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ENZALUTAMIDE AND OVERALL SURVIVAL IN PATIENTS WITH PROSTATE CANCER AFTER CHEMOTHERAPY

Jurayev Shakhzod Shavkatovich
Saint Petersburg State Pediatric Medical University
Email: dr.shaxzod.shavkatovich@gmail.com

Abstract: Enzalutamide (MDV3100), an androgen receptor signaling pathway inhibitor, was investigated in an international phase III randomized trial involving 1,199 patients with castration-resistant prostate cancer after chemotherapy. Administration of enzalutamide at a dose of 160 mg/day significantly increased overall survival compared with placebo (18.4 vs. 13.6 months; HR 0.63; $p<0.001$) and demonstrated superiority across all secondary endpoints, including reduction in PSA levels, objective tumor response, improvement in quality of life, and prolonged time to progression. The main adverse events were fatigue, diarrhea, and hot flashes, with seizures observed in rare cases. These findings confirm the significant clinical efficacy of enzalutamide in patients with metastatic castration-resistant prostate cancer following chemotherapy.

Keywords: Enzalutamide; castration-resistant prostate cancer; survival; chemotherapy; clinical efficacy.

Introduction

Prostate cancer belongs to the group of androgen-dependent tumors, which at early stages respond well to therapies aimed at reducing circulating testosterone levels or blocking its binding to androgen receptors. However, as the disease progresses, resistance to these treatment methods develops, and despite castration levels of testosterone, tumor growth reactivates. This process marks the transition to the castration-resistant stage of prostate cancer (CRPC), characterized by aggressive progression and poor prognosis. Previously, this condition was referred to as androgen-independent or hormone-refractory cancer; however, modern studies have demonstrated that androgen receptor signaling pathways continue to play a central role in pathogenesis, with hyperactivation occurring, among other reasons, due to receptor overexpression. In preclinical models, such overexpression has been associated with shorter tumor latency and resistance to standard antiandrogens (e.g., bicalutamide).

Enzalutamide (formerly MDV3100) was developed as a next-generation androgen receptor signaling pathway inhibitor. Its mechanism of action fundamentally differs from that of existing agents: it blocks nuclear translocation of the receptor, DNA binding, and coactivator recruitment; it also exhibits a higher binding affinity to the receptor and induces tumor regression in preclinical models, whereas traditional agents merely slow tumor growth. Unlike most antiandrogens, enzalutamide does not display agonistic activity. Phase I–II clinical trials demonstrated pronounced antitumor activity in CRPC patients both before and after chemotherapy, which allowed the determination of the optimal dose for further trials and

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justified the need for a large-scale international phase III study.

Methods

The AFFIRM study (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) was an international, multicenter, randomized, double-blind, placebo-controlled phase III clinical trial. Eligible participants were patients with a histologically or cytologically confirmed diagnosis of prostate cancer, castration-level testosterone (<50 ng/dL), and progressive disease following one or two lines of chemotherapy (mandatory inclusion of docetaxel). Disease progression was defined according to PCWG2 criteria and included both prostate-specific antigen (PSA) dynamics and radiologically confirmed disease spread.

Patient enrollment was conducted between September 2009 and November 2010 across 156 clinical sites in 15 countries. Randomization was centralized in a 2:1 ratio using an interactive voice response system, stratified by baseline ECOG performance status (0–1 vs. 2) and pain intensity according to the BPI-SF scale (0–3 vs. 4–10). Patients received enzalutamide at a dose of 160 mg orally once daily (four 40 mg capsules) or the corresponding placebo. Concomitant use of prednisone or other glucocorticoids was permitted but not required. Treatment continued until objective progression confirmed radiographically and requiring initiation of a new systemic antineoplastic therapy.

The primary endpoint was overall survival, defined as the time from randomization to death from any cause. Secondary endpoints included response outcomes (PSA decline, objective soft tissue response, improvement in quality of life) and progression measures (time to biochemical progression, radiographic progression-free survival, time to first skeletal-related event). Quality of life was assessed using the FACT-P questionnaire, and objective tumor response was evaluated according to RECIST 1.1 criteria.

Statistical analysis was performed according to the intention-to-treat principle. Overall survival was compared using the log-rank test stratified by ECOG and BPI-SF. The study was powered at 90% to detect a difference with a hazard ratio of 0.76 at a two-sided significance level of 0.05. An interim analysis was planned after 520 deaths, applying O'Brien–Fleming stopping boundaries.

