

# Enzalutamide in castrate-resistant prostate cancer after chemotherapy

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**E**nzalutamide is an androgen receptor-signaling inhibitor that is reported to differ from conventional antiandrogen agents in that it inhibits androgen receptor nuclear translocation, DNA binding, and coactivator recruitment; exhibits increased affinity for the androgen receptor; and induces tumor reduction, rather than slowing growth, in preclinical models. The recently reported AFFIRM study showed that enzalutamide treatment after chemotherapy significantly prolonged overall survival (OS), radiographic progression-free survival (PFS), time to prostate-specific antigen (PSA) progression, and time to skeletal-related events (SREs) in men with castration-resistant prostate cancer. This trial formed the basis for the recent approval of enzalutamide for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

In the double-blind AFFIRM trial,<sup>1</sup> 1,199 patients with castration-resistant prostate cancer who had received at least 1 docetaxel-containing chemotherapy regimen were randomized (2:1) to oral enzalutamide 160 mg once daily (800 patients) or placebo (399 patients). Treatment was continued until radiographic confirmation of disease progression requiring initiation of new systemic antineoplastic treatment. Enzalutamide has been associated with a lowered seizure threshold; thus, patients with a history of or risk factors for seizure or who were taking medications known to decrease seizure threshold were excluded from the trial. All of the patients continued androgen deprivation therapy. Patients were permitted to start or continue corticosteroid treatment during the study. The primary endpoint of the trial was OS.

The median age in both groups was 69 years, with 26% of enzalutamide patients and 27% of placebo patients being 75 years of age or older. Similar proportions of enzalutamide and placebo patients had a Gleason score > 7 (50% vs 52%, respectively), and ECOG performance status of 0 or 1 (91% vs 92%), a pain score  $\geq$  4 (28% vs 29%), 1 prior chemotherapy regimen (72% vs 74%), bisphosphonate use at baseline (43% in both groups), prior radiation therapy (71% vs 72%), bone disease (92% vs 92%, with 38% in both groups having > 20 lesions), soft

## What's new, what's important

Enzalutamide is an androgen receptor-signaling inhibitor. It inhibits androgen receptor nuclear translocation, DNA binding, and coactivator recruitment; exhibits increased affinity for the androgen receptor; and induces tumor reduction, rather than slowing growth.

Enzalutamide has been approved by Food and Drug Administration for prostate cancer patients who have been previously treated with docetaxel. The dose of enzalutamide is 160 mg (four 40-mg capsules) administered orally once daily. In the randomized trial on which the approval was based, the median overall survival for patients who received enzalutamide was 18.4 months, compared with 13.6 months for the patients who received placebo. The most common side effects of enzalutamide were weakness or fatigue, back pain, diarrhea, joint pain, hot flush, tissue swelling, musculoskeletal pain, headache, upper-respiratory infections. About 0.6% of the patients who were treated with enzalutamide 160 mg once daily experienced a seizure. It is exciting to see that patients with castrate-resistant metastatic prostate cancer have one more treatment option with a different mechanism of action.

— Jame Abraham, MD

tissue disease (71% vs 69%), PSA progression at baseline (89% vs 90%), and radiographic progression at baseline (59% in both groups). Median PSA levels at baseline were 108 ng/mL and 128 ng/mL. The median number of prior docetaxel cycles was 8.5 in the enzalutamide group and 8.0 in the placebo group. During the study, 48% of enzalutamide patients and 46% of placebo patients received corticosteroid treatment.

At the time of a preplanned interim analysis, median durations of treatment were 8.3 months in the enzalutamide group and 3.0 months in the placebo group. The median duration of follow-up to assess survival outcomes

## My role in treating patients with CRPC

In my experience as a urologist, once a patient develops castration-resistant prostate cancer (CRPC) I usually refer him to a medical oncologist. This shift of care is anxiety producing for both the patient and the urologist, because we have had the luxury of caring for our patients with suspected or diagnosed prostate cancer for many years, often several decades. This is because of 2 rather unique phenomena:

- The biology of prostate cancer is in general a relatively slow-growing cancer so that patients are often seen early on for abnormal prostate-specific antigen (PSA), lower urinary tract symptoms, or positive family history, and so on, meaning that many patients will have multiple evaluations and numerous treatments over many years.
- No other physician discipline is as intimately involved with prostate cancer patients from their initial evaluation to the time they develop, if ever, castration-resistant disease.

