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

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Summary

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 Dec 1, 2014, and Feb 15, 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.

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Introduction

Prostate cancer is the malignancy with the fourth highest incidence worldwide. In 2020 alone, more than 1·4 million cases were recorded worldwide, leading to approximately 375 000 deaths.[1] An estimated 10–20% of men with prostate cancer develop metastatic castration-resistant prostate cancer (mCRPC), which causes substantial morbidity and mortality.[2] Despite the availability of new first-line therapies, metastatic prostate cancer is a lethal disease and new therapeutic approaches are urgently needed.[3]

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Research in context

Evidence before this study

The AFFIRM (2012), PREVAIL (2014), and PROSPER (2018) phase 3 trials showed that enzalutamide administration before or after docetaxel was effective in treating metastatic castration-resistant prostate cancer (mCRPC) or non-metastatic castration-resistant prostate cancer; however, in each trial, enzalutamide was discontinued at disease progression. To find randomised trials published in English that evaluated the continuation of a second-generation hormonal drug after progression, we used the terms "androgen receptor blockade", "enzalutamide", "abiraterone acetate", "apalutamide", "darolutamide", "beyond progression", in combination with "chemotherapy/docetaxel/taxane" to search MEDLINE (between Jan 1, 1966, and Jan 31, 2022), Embase (between Jan 1, 1982, and Jan 31, 2022), and major urology and oncology conference proceedings (between Jan 1, 1990, and Jan 31, 2022). We found no published randomised controlled trials that involved concomitant administration of a second-generation hormonal agent with docetaxel after disease progression on previous second-generation hormonal agents. One study that evaluated abiraterone acetate in combination with docetaxel after progression on abiraterone acetate (ABIDO, 2020) was presented at the 2020 American Society of Clinical Oncology Annual Meeting, but not published. The CHEIRON study (2021) assessed the safety and efficacy of first-line administration of enzalutamide and docetaxel for mCRPC and showed that although the combination conferred a clinical benefit, adverse events were frequent. The PLATO study (2018) assessed continuing enzalutamide after progression in patients with mCRPC starting abiraterone acetate and found no clinical benefit.

Added value of this study

To our knowledge, PRESIDE is the first study to report an improvement in progression-free survival and secondary outcome measures by continuing a second-generation hormonal agent in patients with mCRPC after progression and during docetaxel administration. These data support the persistence of enzalutamide-sensitive clones in patients with prostate-specific antigen (PSA) or radiographic disease progression being treated with enzalutamide plus androgen deprivation therapy alone.

Implications of all the available evidence

The available evidence suggests that continuing enzalutamide therapy in patients with mCRPC who have progressed with this drug and who have started docetaxel therapy might confer the clinical benefit of delaying the time to progression in patients with a confirmed initial PSA response. The absence of a benefit when enzalutamide was continued with abiraterone acetate therapy (as in the PLATO study) suggests that the effect is observed only when an effective treatment is used to control clones that do not respond to enzalutamide therapy. Although the benefit seen in PRESIDE is statistically significant, the magnitude of the effect is small. Larger studies and translational work are required to establish which patients might benefit the most from this approach and to confirm whether this strategy improves overall survival. PRESIDE provides a rationale for evaluating disease that persists because of androgen signalling in patients who progress after treatment with second-generation hormonal drugs.

In 2004, two studies showed that docetaxel significantly improved overall survival in men with mCRPC.[4,5] Although docetaxel is known for its microtubular-based mechanism of action, growing evidence suggests that this taxane might also confer a benefit in patients with prostate cancer by acting on androgen receptor signalling and inhibiting translocation into the nucleus.[4–6] Enzalutamide is a second-generation hormonal agent that inhibits the androgen receptor and is approved for the treatment of men with metastatic hormone-sensitive prostate cancer, also known as metastatic castration-sensitive prostate cancer, and both metastatic and non-metastatic castration-resistant prostate cancer.[7–9] Docetaxel and enzalutamide have been shown to be effective first-line therapies and, when used consecutively, to reduce the risk of death by 37% in men with mCRPC.[4,10,11] The PREVAIL and AFFIRM studies showed the benefit of administering enzalutamide before and after docetaxel, respectively;[10,11] however, the optimal treatment sequence to maximise benefit remains unclear.

Enzalutamide cross-resistance was observed in studies of patients with mCRPC investigating docetaxel administration after enzalutamide[12] and enzalutamide administration before and after abiraterone acetate.[13,14] Therefore, identifying a viable and beneficial strategy to treat patients with mCRPC who progress on enzalutamide has become increasingly necessary.

We herein report the findings from PRESIDE, a phase 3b trial that evaluated the efficacy of a novel treatment sequence for chemotherapy-naive patients with mCRPC who progressed after treatment with enzalutamide. Patients received either enzalutamide plus docetaxel and prednisolone or placebo plus docetaxel and prednisolone with continued androgen deprivation therapy. Current treatment guidelines suggest that continuing a therapeutic agent after disease progression might improve outcomes in many cancers, but this treatment sequence has not been formally tested in patients with mCRPC.[3,15] Phase 2 data have indicated that simultaneous administration of enzalutamide, docetaxel, and prednisolone for mCRPC significantly controls disease progression.[16] We hypothesised that this combination would be effective because continued administration of enzalutamide might improve the control of androgen receptor-dependent and castration-resistant prostate cancer lesions, whereas concordant docetaxel administration would better target lesions that adopted alternative pathways conferring resistance to androgen

receptor inhibition. To investigate this hypothesis, we tested for an improvement in progression-free survival.

