# Long-Term Antitumor Activity and Safety of Enzalutamide Monotherapy in Hormone Naïve Prostate Cancer: 3-Year Open Label Followup Results

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**Purpose:** A phase 2 study of enzalutamide monotherapy in patients with hormone naïve prostate cancer demonstrated high prostate specific antigen response rates at 25 weeks, 1 year and 2 years with minimal effects on total body bone mineral density and favorable safety. In this followup analysis we evaluated enzalutamide antitumor activity and safety at 3 years.

**Materials and Methods:** In a single arm analysis 67 patients with hormone naïve prostate cancer and noncastrate testosterone (230 ng/dl or greater) received enzalutamide 160 mg per day orally until disease progression or unacceptable toxicity. The primary end point was the prostate specific antigen response (80% or greater decline from baseline).

**Results:** No patients discontinued treatment during year 3. Of 42 patients with prostate specific antigen assessments at 3 years 38 (90.5%, 95% CI 77.4–97.3) maintained a prostate specific antigen response. Of 26 patients with metastases at baseline 17 (65.4%) had a complete or partial response as the best overall response during 3 years. In patients who completed the 3-year visit minimal mean changes from baseline were observed in total body bone mineral density or bone mineral density of the femoral neck, trochanter, spine L1–L4 or forearm (range −2.7% to −0.1%). At 3 years total body fat had increased a mean of 16.5%, total lean body mass had decreased a mean of −6.5% and global health status had minimally decreased from baseline. Common adverse events were gynecomastia, fatigue, hot flush and nipple pain.

**Abbreviations and Acronyms**

ADT = androgen deprivation therapy

AE = adverse event

bALP = bone alkaline phosphate

BMD = bone mineral density

CR = complete response

EORTC = European Organisation for Research and Treatment of Cancer

HNPC = hormone naïve prostate cancer

mCRPC = metastatic castration resistant prostate cancer

PR = partial response

PSA = prostate specific antigen

QLQ-C30 = Quality of Life Questionnaire-Core Questionnaire

QLQ-PR25 = Quality of Life Questionnaire-Prostate Cancer Module

TEAE = treatment emergent AE

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**Conclusions:** Enzalutamide antitumor activity was maintained in patients with hormone naïve prostate cancer at 3 years. Overall bone mineral density, global health status and safety results were similar to those at 2 years.

**Key Words:** prostatic neoplasms, prostate-specific antigen, MDV 3100, bone density, drug related side effects and adverse reactions

ANDROGEN deprivation therapy decreases levels of serum testosterone and remains the current standard of care for advanced prostate cancer.[1,2] However, ADT causes side effects, including sarcopenia, cognitive disorders, decreased BMD and bone fracture, loss of libido and erectile dysfunction.[3–5] ADT also induces metabolic changes such as increased serum cholesterol and triglycerides, and peripheral resistance to insulin, which could lead to diabetes and cardiovascular disease.[3,6,7] In contrast, therapy with nonsteroidal antiandrogens such as bicalutamide have been shown to inhibit the androgen receptor without decreasing testosterone levels. Despite the improved safety profile of bicalutamide compared with ADT, bicalutamide has not demonstrated significant improvement in overall survival in patients with locally advanced prostate cancer.[8,9]

Enzalutamide is an oral androgen receptor signaling inhibitor approved to treat patients with mCRPC.[10–12] Enzalutamide acts by preventing the binding of androgens to the androgen receptor, androgen receptor nuclear translocation and androgen receptor mediated DNA binding.[13] In phase 3 clinical trials enzalutamide significantly prolonged overall survival vs placebo in chemotherapy naïve patients with mCRPC and patients who had progressed on docetaxel therapy.[10,11] In phase 2 clinical trials enzalutamide also significantly prolonged progression-free survival vs bicalutamide in chemotherapy naïve men with nonmetastatic prostate cancer and mCRPC.[12,14] The unique mode of action and the results of early clinical trials have provided a rationale to evaluate the efficacy of enzalutamide as monotherapy in noncastrate men with HNPC.

This phase 2, open label, single arm study (ClinicalTrials.gov NCT01302041) assessed the activity and safety of enzalutamide as monotherapy in patients with HNPC. The study showed that at 25 weeks 92.5% of patients had a PSA decline of 80% or greater regardless of metastases at baseline and favorable tolerability.[15] At 1 and 2-year followups enzalutamide maintained long-term PSA decreases from baseline with minimal impact on total body BMD.[16] We report activity and safety results from a prespecified 3-year followup analysis.

## MATERIALS AND METHODS

### Study Design

The study methodology has been published previously.[15,16] Briefly, this phase 2, multicenter, open label, single arm study of enzalutamide enrolled patients with HNPC. Patients received enzalutamide orally (160 mg per day) until disease progressed or unacceptable toxicity developed. The protocol was approved by the local institutional review boards at participating institutions and by independent ethics committees and authorities. Participants provided written informed consent prior to study entry. The cutoff date of the 3-year analysis was April 16, 2015.

### Outcomes

The primary outcome of PSA response, defined as an 80% or greater decline from baseline, was analyzed at week 25, and at 1, 2 and 3 years. Secondary outcomes included PSA decreases of 90% or greater, 4 ng/ml or less and 0.1 ng/ml or less; PSA progression, defined as a 25% or greater increase and an absolute increase of 2 ng/ml or greater from the nadir as confirmed 2 or more weeks later or a 50% or greater increase and an absolute increase of 5 ng/ml or greater from the nadir as confirmed 2 or more weeks later; an objective tumor response in patients with metastatic disease; metabolic profiles; quality of life using the EORTC quality of life questionnaires QLQ-C30 and QLQ-PR25; and safety.

### Procedures

Assessments of prostate cancer status were collected during the course of the study, including soft tissue disease on computerized tomography or magnetic resonance imaging, bone disease on radionuclide bone scans, PSA, biomarkers of bone turnover (*N*-terminal telopeptide and bALP), dual energy X-ray absorptiometry scans to measure changes in BMD, fat and lean body mass, insulin sensitivity, serum lipids and quality of life assessments (EORTC QLQ-C30 and QLQ-PR25). Safety was also assessed throughout the study.

### Statistical Analyses

In this study a distinction was made between the 3 calendar years of treatment (156 weeks) and the 3-year analysis visit (week 169). Efficacy outcomes are reported by study visit while the AE incidence is reported by calendar years. PSA response rates were calculated as the number of patients with an 80% or greater PSA decline from baseline at a given time point divided by the number who started treatment or the number of patients remaining on treatment at the time point. Patients who discontinued before the time point were considered