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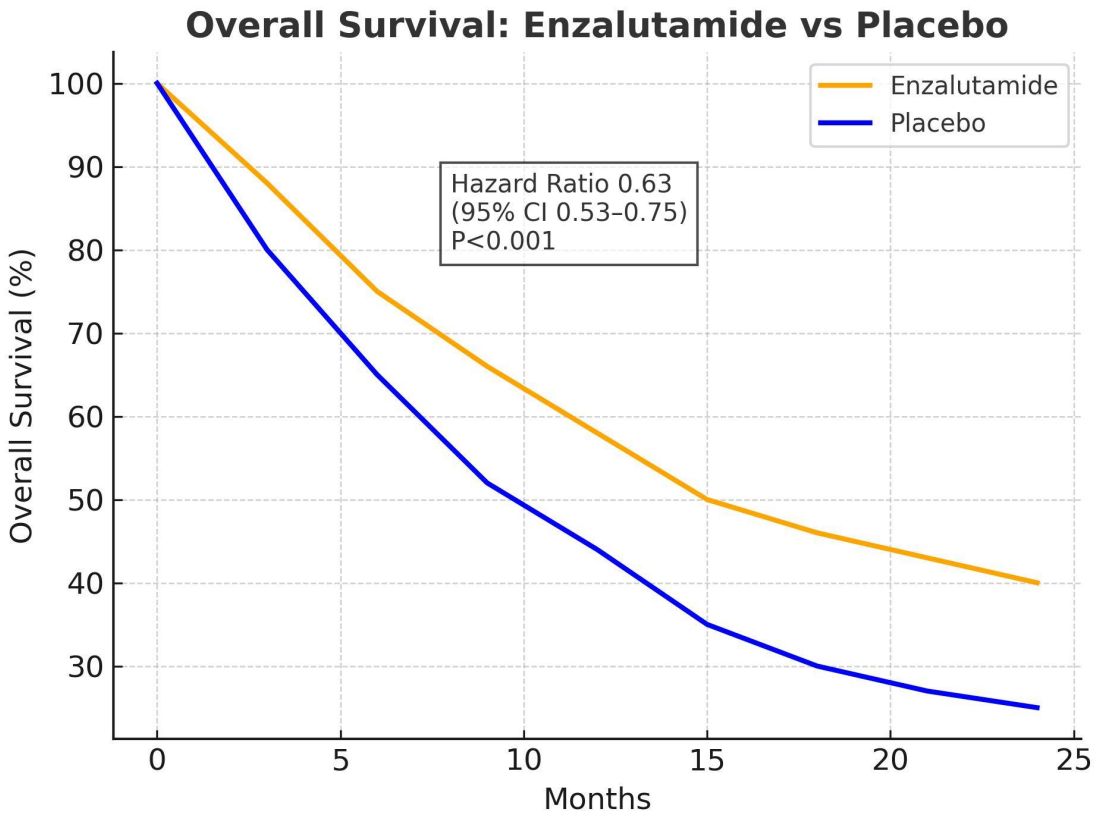