Methods

Study design and participants

PRESIDE was a two-period, multinational, double-blind, randomised, placebo-controlled phase 3b trial (appendix p 21), 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 (appendix pp 1–3). 89 sites participated in screening and 73 sites randomly assigned patients. 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 while being treated with androgen deprivation therapy with a luteinising hormone-releasing hormone agonist or antagonist or after bilateral orchiectomy. Progression at study entry was defined as either three observed increases in prostate-specific antigen (PSA) concentrations, with 1 week or more between each increase, or a PSA value of 2 ng/mL or greater. Patients were considered to have metastatic disease if at least two bone lesions (assessed by a bone scan) or soft tissue disease (assessed by CT or MRI) were documented. Eligible patients had asymptomatic or minimally symptomatic prostate cancer (Brief Pain Inventory—Short Form [BPI-SF] question 3 score of <4), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a life expectancy of 12 months or longer. Key exclusion criteria included previous use of aminoglutethimide, ketoconazole, abiraterone acetate, enzalutamide, or cytotoxic chemotherapy (including for metastatic castration-sensitive prostate cancer) and of antiandrogens, 5-α reductase inhibitors, oestrogens, or opiate analgesia within 4 weeks before initiation of study drug. Full inclusion and exclusion criteria are listed in the protocol (appendix). Patients were excluded if they had undergone major surgery within 4 weeks before initiation of study drug, had suspected brain metastasis or active leptomeningeal disease, or had a history of seizure, other malignancy, or clinically significant cardiovascular disease. A protocol amendment on June 19, 2015, allowed patients participating in the control group of separate interventional studies that included only standard of care or in the observational phase of an interventional study to enrol in PRESIDE if they met all inclusion and exclusion criteria.

Patients who did not have a PSA response or evidence of radiographic progression at week 13 were excluded from preiod 2 (P2) of the study. Patients were considered to have progressed if they had either PSA progression (defined as a ≥25% increase or rise in absolute concentration ≥2 ng/mL above nadir and PSA doubling time of ≤12 weeks documented in at least three PSA measurements at intervals of 4 or more weeks apart, across 3 or more months), bone disease progression (defined as the appearance of two or more new bone lesions on bone scan as per the Prostate Cancer Working Group 2 criteria), or soft tissue disease progression (as per Response Evaluation Criteria in Solid Tumours version 1.1).[17] PSA responses were confirmed by a subsequent test 3 weeks after the recorded response. Radiographic progression by bone scan at week 13 required a confirmatory scan 6 weeks later. Patients assessed by the investigator to be benefitting from treatment but ineligible for P2 were allowed to continue in P1 despite disease progression, until initiation of new therapy or consent withdrawal. Patients still receiving treatment in P1 when P2 enrolment closed were permitted to continue receiving treatment in an extension period.

See Online for appendix

Eligible patients for P2 had an ECOG performance score of 0–2, and if they had been receiving bisphosphonates or denosumab for bone health, they must have done so for at least 4 weeks during P1. All patients were required to receive ongoing androgen deprivation therapy with either a luteinising hormone-releasing hormone agonist or antagonist at a stable dose and schedule for at least 4 weeks, or to have a bilateral orchiectomy to be eligible for the study.

The study protocol and all amendments were approved by local independent review boards and the study was conducted in accordance with the current International Conference on Harmonization guidelines for Good Clinical Practice, as well as the Declaration of Helsinki. All patients provided written informed consent.

Randomisation and masking

In P2 of the study, patients were randomly assigned (1:1) to the enzalutamide or placebo groups through an interactive response technology system. Randomisation was stratified by type of disease progression, based on evidence or no evidence of radiographic progression during P1. The block size was four and the overall number of blocks was 400. The interactive response technology system maintained masking by providing each site with patient number and study medication assignment for each participant. Placebo capsules were identical in appearance to enzalutamide capsules. All patients, investigators, clinical staff, and the sponsor's management team were masked to treatment assignment.

Procedures

Patients enrolled in P1 received open-label oral enzalutamide 160 mg (four 40 mg capsules) per day until disease progression and subsequent random assignment into P2 or discontinuation. Disease progression was evaluated through PSA and radiographic assessment at week 13 and every 12 weeks thereafter to assess eligibility for P2. Patients enrolled into the double-blind P2 stage received either oral enzalutamide 160 mg (four 40 mg

capsules) per day or four capsules of oral placebo, plus intravenous docetaxel 75 mg/m² every 3 weeks and oral prednisolone 10 mg/day as two 5 mg tablets. Administration of docetaxel continued for up to ten cycles and, if the treatment was beneficial, patients were permitted to receive additional cycles of docetaxel (for up to ten cycles; if the treatment was beneficial, patients were permitted to continue on docetaxel specifically for additional cycles) or receive enzalutamide or placebo only. Physicians and patients decided what regimen was most appropriate on the basis of the benefit–risk balance. Patients discontinued treatment if they: developed progressive disease (assessed by PSA increase or imaging) at week 13 of P1; met the criteria for disease progression in P1 but not for randomisation into P2; in either period, developed an adverse event that made continued administration of study drug unwarranted; or withdrew consent for further treatment. Patients who had a grade 3 or worse adverse event that did not improve with medical attention interrupted treatment for 1 week until their symptoms improved to grade 2 or better. Treatment was then resumed at the same dose or at a reduced dose (120 mg or 80 mg per day) if necessary. Physicians and patients decided what dosage was most appropriate once treatment was resumed to reach the appropriate benefit–risk balance. In P2, patients who discontinued study drug for a reason other than disease progression were asked to continue attending their scheduled study visits every 12 weeks. In both P1 and P2, patients who discontinued study treatment had a safety follow-up visit at 30 days after their last dose of the study medication. If patients progressed in P2, they were permitted to continue receiving double-blind treatment during a study extension period. Efficacy follow-up in P2 was planned for a maximum of 112 days after treatment discontinuation or until radiographic progression or initiation of a new antineoplastic therapy.

Radiographic assessment was done by abdominopelvic CT or MRI scan for soft tissue disease and whole-body radionuclide bone scan for bone lesions. A chest x-ray was done at both the P1 screening visit and P2 eligibility assessment. Chest CT or MRI scans were required if the screening x-ray or CT scan indicated the presence of lung metastasis or in case of clinical suspicion of the presence of metastases. P1 imaging was done during the screening window and then every 12 weeks thereafter. In P2, an imaging evaluation was done during the eligibility assessment window and then every 12 weeks thereafter. Scans could be done up to 7 days before each visit. Each study site had a designated radiologist or investigator as the primary imaging reviewer. The designated reviewer would evaluate the same images for any one participant for the duration of the trial. Clinical laboratory assessments (haematology and chemistry) were obtained at each scheduled clinic visit before administration of the study drug and analysed at a central laboratory (Bio Analytical Research Corportation; Barc Lab; Ghent, Belgium).

