Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic castration-resistant prostate cancer (PROSPER): an international, randomised, phase 3 trial

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Summary

Background In the phase 3, double-blind, placebo-controlled PROSPER trial of patients with non-metastatic castration-resistant prostate cancer, enzalutamide significantly improved metastasis-free survival (primary endpoint). Here, we report the results of patient-reported outcome (PRO) measures of this study.

Methods Patients ≥18 years of age with non-metastatic castration-resistant prostate cancer and a prostate-specific antigen doubling time of ≤10 months were randomised (2:1) via interactive voice/web recognition system to receive enzalutamide (160 mg/day) or placebo. Randomisation was stratified by prostate-specific-antigen-doubling time (<6 months *vs* ≥6 months) and baseline use of a bone-targeting agent (yes or no). The primary endpoint was metastasis-free survival (MFS), reported elsewhere. Exploratory endpoints, reported here, included pain progression and health-related quality of life (HRQoL), assessed by the Brief Pain Inventory Short Form (BPI-SF), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PR25), the Functional Assessment of Cancer Therapy-Prostate (FACT-P), and the EuroQoL 5-Dimensions 5-Levels health questionnaire visual analogue scale (EQ-VAS). Patients completed questionnaires at baseline, Week 17, and every 16 weeks thereafter during treatment. Pre-defined questionnaire thresholds were used to identify clinically meaningful changes. Enrollment for PROSPER is complete and follow-up continues. This trial is registered with ClinicalTrials.gov (NCT02003924).

Findings Patients were enrolled from 26 November 2013 to 28 June 2017. Median follow-up time for all patients was 18·5 months (interquartile range [IQR] 10·7–29·2 months) in the enzalutamide group and 15·1 months (IQR 7·4–25·9 months) in the placebo group. Patients randomised to receive enzalutamide or placebo had similar baseline PRO scores. Changes in

least squares (LS) mean from baseline to Week 97 favoured enzalutamide for FACT-P social/family wellbeing (0·30 *vs* −0·64; LS mean difference 0·94 [95% confidence interval (CI) 0·02–1·85]) and disfavoured enzalutamide for EORTC QLQ-PR25 hormonal treatment-related symptoms (1·55 *vs* −1·83; LS mean difference 3·38 [95% CI 1·24–5·51]); neither of these changes were clinically meaningful. Compared with placebo, enzalutamide delayed time (months) to clinically meaningful pain progression as assessed by BPI-SF pain severity (36·83 [95% CI 34·69–not yet reached (NYR) *vs* NYR]; HR 0·75 [95% CI 0·57–0·97]) and clinically meaningful symptom worsening, including EORTC QLQ-PR25 urinary symptoms (36·86 [95% CI 33·35–NYR] *vs* 25·86 [95% CI 18·53–29·47]; HR 0·58 [95% CI 0·46–0·72]) and bowel symptoms (33·15 [95% CI 29·50–NYR] *vs* 25·89 [95% CI 18·43–29·67]; HR 0·72 [95% CI 0·59–0·89]), and clinically meaningful HRQoL as assessed by FACT-P total score (22·11 [95% CI 18.63–25.86] *vs* 18·43 [95% CI 14·85–9·35]; HR 0·83 [95% CI 0·69–0·99]). Time to clinically meaningful deterioration in EORTC QLQ-PR25 hormonal treatment-related symptoms was shorter with enzalutamide (33·15 [95% CI 29·60−NYR] *vs* 36·83 [95% CI 29·47−NYR]; HR 1·29 [95% CI 1·02–1·63]).

Interpretation Patients with non-metastatic castration-resistant prostate cancer receiving enzalutamide had longer metastasis-free survival than those who received placebo while maintaining low pain levels and prostate-cancer symptom burden and high HRQoL. Enzalutamide demonstrated a clinical benefit by delaying pain progression, symptom worsening, and functional status decline compared with placebo.

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Research in context

Evidence before this study

There are limited clinical trial data on potential treatments for non-metastatic castration-resistant prostate cancer and how these treatments and the disease affect patients' health-related quality of life (HRQoL). We searched PubMed up to 1 February 2018 (with no pre-specified start date) to identify published articles in English with the following terms: (nonmetastatic castration-resistant prostate cancer) OR (non-metastatic castration resistant prostate cancer) AND (quality of life) OR (patient-reported outcomes) OR (pain) OR (symptoms). We identified 71 publications, only three of which we deemed relevant. A single-arm phase 2 study (BATMAN) evaluated bipolar androgen therapy in patients with non-metastatic castration-resistant prostate cancer. Improvements in QoL (assessed by the 36-item Short Form Health Survey, the Functional Assessment of Cancer Therapy, and the International Index of Erectile Function) were observed after 6 months of bipolar androgen therapy, complementing a reduction in prostate-specific antigen levels after 18 months of treatment. We discuss the results of our study in the context of the other two publications (patient-centred conceptual model in non-metastatic castration-resistant prostate cancer and a phase 3 study of apalutamide), highlighting any notable similarities or differences.

