- In AFFIRM, enzalutamide increased median overall survival by 4.4 months (P<0.001; hazard ratio [HR], 0.519) vs placebo. 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,1,2 stimulating human sparse gene expression,3,4 by promoting downstream expression of the heat shock protein 90 and interleukin 6.

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 have an inferior outcome in the post-docetaxel setting, but will still benefit from enzalutamide therapy.

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, and Australia.

- 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 non significant (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 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 (0 vs >0). Median survival (95% CI), PFS=progression-free survival.

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 two treatment groups.
- Baseline oral corticosteroid use was associated with an inferior overall survival (Table 3) in independent study of treatment 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 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 with 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 corticosteroids itself, such as stimulation of "promiscuous" ARs.

Acknowledgments

This study would not have been possible without the contributions of all the patients, their caregivers and families, and all of the AFFIRM investigators and their staff.

Enzalutamide is being co-developed by Medivation, Inc., and Astellas. Funding was provided by both for the AFFIRM trial and post-hoc analysis. Assistance with post-hoc analysis was provided by Susan Sloan (PhD), from Complete Healthcare Communications, Inc., and Gert Salm, PhD, from Meditextus, Inc.

All authors assume responsibility for this paper, as well as the completeness and integrity of data.

References