All adverse events were collected from the time the patient consented to the study until 30 days after the last dose of enzalutamide. Adverse events were assessed at every visit, the frequency of which varied depending on the treatment schedule of the patient. During P1, adverse events were assessed at each visit (or every third month). During P2, adverse events were assessed every 3 weeks, when docetaxel was administered. After docetaxel treatment was concluded, the visit schedule returned to every third month. Severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events guidelines version 4.03. All treatment-emergent adverse events (any adverse event that occurred after the start of study treatment) were followed up until judged by the investigator to be no longer clinically significant or until they became chronic.

Outcomes

All endpoints were measured with the date of random assignment (week 1 of P2) as baseline. The primary endpoint was progression-free survival, defined as the time (in months) from random assignment to the first progression event. A progression event was defined as radiographic progression (of bone or soft tissue disease); unequivocal clinical progression (any new onset of cancer pain requiring opiate analgesia; deterioration to an ECOG performance status score to 3 or higher due to prostate cancer; or initiation of subsequent lines of cytotoxic chemotherapy, radiotherapy, or surgical intervention because of complications of tumour progression); or death within 112 days of treatment discontinuation without objective evidence of radiographic progression.

The secondary endpoints were: time to PSA progression (the time from randomisation to the date when a 25% or more increase and an absolute increase of 2 ng/mL or more above the nadir in PSA value were recorded in P2 and confirmed by a second consecutive value obtained at least 3 weeks later); PSA response (a decrease from PSA concentration at the time of random assignment of 50% or more); objective response rate (best overall radiographic response for soft tissue disease, based on Response Evaluation Criteria in Solid Tumours version 1.1[17]); time to pain progression (the time to an increase in mean BPI-SF pain intensity scores [items 3–6] of 30% or more from random assignment; only patients with mean pain item scores of at least 4 at that time of progression were included); time to opiate use for cancer-related pain (the time from random assignment to initiation of chronic administration of opiate analgesia); time to first skeletal-related event (the time from random assignment to first incidence of radiotherapy to the bone or bone surgery, pathological bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain); and quality of life as measured by time (in months) to degradation (defined as a 10-point or greater decrease in global score from baseline) on the Functional Assessment of Cancer

Therapy-Prostate (FACT-P) scale and change from baseline in European Quality of Life 5 Dimensions, 5 Levels (EQ-5D-5L).

Safety endpoints were changes in vital signs (including blood pressure, pulse rate, and temperature), treatment-emergent adverse events, and serious treatment-emergent adverse events per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, laboratory assessments, physical examination, and electrocardiogram assessments.

Additional endpoints were cumulative dose of docetaxel and health resource use. The single exploratory endpoint was analysis of candidate circulating biomarkers of response, progression, or resistance. The additional and exploratory endpoints are not reported herein.

Statistical analysis

The data analysis cutoff was April 30, 2020. Analysis of the primary endpoint was a between-group comparison of progression-free survival in the full analysis set (ie, all randomly assigned patients who received at least one dose of study drug in P2), with the null hypothesis that progression-free survival would be the same between the enzalutamide and placebo groups (ie, a hazard ratio [HR] equal to 1·0). The primary endpoint analysis was planned at 182 progression-free survival events to provide a power of 80% to detect a treatment effect, with an HR of 0·66 for disease progression or death based on a two-sided stratified log-rank test, an overall significance level of 0·05, and an expected median progression-free survival of 6 months for the placebo group. To allow for attrition before random assignment, an estimated 650 patients were expected to be enrolled to achieve the required 182 progression events in P2.

The Kaplan-Meier method was used to estimate survival functions for both study groups. A stratified log-rank test was used to evaluate progression-free survival in both treatment groups, with stratification according to type of disease progression in P1 (data shown are not stratified by disease progression). A Cox proportional hazards model was applied if the proportional hazards assumption was met, with covariates for treatment and evidence of radiographic progression in P1. HRs for the treatment group, 95% CIs, and the corresponding p values were estimated using an unstratified Cox proportional hazards model. A prespecified sensitivity analysis for progression-free survival was also done using an unstratified log-rank test for the full analysis set (all patients who were randomly assigned and received at least one dose of the study drug).

Post-hoc subgroup analyses were done for progression-free survival in P2 by key patient characteristics: ECOG performance status, age, Gleason score, disease location at screening, baseline PSA, baseline lactate dehydrogenase, baseline haemoglobin, baseline alkaline phosphatase, and previous use of anti-androgen therapy or bisphosphonates.

The secondary endpoints of time to PSA progression, time to pain progression, time to opiate use for cancer-related pain, time to first skeletal-related event, and time to degradation of FACT-P were analysed in the same way that the primary endpoint was analysed, by a log-rank test stratified by type of disease progression in P1 (data shown are not stratified by disease progression). PSA response was reported as waterfall plots for each treatment group. Objective response rate was compared between treatment group using a Cochran-Mantel-Haenszel test stratified by type of disease progression in P1 for the full analysis set. The median change from baseline of EQ-5D-5L visual analogue scale was calculated as the post-baseline value at week 25 (last non-missing value before the first dose in the analysis period) minus the baseline value. Safety analysis was split into safety analysis set 1 for patients who received at least one dose of treatment in P1, and safety analysis set 2 for the equivalent in P2. Safety data for both sets are presented using descriptive statistics.

All analyses were done using SAS version 9.3. An independent data monitoring committee was responsible for reviewing the safety data for this study. This trial is registered with ClinicalTrials.gov, NCT02288247.

Role of the funding source

This trial was sponsored and designed by Astellas Pharma and Pfizer. Astellas Pharma oversaw the collection of data by investigators, and the statistical analysis of data was done by the sponsors and interpreted by the sponsors and authors. All authors had full access to all the data in the study. The manuscript was written with medical writing assistance funded by Astellas Pharma and Pfizer, with critical review and input by the authors. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol.

