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Antitumour Activity and Safety of Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer Previously Treated with Abiraterone Acetate Plus Prednisone for ≥24 weeks in Europe

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Abstract

Background: Enzalutamide and abiraterone acetate plus prednisone, which target the androgen receptor axis, have expanded the treatment of advanced prostate cancer. Retrospective analyses suggest some cross-resistance between these two drugs when used sequentially, but robust, prospective studies have not yet been reported.
Objective: To fulfil a regulatory postregistration commitment by evaluating the efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) who progressed following abiraterone acetate plus prednisone treatment.
Design, setting, and participants: Multicentre, single-arm, open-label study, enrolled patients with progressing mCRPC after ≥24 wk of abiraterone acetate plus prednisone treatment. All patients maintained castration therapy during the trial. Prior chemotherapy was allowed but not required.
Intervention: Patients received enzalutamide 160 mg/d orally.
Outcome measurements and statistical analysis: The primary endpoint was radiographic progression-free survival. Secondary endpoints were overall survival, prostate-specific antigen (PSA) response, and time-to-PSA progression. Safety data were also assessed. Kaplan-Meier methods were used to descriptively analyse time-to-event endpoints.
Results and limitations: Overall, 214 patients received enzalutamide treatment, 145 of whom were chemotherapy-naïve. Median radiographic progression-free survival was 8.1 mo (95% confidence interval: 6.1–8.3); median overall survival had not been reached. Unconfirmed PSA response rate was 27% (48 of 181). Median time-to-PSA progression was 5.7 mo (95% confidence interval: 5.6–5.8). The most common treatment-emergent adverse events were fatigue (32%), decreased appetite (25%), asthenia (18%), back pain (17%), and arthralgia (16%). No seizures were reported.

† An employee of Medivation, Inc at the initiation of this work.
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Conclusions: Enzalutamide showed antitumour activity in some patients with mCRPC who had previously progressed following ≥24 wk of abiraterone acetate plus prednisone treatment.

Patient summary: Patients with mCRPC who progressed on previous abiraterone acetate plus prednisone treatment, with or without prior chemotherapy, received enzalutamide. Although cross-resistance between the two agents was observed in a majority of patients, some still benefited from enzalutamide treatment.

1. Introduction

Prostate cancer remains the second most common form of cancer among men worldwide [1], and the management of these patients continues to change with the approval of targeted agents such as enzalutamide and abiraterone acetate [2].

Enzalutamide is an androgen receptor inhibitor approved for treating patients with metastatic castration-resistant prostate cancer (mCRPC) [3–5]. It acts by inhibiting the binding of androgens to the androgen receptor, androgen-receptor nuclear translocation, and androgen-receptor-mediated DNA binding [6]. Enzalutamide significantly prolonged overall survival (OS) versus placebo for chemotherapy-naïve men with mCRPC and men who had progressed on docetaxel therapy (PREVAIL and AFFIRM trials, respectively) [3,4]. Enzalutamide also significantly prolonged progression-free survival (PFS) versus bicalutamide in chemotherapy-naïve men with non-metastatic prostate cancer (STRIVE) [7] and mCRPC (STRIVE and TERRAIN) [5,7].

Abiraterone acetate is a steroidal 17α-hydroxylase/17,20-lyase inhibitor approved in combination with prednisone for treating patients with mCRPC [8,9]. Abiraterone acetate plus prednisone (referred to from here on as "abiraterone") significantly prolonged OS versus prednisone alone for chemotherapy-naïve men (COU-AA-302) [9] and men who had progressed on docetaxel (COU-AA-301) [8,10]. However, a more modest response to abiraterone following progression on docetaxel and enzalutamide was observed in a limited number of patients with mCRPC after discontinuation from the AFFIRM trial, including <10% of patients achieving ≥50% decline in prostate-specific antigen (PSA) on subsequent abiraterone [11,12]. Following the publication of these results, the European Medicines Agency requested the developers of enzalutamide to conduct a study to assess the efficacy of enzalutamide in patients who had progressed following abiraterone.

In response, this postregistration study (ClinicalTrials.gov, NCT02116582) was performed to evaluate the efficacy and safety of enzalutamide treatment in patients with mCRPC following disease progression after at least 24 wk of abiraterone.

2. Patients and methods

2.1. Study design

This phase 4, open-label, single-arm study of enzalutamide enrolled patients with mCRPC who had progressive disease following prior abiraterone treatment from multiple clinical sites in Europe. The study protocol was approved by the review boards of participating institutions, and the trial was in accordance with the Declaration of Helsinki. Written informed consent from the patients were obtained prior to any study-related screening procedures.

Patients must have had metastatic disease (Supplementary data) and must have received a minimum of 24 wk of abiraterone treatment and discontinued its use for ≥4 wk prior to enzalutamide treatment in the study (this inclusion criterion was an amendment to the initial study design). Previous chemotherapy for prostate cancer was limited to ≤1 prior line of docetaxel, which must have been prior to abiraterone treatment. Patients received enzalutamide 160 mg/d orally and continued ongoing androgen deprivation with luteinising hormone-releasing hormone analogues for the duration of the study, or had a bilateral orchiectomy (Supplementary Fig. 1). More details regarding the study methodology, including key inclusion and exclusion criteria, are described in the Supplementary data.

2.2. Outcomes

The primary study endpoint was radiographic PFS (rPFS), defined as the time from the first dose of enzalutamide to objective evidence of radiographic disease progression or death from any cause, whichever occurred first. Bone disease progression was considered when ≥2 new lesions were observed, but if progression was first observed at (or before) wk 13, a confirmatory scan demonstrating ≥2 new additional lesions had to be performed after ≥6 wk. More details regarding confirmation of rPFS are described in the Supplementary data.

Secondary endpoints included: (1) OS, defined as the time from first dose to death from any cause, (2) PSA response, defined as ≥50% decrease from baseline in PSA, which was a binary variable for achieving (or not achieving) this criterion based on the lowest PSA value observed postbaseline (response confirmation, defined as a second consecutive PSA value obtained ≥3 wk later, was not required), and (3) time-to-PSA progression. More details of secondary and exploratory endpoints are described in the Supplementary data.

2.3. Procedures

PSA, soft tissue disease on computed tomography scan or magnetic resonance imaging, and bone disease on radionuclide bone scans data were collected at baseline, wk 13, and every 12 wk until the analysis data cut-off point or

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