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RESEARCH HIGHLIGHT

Enzalutamide (formerly MDV3100) as a new therapeutic option for men with metastatic castration-resistant prostate cancer

Jeanny B Aragon-Ching

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Enzalutamide marks the latest addition to the drugs currently approved by the US Food and Drug Administration for metastatic, castration-resistant prostate cancer (mCRPC). AFFIRM was a phase III international randomized trial that evaluated the clinical utility of enzalutamide versus placebo in men with mCRPC who have failed prior docetaxel-containing chemotherapy. Enzalutamide showed a remarkable 37% decreased risk of death with a median overall survival of 18.4 months versus 13.6 months for those who received placebo. These findings confirm the validity of further targeting the androgen receptor as a valid therapeutic approach in prostate cancer despite emergence of castration resistance.

Recent advances in the treatment of metastatic castration-resistant prostate cancer (mCRPC) have brought about a cascade of therapeutic agents including sipuleucel-T, cabazitaxel, abiraterone acetate and denosumab. The most recent addition to the therapeutic armamentarium is enzalutamide, formerly called MDV3100, a once-daily oral androgen receptor–signaling inhibitor. Earlier phase 1–2 trials showed promising results for enzalutamide that improved upon the function of earlier antiandrogens such as bicalutamide, nilutamide or flutamide, characterized by greater affinity for the androgen receptor but inhibition of nuclear translocation of the androgen receptor, DNA binding and coactivator recruitment.[1]

The AFFIRM (a study evaluating the efficacy and safety of the investigational drug MDV3100) trial was an international phase III double-blinded placebo-controlled trial that randomized 1199 patients with mCRPC who failed prior docetaxel-containing regimen in 166 sites in a 2 : 1 fashion to receive either 160 mg daily of enzalutamide (n=800) or placebo (n=399) with the primary endpoint of overall survival and secondary endpoints that included time to prostate-specific antigen (PSA) progression, radiographic progression-free survival, quality-of-life scores and time to the first skeletal-related event.[2] The eligibility included mCRPC progression from prior chemotherapy which should have contained docetaxel, adequate organ function and Eastern Cooperative Oncology Group performance status of 0–2. The study was designed to have a power of 90% to detect a hazard ratio of 0.76 for death in the enzalutamide group, as compared with the placebo group, with a two-sided type I error rate of 0.05. Further subgroup analyses were performed. The study mandated the testing of the key secondary endpoints to be undertaken only if the overall survival analysis showed statistical superiority of enzalutamide over placebo. A prespecified single interim analysis was planned to be performed after 520 deaths (80% of the 650 total events) had occurred and given the positive findings of improved survival in men with mCRPC after chemotherapy by a median of 4.8 months as well as a decreased risk of death from any cause by 37% *vs.* placebo, the independent data and safety monitoring committee recommended stopping the study with unblinding and allowing crossover of the placebo to the enzalutamide arm. The median overall survival was 18.4 months (95% confidence interval, 17.3 to not yet reached) among patients receiving enzalutamide and 13.6 months (95% confidence interval, 11.3–15.8) among patients who received placebo. Furthermore, enzalutamide was shown to have statistically improved all secondary endpoints over placebo, including PSA-level response rate (54% *vs.* 2%), soft-tissue response rate (29% *vs.* 4%), time to PSA progression (8.3 *vs.* 3.0 months), radiographic progression-free survival (8.3 *vs.* 2.9 months) and the time to the first skeletal-related event (16.7 *vs.* 13.3 months).

The results of this phase III trial provide yet again another proof that the androgen receptor remains a valid therapeutic target despite emergence of castration resistance. The benefits of enzalutamide seen in this trial are remarkable such that the survival benefit was observed despite a significant number of patients who crossed over and received subsequent therapies. One prevailing question in the prostate cancer community has been the rational sequencing of these agents. Since abiraterone acetate was first approved (by the Food and Drug Administration in the United States in 2011 and the recently concluded National Institute for Health and Clinical Excellence guidelines in the United Kingdom) before enzalutamide was widely available in the AFFIRM trial (also since prior abiraterone use was an exclusion criterion), there were about 21% of patients who received abiraterone after going off trial (and 24% in the placebo arm) and about 10% receiving further cabazitaxel, a second-line chemotherapy drug that has also been shown to improve survival. Further subgroup analysis showed that enzalutamide use was favorable across all poor risk status including those with worse hemoglobin, Eastern Cooperative Oncology Group performance status, alkaline phosphatase, visceral disease or pain status. However, among those who have poor performance status of 2 and those who had received two or more prior chemotherapy, receipt of enzalutamide did not differ dramatically from

Department of Medicine, Division of Hematology and Oncology, George Washington University Medical Center, Washington, DC 20037, USA
Correspondence: Dr JB Aragon-Ching (jaragonching@mfa.gwu.edu)

placebo (with hazard ratios based on non-stratified proportional hazards model approaching 1), suggesting benefit perhaps when used earlier in the sequence. The question of possible combinatorial strategies, rather than sequential administration of drugs has also been brought under consideration, especially since enzalutamide exerts its activity despite the presence of low levels of circulating androgens, whereas increased androstenedione levels, for instance, have been found to predict likelihood of response to ketoconazole with improved survival compared to patients with lower levels,[3] with similar findings with use of abiraterone. In addition, one hypothesized mechanism of resistance that has emerged with the use of abiraterone has been activation of the mutated androgen receptor induced by glucocorticoid use (a necessary treatment to obviate the mineralocorticoid side effects with abiraterone) that can be inhibited by coadministration with enzalutamide,[4] providing a potential rationale for combination treatment.

The side effect profile of enzalutamide was also favorable, with very little difference over placebo despite a longer observation period of events (given longer times on-study for those on enzalutamide), with slightly more common adverse effects such as fatigue, diarrhea, musculoskeletal pain, headache, hypertension and hot flashes. In fact, the enzalutamide group had a lower incidence of adverse events of grade 3 or above (45.3%, *vs.* 53.1% in the placebo group). The main adverse effect of interest that has caught interest in the study primarily included seizures, which while it occurred in only about five patients overall (0.6%) and would conceivably be a minute number given all potential patient characteristics that resulted in a higher seizure risk (2 patients had brain metastases, 1 had received lidocaine and 1 had brain atrophy with alcohol use), the concern has crossed over to the potential future use of enzalutamide, specifically in the prechemotherapy setting, where men who are largely asymptomatic and have not had multiple prior therapies are potentially susceptible. Of note, the AFFIRM trial excluded patients who were on medications that were known to lower seizure threshold (i.e., insulin, anti-arrythmics, *etc.*). The exact mechanism by which it occurs has not yet been clearly elucidated but postulated to be related to inhibition of the γ-aminobutyric acid-gated chloride channels by enzalutamide which lowers the seizure threshold.

Enzalutamide joins the series of drugs currently available for the treatment of metastatic CRPC. The AFFIRM trial presented data on the use of enzalutamide in the post-docetaxel setting but accrual to the PREVAIL study, the prechemotherapy population[5] is currently underway and eagerly anticipated. As more drugs become available in the horizon, multiple challenging questions as to how best combine, sequence and apply concepts of treatment to earlier phases of disease are rapidly emerging bringing about one of the most exciting times in the treatment of prostate cancer.

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