Results

Between Dec 1, 2014, and Feb 15, 2016, 816 patients were screened for P1 of the study. 688 were enrolled in P1 and 687 received open-label enzalutamide (figure 1). One individual was enrolled but never treated. Patient characteristics at baseline in P1 are summarised in the appendix (pp 4–5). The median duration of enzalutamide exposure in P1 was 62·6 weeks (IQR 46·1–110·0). 392 (57%) of 687 treated patients had disease progression and 295 (43%) either did not progress, did not have a response, or discontinued treatment (and the study) because of withdrawal, adverse events, or death (figure 1; appendix p 6). The 392 patients with disease progression discontinued open-label treatment and were evaluated for their eligibility to enter P2. One patient assigned to the placebo group was unmasked by site investigators during P2. 41 patients continued enzalutamide therapy in P1 after the clinical cutoff for data analysis on April 30, 2020 (figure 1).

At the end of P1, 273 (70%) of 392 patients were eligible to be randomly assigned in P2, with 271 patients receiving treatment (appendix pp 7–9). 136 (50%) of 271 patients received enzalutamide plus docetaxel and prednisolone and 135 (50%) received placebo plus docetaxel and prednisolone. 61 (23%) of 271 patients were randomly assigned into P2 on the basis of PSA progression only (enzalutamide: 31 [23%] of 136 patients; placebo: 30 [22%] of 135 patients) and 210 on the basis of radiographic progression (enzalutamide: 105 [77%] of 136 patients; placebo: 105 [78%] of 135 patients). Demographic and baseline characteristics were similar between the two treatment groups (table 1). In P2, the median duration of exposure to study drug was 36·1 weeks (IQR 16·9–48·7) for the enzalutamide group and 30·1 weeks (0·4–94·4) for the placebo group. The median follow-up time was 8·1 months (IQR 3·2–11·1) in the enzalutamide group and 6·3 months (3·1–10·5) in the placebo group. 21 (15%) of 136 patients in the enzalutamide group and 48 (36%) of 135 patients in the placebo group had dose reductions or interruptions. Prednisolone was administered for the full duration of the study. The median number of cycles of docetaxel was 6·0 (IQR 4·0–10·0) in the enzalutamide group and 7·0 (4·0–10·0) in the placebo group.

Median progression-free survival was 9·5 months (95% CI 8·3–10·9) in the enzalutamide group and 8·3 months (6·3–8·7) in the placebo group, representing a significant improvement in the risk of progression (HR 0·72 [95% CI 0·53–0·96]; p=0·027; figure 2; appendix p 10). 93 (74%) of 125 patients in the enzalutamide group had disease progression (number of events plus number censored), versus 93 (76%) of 123 patients in the placebo group. 36 (26%) of 136 patients in the enzalutamide group and 37 (27%) of 135 patients in the placebo group had bone disease progression; 36 (26%) of 136 patients in the enzalutamide group and 45 (33%) of 135 patients in the placebo group had soft tissue disease progression. 33 patients had unequivocal clinical progression (enzalutamide: 19 [14%] of 136 patients; placebo: 14 [10%] of 135 patients). Death within 112 days of treatment discontinuation occurred in eight (6%) of 136 patients in the enzalutamide group and five (4%) of 135 patients in the placebo group.

A prespecified sensitivity analysis was done for progression-free survival using an unstratified log-rank test and reflected the same results as those in the primary analysis (appendix p 11). Similarly, results of post-hoc subgroup analyses for progression-free survival were consistent with those in the overall population (appendix p 22).