However, all this changes once a patient on definitive hormonal therapy develops a rising PSA level and/or develops radiographic and/or symptomatic metastases. At that stage in the disease, most urologists are not comfortable with prescribing therapies and monitoring patient responses, so they refer the patient to a medical oncologist. This is also difficult for the medical oncologist who generally receives a patient who has a

rapid PSA doubling time and/or debilitating disease that is associated with a poor performance status. It has been my experience over more than 30 years in practice that most such patients desire some form of additional treatment but very few receive definitive therapy. Medical oncologists often continue with some form of hormonal manipulation be it continuance of luteinizing hormone-releasing hormone therapies, withdrawal of anti-androgens, and so on. The number of patients who are considered for cytotoxic chemotherapy and who actually complete a full course is relatively modest in my experience.

There are a host of therapies available for men who develop CRPC. These include agents aimed at improving survival and those that delay events and are palliative. They include chemotherapy, additional hormonal treatments after failed chemotherapy, local radiation, modalities aimed at delaying skeletal-related events, the use of vaccines, and supportive efforts. The National Comprehensive Cancer Network guidelines recommend categorizing CRPC patients as those who do not have metastatic disease and those who demonstrate metastatic disease. The first group is offered observation or additional hormonal manipulation, whereas the latter group is offered more definitive therapy. Both groups are encouraged to enroll in clinical trials.

— John A. Fracchia, MD

was 14.4 months. The trial was stopped early, after the interim analysis showed that median OS was 18.4 months in the enzalutamide, compared with 13.6 months in the placebo group, which represented a significant 37% reduction in risk of death with enzalutamide (hazard ratio [HR], 0.63; 95% CI, 0.53-0.75,  $P < .001$ ).

The benefit of enzalutamide was consistent across all subgroups, including age, baseline pain intensity, geographic region, and type of disease progression at study entry. The few subgroups for which the reduction in risk of mortality with enzalutamide was not statistically significant were patients with ECOG performance status of 2, patients who received 2 or more prior chemotherapy regimens, and patients with visceral disease at baseline, although HRs favored enzalutamide in each of these subgroups. The OS benefit of enzalutamide was maintained (HR, 0.58; 95% CI, 0.49-0.70,  $P < .001$ ) on multivariate analysis adjusting for significant stratification and prognostic factors, including ECOG score, pain score, type of progression at study entry, visceral

disease at entry, baseline hemoglobin, and baseline alkaline phosphatase.

Systemic treatment was used after discontinuation of study treatment in 42% of enzalutamide patients and 61% of placebo patients. Treatments included abiraterone acetate in 21% of enzalutamide patients and 24% of placebo patients, and cabazitaxel in 14% and 10%, respectively; both agents have been shown to prolong survival in this setting.

Significant improvements with enzalutamide treatment were shown for all secondary endpoints, including PSA response compared with placebo ( $\geq 50\%$  decrease from baseline; 54% vs 2%), soft tissue response (29% vs 4%), FACT-Prostate quality of life response (43% vs 18%), time to PSA progression (median 8.3 vs 3.0 months), radiographic PFS (median 8.3 vs 2.9 months; HR, 0.40), and time to first SRE (median 16.7 vs 13.3 months), all with a  $P$  value  $< 0.001$ .

Adverse events that occurred in at least 10% of enzalutamide patients and with at least a 2% greater frequency

than in placebo patients included fatigue (34% vs 29%), diarrhea (21% vs 18%), hot flash (20% vs 10%), musculoskeletal pain (14% vs 10%), and headache (12% vs 6%). Adverse events of  $\geq$  grade 3 occurred in 45% of enzalutamide patients and 53% of placebo patients.<sup>2</sup> The median time to any initial grade 3 or higher adverse event was 8.4 months longer in the enzalutamide group than in the placebo group (12.6 vs 4.2 months), which suggested improved long-term control of disease-related symptoms. Hypertension occurred in 6.6% of enzalutamide patients and 3.3% of placebo patients. However, the frequency of hyperglycemia, weight gain, hyperlipidemia, and glucose intolerance were similar in the 2 groups, suggesting that enzalutamide was not associated with excess risk of developing metabolic syndrome. Liver function abnormalities occurred in 1% of enzalutamide patients and 2% of placebo patients.

Serious adverse events occurred in 34% of the enzalutamide group and 39% of the placebo group. Adverse events resulted in discontinuation of study treatment in 8% and 10% and adverse events led to death in 3% and 4%. Among clinically significant adverse events, cardiac disorders occurred in 6% of both groups, with myocardial infarction occurring in 2 patients in each group. Seizure occurred in 5 enzalutamide patients (0.6%) and none of the placebo patients.

#### References

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