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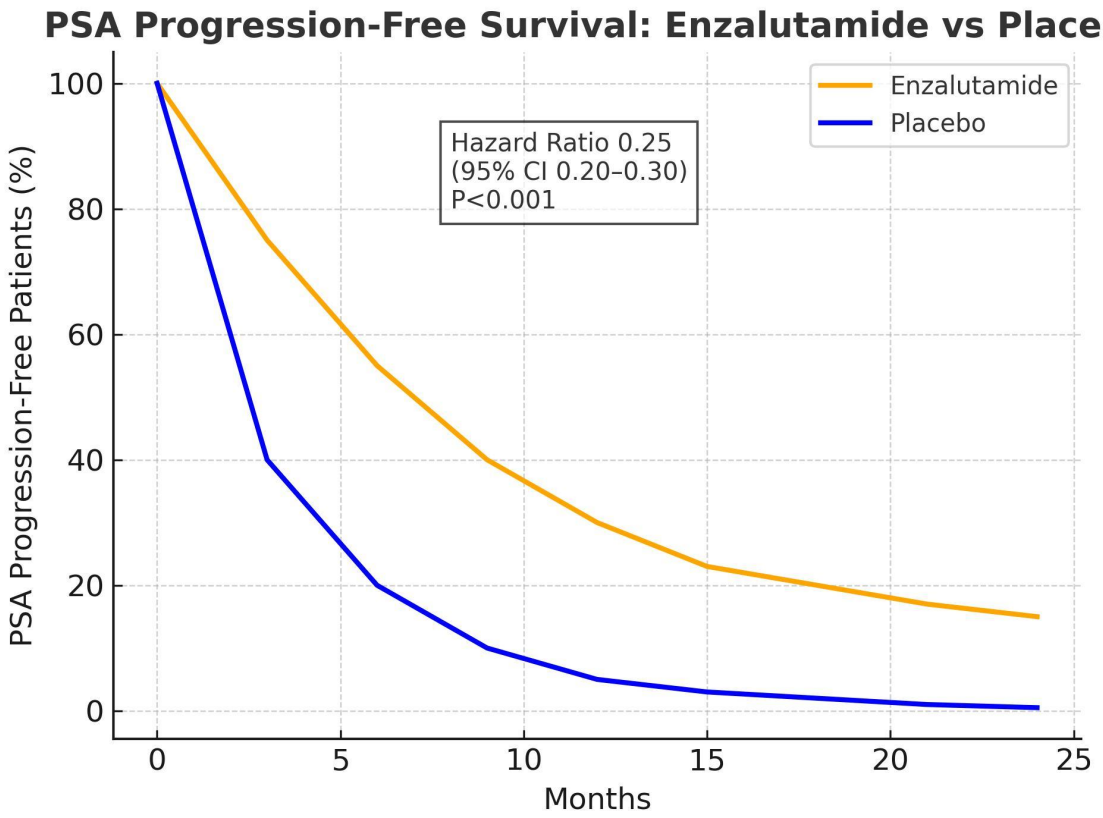

Figure 1. Kaplan–Meier Estimates of Primary and Secondary Endpoints in the Intention-to-Treat Population.

Presented are data on overall survival (primary endpoint, Panel A), as well as two secondary endpoints - time to prostate-specific antigen (PSA) progression (Panel B) and radiographic progression-free survival in the enzalutamide group compared with the placebo group.

Statistical Analysis

Overall survival was analyzed using the unstratified log-rank test and Cox proportional hazards models. Subgroup analyses were additionally performed to assess the consistency of treatment effects across different patient categories. A multivariate analysis was also conducted.

Testing of key secondary endpoints was permitted only in the presence of statistically significant superiority of enzalutamide over placebo for overall survival. These endpoints were evaluated sequentially in a pre-specified hierarchical order: time to prostate-specific antigen (PSA) progression, radiographic progression-free survival, and time to first skeletal-related event. Each endpoint was assessed using the stratified log-rank test within a protected hierarchical sequence at a two-sided significance level of 0.05.

Results

Patients and Treatment

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A total of 1,199 patients were enrolled in the study and randomized to receive either enzalutamide (n=800) or placebo (n=399). The process of enrollment, follow-up, and data analysis is presented in Figure 1S of the Supplementary Appendix. Baseline patient characteristics were comparable between the two groups in terms of demographics, prior treatments, and disease burden (Table 2S in the Supplementary Appendix). At the time of the interim analysis, the median duration of treatment was 8.3 months in the enzalutamide group and 3.0 months in the placebo group. The median follow-up duration for survival status assessment was 14.4 months.

Efficacy

The median overall survival was 18.4 months (95% CI: 17.3 – not reached) in patients receiving enzalutamide compared with 13.6 months (95% CI: 11.3–15.8) in the placebo group (Figure 1A). Treatment with enzalutamide resulted in a 37% reduction in the risk of death compared with placebo (hazard ratio for death, 0.63; 95% CI: 0.53–0.75; $p<0.001$). Based on these findings, the Independent Data and Safety Monitoring Committee recommended early termination of the trial and unblinding, allowing patients in the placebo group who met the eligibility criteria to receive enzalutamide. These results were confirmed at the time of the final database lock.

The AFFIRM trial convincingly demonstrated that enzalutamide significantly prolongs overall survival in patients with metastatic castration-resistant prostate cancer after chemotherapy, reducing the risk of death by 37% compared with placebo. The drug also showed superiority across several secondary endpoints, including time to PSA progression, radiographic progression-free survival, and time to skeletal-related events, thereby confirming its strong clinical efficacy. The safety profile of enzalutamide was generally favorable, and adverse events were manageable. Collectively, these findings establish enzalutamide as an important therapeutic option for patients with this type of tumor, improving both survival and quality of life.

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