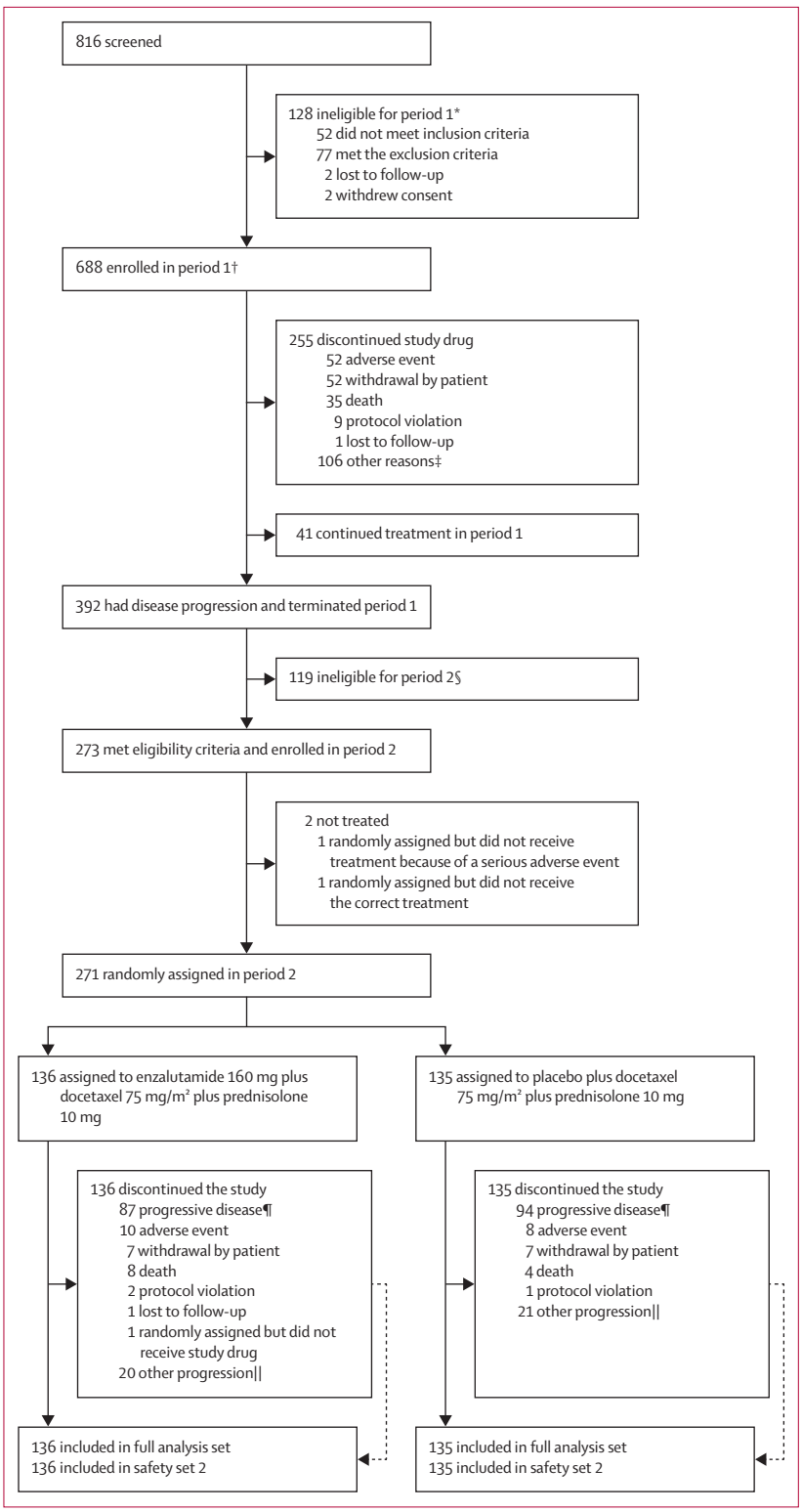

Figure 1: **Trial profile**
*Reasons for ineligibility were not mutually exclusive. †688 patients were enrolled, but one never received study treatment; 687 patients were included in safety analysis set 1. ‡Other reasons for treatment discontinuation and study termination at period 1 are listed in the appendix (p 6). §Details of all 119 patients who did not meet the inclusion criteria or met exclusion criteria for period 2 can be found in the appendix (pp 7–9). ¶The reason for the discrepancy between progressive disease numbers in the figure and main text is that not all patients who progressed had progression as the primary reason for discontinuation. ||Patients who progressed but not under the protocol definition.

Enzalutamide was associated with a significant reduction in risk of PSA progression (HR 0·58 [95% CI 0·41–0·82]; p=0·0021; appendix p 12). The median time to PSA progression in the enzalutamide group was 8·4 months (95% CI 8·2–9·0) compared with 6·2 months (5·4–8·3) in the placebo group (appendix pp 12, 23).

At week 13 (P2), patients treated with enzalutamide showed a decrease in mean percentage change from baseline PSA concentrations (–37·12% [SD 48·10]) compared with those treated with placebo (9·11% [SD 97·96]; appendix p 24). 61 (45%) of 136 patients in the enzalutamide group and 34 (25%) of 135 patients in the placebo group had a PSA response (decrease in PSA concentration of ≥50% from week 1) at any time within P2 (p<0·0001).

The overall response rate in patients with soft tissue disease in the enzalutamide group was 41% (21 of 51 patients; eight complete responses and 13 partial responses) compared with 39% in the placebo group (23 of 39 patients; seven complete responses and 16 partial responses; appendix p 13). No patients in either treatment group reported pain progression, defined as an increase of at least 30% from baseline in mean BPI-SF pain intensity scores (items 3–6); therefore, time to pain progression was not calculated. At data cutoff, the proportion of patients who initiated chronic administration of opiate analgesia was similar between the enzalutamide group (13 [10%] of 136 patients) and the placebo group (ten [7%] of 135 patients). The median time to first skeletal-related event was 22·0 months (95% CI 15·2 to not evaluable [NE]) in the enzalutamide group compared with 17·4 months (17·4 to NE; HR 1·00, 95% CI 0·47–2·13; p=0·99) in the placebo group (appendix p 25). 17 (13%) of 136 patients in the enzalutamide group and 12 (9%) of 135 patients in the placebo group had a skeletal-related event. 32 (24%) of 136 patients in the enzalutamide group and 50 (37%) of 135 patients in the placebo group received drugs for the treatment of bone diseases. Degradation of FACT-P (global score, measured in months) in P2 was similar across the two treatment groups. The median time to FACT-P degradation was 8·4 months (95% CI 5·6 to NE) in the enzalutamide group and 11·1 months (8·3 to NE) in the placebo group (HR 1·25, 95% CI 0·81–1·94; p=0·31). Time to FACT-P degradation was reported in 48 [37%] of 130 patients (number of events plus number censored) in the enzalutamide group and 38 [28%] of 134 patients in the placebo group. The median change from baseline in EQ-5D-5L visual analogue scale at week 25 was 0·0 (IQR –15 to 10) in the enzalutamide group and 0·0 (–10 to 10) in the placebo group.

A similar number of patients in both treatment groups reported treatment-emergent adverse events and drug-related treatment-emergent adverse events in P2 (table 2). The enzalutamide and placebo groups had similar total incidences of grade 3 treatment-emergent adverse events (51 [38%] of 136 patients in the enzalutamide group *vs* 50 [37%] of 135 patients in the placebo group) and grade 4 treatment-emergent adverse events (33 [24%] patients in the enzalutamide group *vs* 34 [25%] patients in the placebo group; table 3). 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 was neutropenia (23 [17%] of 136 patients in the enzalutamide group *vs* 28 [21%] of 135 patients in the placebo group). In P1, the most common treatment-emergent adverse events of any grade (in at least 10% of patients) were fatigue, back pain, asthenia, and hypertension (appendix p 14). In P2, the most common treatment-emergent adverse events of any grade (in at least 10% of patients) were asthenia, neutropenia, alopecia, fatigue, diarrhoea, and anaemia (table 3). Treatment-emergent adverse events that occurred more frequently with enzalutamide than with placebo were grade 1–2 fatigue (37 [27%] of 136 patients in the enzalutamide group *vs* 24 [18%] of 135 patients in the placebo group); grade 1–2 anaemia (22 [16%] *vs* 13 [10%]); grade 1–2 arthralgia (25 [18%] *vs* ten [7%]); and grade 1–2 peripheral neuropathy (20 [15%] *vs* ten [7%]; table 3). In the enzalutamide group, six (4%) of 136 patients reported

	Enzalutamide plus docetaxel plus prednisolone (n=136)	Placebo plus docetaxel plus prednisolone (n=135)
Race		
White	133 (98%)	134 (99%)
Black or African American	3 (2%)	0
Hispanic	0	1 (1%)
Age, years	71·5 (65·0–75·0)	69·0 (65·0–74·0)
Weight, kg	83·0 (76·0–96·0)	86·0 (77·5–97·0)
BMI, kg/m²	27·6 (25·5–30·7)	28·4 (26·3–31·2)
Eastern Cooperative Oncology Group performance status for P2		
0	61 (45%)	67 (50%)
1	68 (50%)	63 (47%)
2	7 (5%)	5 (4%)
Baseline serum PSA, µg/L*	36·9 (13·6–80·8)	28·1 (13·7–92·3)
Gleason score at diagnosis		
<8	54 (40%)	55 (41%)
≥8	76 (56%)	77 (57%)
Unknown	6 (4%)	3 (2%)
Location of metastases†		
Bone	57 (42%)	47 (35%)
Soft tissue	29 (21%)	24 (18%)
Bone and soft tissue	50 (37%)	64 (47%)

Data are n (%) or median (IQR). All patients who were randomly assigned in P2 and received at least one dose of investigational medicinal product are included (full analysis set). *Baseline serum PSA was defined as the value recorded at P1, week 1, or at screening if missing. †Disease location was based on target lesion and non-target lesion assessments and bone scan results.

