Prostate

Continuous enzalutamide after progression of metastatic castration-resistant prostate cancer treated with docetaxel (PRESIDE): an international, randomised, phase 3b study

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Clinical Trial

BACKGROUND

Although androgen deprivation therapy is typically given long-term for men with metastatic prostate cancer, second-generation hormone therapies are generally discontinued before the subsequent line of treatment. We aimed to evaluate the efficacy of continuing enzalutamide after progression in controlling metastatic castration-resistant prostate cancer (mCRPC) treated with docetaxel and prednisolone.

METHODS

PRESIDE was a two-period, multinational, double-blind, randomised, placebo-controlled, phase 3b study done at 123 sites in Europe (in Austria, Belgium, Czech Republic, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden, Switzerland, Turkey, and the UK). Patients were eligible for period 1 (P1) of the study if they had histologically confirmed prostate adenocarcinoma without neuroendocrine differentiation or small-cell features, serum testosterone concentrations of 1·73 nmol/L or less, and had progressed during androgen deprivation therapy with a luteinising hormone-releasing hormone agonist or antagonist or after bilateral orchiectomy. In P1, patients received open-label enzalutamide 160 mg per day orally. At week 13, patients were assessed for either radiographic or prostate-specific antigen (PSA) progression (25% or more increase and 2 ng/mL or more above nadir). Patients who showed any decline in PSA at week 13 and subsequently progressed (radiographic progression, PSA progression, or both) were screened and enrolled in period 2 (P2), during which eligible patients were treated with up to ten cycles of intravenous docetaxel 75 mg/m² every 3 weeks and oral prednisolone 10 mg/day, and randomly assigned (1:1) to oral enzalutamide 160 mg/day or oral placebo. Patients were stratified by type of disease progression. The block size was four and the overall number of blocks was 400. Patients, investigators, and study organisers were masked to treatment assignment. The primary endpoint was progression-free survival analysed in all patients in P2. This trial is registered with ClinicalTrials.gov, NCT02288247, and is no longer recruiting.

FINDINGS

Between 1 Dec 2014, and 15 Feb 2016, 816 patients were screened for P1 of the study. 688 patients were enrolled in P1 and 687 received open-label enzalutamide. In P2, 271 patients were randomly assigned at 73 sites to receive enzalutamide (n=136) or placebo (n=135). The data cutoff for analysis was April 30, 2020. Median progression-free survival with enzalutamide was 9·5 months (95% CI 8·3-10·9) versus 8·3 months (6·3-8·7) with placebo (hazard ratio 0·72 [95% CI 0·53-0·96]; p=0·027). The most common grade 3 treatment-emergent adverse events were neutropenia (17 [13%] of 136 patients in the enzalutamide group vs 12 [9%] of 135 patients in the placebo group) and asthenia (ten [7%] vs six [4%]). The most common grade 4 treatment-emergent adverse event in P2 was neutropenia (23 [17%] of 136 patients in the enzalutamide group vs 28 [21%] of 135 patients in the placebo

group). Serious treatment-emergent adverse events were reported in 67 (49%) of 136 patients in the enzalutamide group and 52 (39%) of 135 patients in the placebo group. Two (15%) of 13 deaths in the enzalutamide group (caused by septic shock and haematuria) and one (14%) of seven deaths in the placebo group (caused by actue kidney injury) were associated with docetaxel.

INTERPRETATION

PRESIDE met its primary endpoint and showed that continuing enzalutamide with docetaxel plus androgen deprivation therapy delayed time to progression compared with docetaxel plus androgen deprivation therapy alone, supporting the hypothesis that enzalutamide maintenance could control persistent androgen-dependent clones in men with mCRPC who progress after treatment with enzalutamide alone.