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Prostate Cancer

The PREVAIL Study: Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-treated Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer

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Abstract

Background: Enzalutamide, an oral androgen receptor inhibitor, significantly improved overall survival (OS) and radiographic progression-free survival (rPFS) versus placebo in the PREVAIL trial of men with chemotherapy-naïve metastatic castration-resistant prostate cancer.
Objective: To assess the effects of enzalutamide versus placebo in patients from PREVAIL based on site and extent of baseline disease.
Design, setting, and participants: One thousand seven hundred and seventeen asymptomatic or minimally symptomatic patients were randomized to enzalutamide ($n = 872$) or placebo ($n = 845$). Subgroup analyses included nonvisceral (only bone and/or nodal; $n = 1513$), visceral (lung and/or liver; $n = 204$), low-volume bone disease (<4 bone metastases; $n = 867$), high-volume bone disease (≥4 bone metastases; $n = 850$), lymph node only disease ($n = 195$).
Intervention: Oral enzalutamide (160 mg) or placebo once daily while continuing androgen deprivation therapy.
Outcome measurements and statistical analysis: Coprimary endpoints (rPFS, OS) were prospectively evaluated in nonvisceral and visceral subgroups. All other efficacy analyses were post hoc.

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Results and limitations: Enzalutamide improved rPFS versus placebo in patients with nonvisceral disease (hazard ratio [HR], 0.18; 95% confidence interval [CI], 0.14–0.22), visceral disease (HR, 0.28; 95% CI, 0.16–0.49), low- or high-volume bone disease (HR, 0.16; 95% CI, 0.11–0.22; HR, 0.22; 95% CI, 0.16–0.29, respectively), and lymph node only disease (HR, 0.09; 95% CI, 0.04–0.19). For OS, HRs favored enzalutamide (<1) across all disease subgroups, although 95% CI was >1 in patients with visceral disease (HR, 0.82; 95% CI, 0.55–1.23). Enzalutamide was well tolerated in patients with or without visceral disease.
Conclusions: Enzalutamide provided clinically significant benefits in men with chemotherapy-naïve metastatic castration-resistant prostate cancer, with or without visceral disease, low- or high-volume bone disease, or lymph node only disease.
Patient summary: Patients with metastatic castration-resistant prostate cancer—including those with or without visceral disease or widespread bone disease—benefitted from enzalutamide, an active well-tolerated therapy.

1. Introduction

Prostate cancer is the second most common cancer in men, trailing only lung cancer in global incidence [1]. In 2012, approximately 1.1 million men worldwide were diagnosed with prostate cancer. In the USA, it is estimated that in 2015 there will be 220 080 new cases of prostate cancer and 27 540 deaths due to this disease, accounting for 5% of all US cancer deaths [2]. The majority of deaths occur due to metastatic castration-resistant prostate cancer (mCRPC), when disease progression occurs despite maintaining castrate levels of testosterone with medical or surgical castration. Bone and/or lymph node metastases are common in patients with mCRPC, with bone metastases contributing to skeletal-related complications that can reduce quality of life and increase the risk of death [3,4]. Visceral disease in the lung and/or liver occurs in about 20–30% of mCRPC patients and is associated with a particularly poor prognosis [5–10].

Until recently, standard first-line therapy for patients progressing on androgen deprivation therapy (ADT) was docetaxel plus prednisone [5]. Over the last few years, several agents with distinct mechanisms of action have demonstrated benefit in phase 3 trials in men with asymptomatic or minimally symptomatic mCRPC who had not received previous chemotherapy. Sipuleucel-T, an autologous immunotherapy, prolonged survival but did not delay disease progression in this setting [11]. Abiraterone acetate, an androgen biosynthesis inhibitor, significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) [12]. Most recently, the oral androgen receptor inhibitor enzalutamide significantly prolonged OS and rPFS in the PREVAIL trial of men with chemotherapy-naïve mCRPC progressing despite ADT [13]. The benefit of enzalutamide was demonstrated for all prespecified secondary endpoints.

The primary findings of PREVAIL were reported previously [13]. The current analyses focus on the effect of enzalutamide versus placebo on clinical outcomes in PREVAIL patients based on the extent of bone and lymph node disease at baseline (including those with or without visceral disease), low- or high-volume bone disease, or lymph node only disease. Our analyses includes secondary outcomes in patients with only bone and or nodal soft-tissue disease, a patient population commonly treated by urologists and medical oncologists.

2. Materials and methods

2.1. Study population

Eligibility criteria for PREVAIL were described in detail previously [13]. Briefly, eligible patients had asymptomatic or minimally symptomatic mCRPC, an Eastern Cooperative Oncology Group Performance Status of 0–1, and had not previously received chemotherapy. PREVAIL allowed patients with visceral disease (metastases to the lung and/or liver).

2.2. Study design and treatment

PREVAIL was a phase 3, multinational, double-blind, randomized, placebo-controlled study (NCT01212991) comparing the efficacy of enzalutamide versus placebo in men with minimally symptomatic or asymptomatic metastatic prostate cancer who had not received chemotherapy. Patients were enrolled at 207 sites in 22 countries between September 2010 and September 2012. Patients were randomized 1:1 to receive either oral enzalutamide (160 mg) or placebo once daily, which they continued until confirmed radiographic disease progression and initiation of cytotoxic chemotherapy or an investigational agent for prostate cancer. Randomization was central and stratified by study site. Patients were required to continue ADT during the study. Patients were allowed to continue or initiate corticosteroids. Radiation therapy and initiation of bisphosphonates or other approved bone-targeting agents were permitted.

Study endpoints have been defined previously [13]. The coprimary endpoints were rPFS and OS. Secondary endpoints included time to first skeletal-related event, time to initiation of cytotoxic chemotherapy, best overall soft-tissue response, time to prostate-specific antigen (PSA) progression, and PSA response ≥50% from baseline. Prespecified exploratory endpoints included quality-of-life assessments using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) and PSA response ≥90% from baseline.

Our analyses were conducted in the following subgroups: (1) the nonvisceral subgroup (patients with only bone or nodal disease at screening), (2) the visceral subgroup (patients with lung and/or liver metastases), (3) the low- and high-volume bone disease subgroups (patients with <4 vs ≥4 bone metastases, respectively), and (4) the subgroup of patients with lymph node only disease. Patients in the visceral subgroup may have also had bone or nodal disease. The

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