Table 1: **Baseline demographics and patient characteristics in period 2**

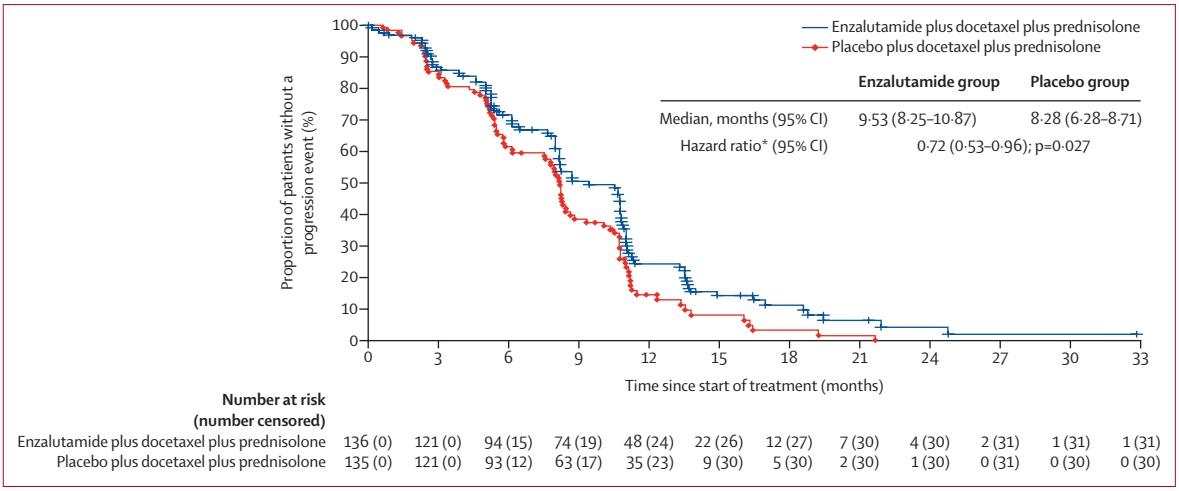

Figure 2: **Kaplan-Meier estimates of progression-free survival**
*From the Cox proportional hazards model with covariates for treatment and disease progression in period 1 of the study.

	Enzalutamide plus docetaxel plus prednisolone (n=136)	Placebo plus docetaxel plus prednisolone (n=135)
Treatment-emergent adverse events	133 (98%)	131 (97%)
Drug-related* treatment-emergent adverse events	63 (46%)	56 (41%)
Docetaxel-related treatment-emergent adverse events†	123 (90%)	122 (90%)
Serious treatment-emergent adverse events†	67 (49%)	52 (39%)
Drug-related* serious treatment-emergent adverse events†	7 (5%)	10 (7%)
Treatment-emergent adverse events leading to discontinuation of study drug	12 (9%)	9 (7%)
Deaths	13 (10%)	7 (5%)

Data are n (%).*Drug-related designation refers to enzalutamide or placebo but not to docetaxel nor prednisolone. Events were considered drug-related if the association was probable or possible, as assessed by an investigator, or in cases where the records of the potential association were missing. †Includes serious treatment-emergent adverse events upgraded by the sponsor, if any upgrade was done, based on review of the sponsor's list of always-serious events.

Table 2: **Summary of treatment-emergent adverse events in period 2 in patients who received at least one dose of study drug**

grade 3 or 4 anaemia compared with three (2%) 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 (table 2). Serious drug-related treatment-emergent adverse events were reported in seven (5%) of 136 patients in the enzalutamide group and ten (7%) of 135 patients in the placebo group. 46 (7%) of 687 patients receiving enzalutamide died in P1. In P2, 20 patients died: 13 (10%) of 136 patients who received enzalutamide and seven (5%) of 135 patients who received placebo. The causes of death were respiratory failure (one patient), heart attack (one patient), metastatic disease progression (eight patients), bacteraemia (one patient), septic shock (two patients), pleural effusion (one patient), overall physical deterioration (one patient), pneumonia (one patient), haematuria and haemorrhagic shock (one patient), acute kidney injury (one patient), and unknown (two patients; appendix p 15). In P2, 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 acute kidney injury) were associated with docetaxel; no other deaths were considered related to study drugs.

Discussion

In PRESIDE, we showed that continued administration of enzalutamide plus docetaxel and prednisolone in men with mCRPC who had progressed on enzalutamide alone reduced the risk of disease progression compared with the administration of placebo plus docetaxel and prednisolone. Although no new safety signals were observed in PRESIDE, an increase in toxic effects was observed with the combination of enzalutamide plus docetaxel. These results were consistent with the known safety profiles of enzalutamide and docetaxel observed in other studies. Although a significant clinical benefit in progression-free survival was observed with enzalutamide plus docetaxel, this benefit must be weighed against the increase in toxic effects observed with this regimen.

Clinical trial data support the benefits of treatment intensification earlier in the course of prostate cancer, such as adding second-generation hormonal therapies to androgen deprivation therapy for the treatment of

	Enzalutamide plus docetaxel plus prednisolone (n=136)				Placebo plus docetaxel plus prednisolone (n=135)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-emergent adverse event	36 (26%)	51 (38%)	33 (24%)	13 (10%)	40 (30%)	50 (37%)	34 (25%)	7 (5%)
Alopecia	41 (30%)	3 (2%)	0	0	36 (27%)	1 (1%)	0	0
Asthenia	37 (27%)	10 (7%)	0	0	29 (21%)	6 (4%)	0	0
Fatigue	37 (27%)	3 (2%)	0	0	24 (18%)	4 (3%)	0	0
Diarrhoea	34 (25%)	3 (2%)	0	0	38 (28%)	6 (4%)	0	0
Nausea	26 (19%)	0	0	0	24 (18%)	2 (1%)	0	0
Arthralgia	25 (18%)	0	0	0	10 (7%)	0	0	0
Increased lacrimation	24 (18%)	1 (1%)	0	0	6 (4%)	0	0	0
Anaemia	22 (16%)	6 (4%)	0	0	13 (10%)	3 (2%)	0	0
Decreased appetite	22 (16%)	1 (1%)	0	0	17 (13%)	0	0	0
Peripheral neuropathy	20 (15%)	2 (1%)	0	0	10 (7%)	2 (1%)	0	0
Dysgeusia	17 (13%)	1 (1%)	0	0	9 (7%)	0	0	0
Peripheral oedema	15 (11%)	1 (1%)	0	0	20 (15%)	0	0	0
Constipation	12 (9%)	0	0	0	15 (11%)	1 (1%)	0	0
Back pain	12 (9%)	3 (2%)	0	0	14 (10%)	2 (1%)	0	0
Bone pain	10 (7%)	2 (1%)	0	0	13 (10%)	2 (1%)	0	0
Mucosal inflammation	10 (7%)	0	0	0	16 (12%)	1 (1%)	0	0
Neutropenia	6 (4%)	17 (13%)	23 (17%)	0	5 (4%)	12 (9%)	28 (21%)	0
Drug-related* treatment-emergent adverse events	45 (33%)	17 (13%)	1 (1%)	0	36 (27%)	8 (6%)	12 (9%)	0
Docetaxel-related† treatment-emergent adverse events	44 (32%)	44 (32%)	33 (24%)	2 (1%)	49 (36%)	38 (28%)	34 (25%)	1 (1%)

Data are n (%). Treatment-emergent adverse events that were reported in ≥10% of patients in either treatment group are shown. All treatment-emergent adverse events of grade 3 or worse are reported in the appendix (p 15). *Drug-related designation refers to enzalutamide or placebo but not to docetaxel nor prednisolone. Events were considered drug-related if the association was probable or possible, as assessed by an investigator, or in cases where the records of the potential association were missing. †Includes serious treatment-emergent adverse events upgraded by the sponsor, if any upgrade was done, based on review of the sponsor's list of always-serious events.

Table 3: **Commonly occurring treatment-emergent adverse events in period 2 in all patients who received at least one dose of study drug**

metastatic castration-sensitive prostate cancer.[18] In the real-world setting, treatment intensification beyond androgen deprivation therapy is substantially underused in patients with metastatic castration-sensitive prostate cancer,[19] despite strong evidence that it is associated with improved overall survival and quality of life.[20] The use of androgen receptor-targeted drugs is likely to increase as access to such treatments becomes easier. Given this expected trend, understanding the potential benefits of continuing enzalutamide therapy after progression to mCRPC upon the addition of docetaxel therapy becomes highly relevant. Furthermore, despite improvements in the treatment of mCRPC, an unmet need for better treatment options remains. In this study, we used therapeutic layering, or combination therapy, a concept that continues to gain support for the treatment of mCRPC.[21] Other studies have explored the potential of layering therapies in combination to treat mCRPC, but with little success. PLATO,[13] in which patients received open-label enzalutamide until progression and were then randomly assigned to receive enzalutamide plus abiraterone acetate or abiraterone acetate alone, is an example of such a study. Patients receiving enzalutamide plus abiraterone acetate had an increased incidence of grade 3 and 4 adverse events and had no improvement in disease outcomes compared with those receiving abiraterone acetate alone.

Differences in the results of PRESIDE compared with PLATO might be attributable to the specific interplay in the mechanism of action between enzalutamide and docetaxel, or the difference in activity of abiraterone acetate and docetaxel after enzalutamide administration. Although evidence suggests that docetaxel might affect androgen receptor signalling, the mechanism of action of docetaxel is not yet fully understood, and a component of its activity might not be androgen-dependent.[22] Furthermore, administration of sequential androgen receptor therapy has not been shown to improve outcomes,[23] a finding that might explain why abiraterone acetate plus enzalutamide therapy after progression on enzalutamide therapy did not improve outcomes in PLATO.[13] The ABIDO trial[24] reported no benefit of continuing abiraterone acetate therapy after progression and starting docetaxel therapy. Differences in trial design, endpoint reporting, and biological mechanisms of actions of abiraterone acetate and docetaxel need to be assessed to refine the layering strategy for the treatment of mCRPC.[24] Continuing enzalutamide treatment can maintain control of mCRPC by targeting residual enzalutamide-sensitive clones, whereas layering docetaxel treatment might target clones that persist after initial enzalutamide treatment.

Although the enzalutamide group of PRESIDE had higher levels of serious treatment-emergent adverse

events than the placebo group, the overall safety findings of the trial are consistent with those of previous studies. The CHEIRON study[16] showed a benefit from the concurrent initiation of enzalutamide plus docetaxel. In PRESIDE, chemotherapy-naive patients with mCRPC who received a combination of enzalutamide and docetaxel as first-line therapy had significantly reduced disease progression compared with those who received docetaxel alone. Patients in the enzalutamide groups in both CHEIRON and PRESIDE had higher levels of grade 3 and 4 anaemia than those in the placebo groups. The ENZAMET study[25] assessed the efficacy of administering enzalutamide with androgen deprivation therapy and early docetaxel in a cohort with metastatic castration-sensitive prostate cancer. Similar to the results of PRESIDE, patients receiving enzalutamide had higher incidences of fatigue than did those receiving placebo. Patients in ENZAMET receiving early docetaxel with enzalutamide reported similar increased rates of lacrimation, fatigue, and peripheral neuropathy.[25]

Although enzalutamide improved outcomes for patients with mCRPC, nearly all patients eventually develop resistance to enzalutamide and face disease progression when androgen receptor signalling is reactivated.[26] PRESIDE provides evidence that concomitant administration of enzalutamide and docetaxel might serve as a treatment option for patients who progress on enzalutamide alone. Although novel therapeutics are being studied to overcome enzalutamide resistance,[27] our results suggest a potential subset of patients who might benefit from the treatment regimen tested in the current study. Continued studies will aim to pinpoint specific biomarkers of enzalutamide resistance to better identify the subsets of patient who will benefit the most from this innovative approach.

We acknowledge that although the primary endpoint included death, overall survival was not assessed in this study. In the absence of published objective data showing patient benefit with the continuation of enzalutamide treatment beyond disease progression, the goal of PRESIDE was to act as an activity-seeking trial and was therefore not powered to assess overall survival. Although the P2 cohort could be interpreted as a selected population, considering PSA progression alone as a progression event, most patients with disease progression in P1 did not fall under this progression category. Furthermore, all patients entering P2 were required to have a PSA response to enzalutamide in P1 and to have subsequent disease progression. The high baseline ECOG and Gleason scores further suggest that the patients in P2 were not a favourable-risk group. However, we acknowledge that stopping enzalutamide because of biochemical disease progression might have limited the full benefit of the therapy in the placebo group. Increasing enzalutamide therapy earlier in the disease continuum might make the results of PRESIDE more pertinent, given a possible increase in the proportion of chemotherapy-fit patients progressing on enzalutamide therapy. Enzalutamide was also significantly associated with a reduced risk of PSA progression and a higher PSA response. Although these outcomes are not validated surrogate efficacy endpoints, they have been shown to correlate with clinical outcome.[28] Further investigation (which could include testing for the effect on overall survival) is warranted and required before clinical practice is altered.

In conclusion, the combination of enzalutamide plus docetaxel and prednisolone in men with mCRPC who progressed on enzalutamide therapy alone significantly reduced the risk of disease progression and could serve as an effective treatment option for this subset of patients. However, because an increase in toxicity was observed with the combination of enzalutamide plus docetaxel, further investigation of this treatment regimen, particularly to identify which patients will most benefit from this approach, is still required.

Contributors

ASM, GA, and SC led the design of the study. ASM, GA, GB, GG, KM, and SC contributed to data acquisition and analysis. ASM, GA, and SC accessed and verified all the underlying raw data. All authors contributed to the interpretation of the study data and writing or critically revising at every development stage. ASM and GA contributed equally as co-lead authors. All authors had full access to the study data and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

ASM reports travel support from Janssen, Astellas Pharma, and Ipsen; honoraria from Janssen, Astellas Pharma, Ipsen, Roche, Bristol Myers Squibb, Eisai, Takeda, Pfizer, and Novartis; funding from Novartis, AstraZeneca, Janssen, Bristol Myers Squibb, and Clovis; and a consultant role with Merck Sharpe & Dohme, Bristol Myers Squibb, Janssen, Astellas Pharma, Ipsen, and Clovis, and as a speaker for Ipsen. GA reports travel support from Janssen, Astellas Pharma, Medivation, Ventana, Abbot, Bayer, ESSA Pharma, Pfizer, and Ferring; honoraria from Janssen and Astellas Pharma; funding from Janssen, Arno Therapeutics, and Innocrin; and a consultant role with Janssen, Veridex, Ventana, Astellas Pharma, Medivation, Novartis, Millennium, Abbott, ESSA Pharma, Bayer, Pfizer, AstraZeneca, and Ferring; as a speaker for Janssen, Astellas Pharma, Takeda, Sanofi, Ventan, Ipsen, AstraZeneca, and Ferring; being on the Institute of Cancer Research rewards to investors list for abiraterone; and being a member of the Institute of Cancer Research. LÀ reports honoraria from Merck Sharpe & Dohme, Pfizer, Merck, and Janssen; acting as a speaker for AstraZeneca; and participating in an advisory board for Merck Sharpe & Dohme. VBM reports honoraria from Astellas Pharma. SB reports uncompensated participation in Astellas Pharma advisory boards and steering committees; and being the President of the Italian Society for Uro-Oncology from Oct 7, 2022. ES reports travel support from Amgen, AstraZeneca, Egis, Novartis, Pfizer, and Roche; grants from Egis, Novartis, Pfizer, Pierre Fabre, and Roche; funding or honoraria from Amgen, AstraZeneca, Cancerodigest, Curio Science, Egis, Eli Lilly, Genomic Health, Gilead, high5md, Novartis, Pfizer, Pierre Fabre, and Roche; acting as a speaker for Amgen, AstraZeneca, Egis, Eli Lilly, Genomic Health, Novartis, Pfizer, Pierre Fabre, and Roche; participating in an advisory board for AstraZeneca, Egis, Eli Lilly, Genomic Health, Gilead, Novartis, Oncompass, Pfizer, Sandoz, and TLC Biopharmaceuticals; participating in clinical research for Amgen, Astellas Pharma, AstraZeneca, Bayer, Eli Lilly, Janssen, Novartis, Pfizer, Roche, and Samsung; being the chair of Stowarzyszenie Różowy Motyl; and ownership of stocks or stock options in AstraZeneca, Eli Lilly, and Pfizer. GB was an employee of Astellas Pharma during the conduct of this study and reports ownership of stocks of Clovis, Gilead Sciences, Bristol Myers Squibb, Opko Health, and Teva Pharmaceuticals. GG and KM are current employees of Astellas Pharma. SC reports honoraria from Clovis and Novartis; funding from Sanofi; acting as speaker for AstraZeneca, Pfizer, and Janssen; and a consultant role with Clovis, Astellas Pharma, Bayer,

Pfizer, Janssen, BeiGene, Remedy Bio, Telix, and Novartis. All other authors declare no competing interests. No authors received any financial compensation related to the development of this manuscript.

Data sharing

Upon request, and subject to certain criteria, conditions, and exceptions, Astellas Pharma will provide access to anonymised patient-level data from completed Astellas Pharma-sponsored phase 1–4 interventional clinical studies for products and indications approved in any country and for studies done for terminated compounds. Approval must have been granted by one of the regulatory agencies of the main regions USA, EU, or Japan. If approval is sought in only one or two regions, approval must have been granted by those agencies. If available, the following anonymised patient-level data and information will be provided for each clinical study: raw dataset, analysis-ready dataset, protocols with any amendments or addenda, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Additional data might be available upon request. Researchers can request access to anonymised participant-level data, trial-level data, and protocols from Astellas Pharma-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas Pharma criteria on data sharing see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx

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