Added value of the study

In PROSPER, patients were generally asymptomatic and had low symptom burden and good HRQoL at baseline; these characteristics were similar to that of men of a similar age without prostate cancer. Compared with placebo, enzalutamide delayed the time to clinically meaningful pain progression and deterioration in HRQoL, except for hormonal treatment-related symptoms in which enzalutamide hastened time to deterioration versus placebo.

Further analyses are needed to determine potential associations between pain, HRQoL, and disease progression in non-metastatic castration-resistant prostate cancer.

Implications of all the available evidence

As patients with non-metastatic castration-resistant prostate cancer generally have low levels of pre-treatment pain and favourable HRQoL compared to patients with advanced disease, treatments should aim to improve clinical outcomes while maintaining pain control and HRQoL. The demonstrated efficacy, tolerability, and HRQoL profile suggest that enzalutamide represents a treatment option for patients with non-metastatic castration-resistant prostate cancer.

Introduction

Prostate cancer is the second most commonly diagnosed cancer worldwide, with over 300,000 men dying from advanced forms of the disease each year.[1] Castration-resistant prostate cancer refers to the stage when the tumour is no longer responsive to androgen-deprivation therapy, despite castration levels of testosterone.[2] Approximately one-third of patients with prostate-specific antigen (PSA) recurrence after radical treatment will develop castration-resistant prostate cancer.[3] The exact proportion of patients who enter castration-resistant prostate cancer before or after metastases have developed is not known, but it is estimated that over 50% of patients with non-metastatic castration-resistant prostate cancer will develop metastases within 3 years.[4] At this point, the disease becomes incurable; survival is estimated to be less than 18 months, although more recent studies indicate it to be approximately 30 months.[5]

Until recently, no treatments with proven efficacy had been approved for non-metastatic castration-resistant prostate cancer. Clinical guidelines recommended continuation of

androgen-deprivation therapy and, in some cases, secondary hormonal treatments (first-generation anti-androgens, ketoconazole, and oestrogens).[6-8] However, the evidence of efficacy for these secondary hormonal treatments was restricted to PSA response rates, mainly in phase 2 trials of castration-resistant prostate cancer.[9] Recently, the new-generation androgen receptor signalling inhibitors enzalutamide and apalutamide have demonstrated a clinical benefit in randomised, placebo-controlled, phase 3 trials of patients with non-metastatic castration-resistant prostate cancer.[10,11] In the PROSPER trial, enzalutamide treatment reduced the risk of metastases or death by 71% compared with placebo.[10] Similar results were obtained with apalutamide in the SPARTAN trial (72% reduction in metastasis or death *vs* placebo).[11] Based on these results, both enzalutamide and apalutamide were recently approved in the USA for non-metastatic castration-resistant prostate cancer.[12]

Overall survival and disease progression outcomes are used to evaluate new treatment approaches, but to be truly valuable to patients, new treatments should not only delay disease progression but also maintain or, ideally, improve, health-related quality of life (HRQoL) without worsening symptoms.[13] Interestingly, HRQoL has been shown to be prognostic of survival in metastatic castration-resistant prostate cancer,[14,15] a finding that was confirmed by analysis of data from two phase 3 studies of enzalutamide in patients with metastatic castration-resistant prostate cancer.[16,17] In addition, HRQoL is central to cost-utility analysis in many countries and is increasingly influencing reimbursement decisions, especially for oncology treatments.[18]

This work reports the results of the patient-reported outcome (PRO) measures used in the PROSPER trial to evaluate pain progression and the impact of prostate cancer-related symptoms on HRQoL in men with non-metastatic castration-resistant prostate cancer treated with enzalutamide.

Methods

Study design and participants

Full details on the study design, patient eligibility criteria, and conduct of the study have been reported elsewhere.[10] Briefly, PROSPER was a multinational, phase 3, randomised, double-blind, placebo-controlled study that assessed the efficacy and safety of enzalutamide versus placebo in men ≥18 years of age with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell, or small cell features. Inclusion criteria included: an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening; PSA-doubling time ≤10 months; and no prior or present evidence of metastatic disease as assessed by computed tomography (CT)/magnetic resonance imaging (MRI) for soft tissue disease and whole-body radionuclide bone scan for bone disease. For patients receiving bisphosphonates or denosumab, doses must have been stable for ≥4 weeks before randomisation. Progressive disease on androgen deprivation therapy at enrolment was defined as a minimum of three rising PSA values assessed by a local laboratory, with an interval of ≥1 week between each determination. All patients were also required to maintain androgen-deprivation therapy during the study, either by use of a gonadotropin-releasing hormone (GnRH) agonist/antagonist or a prior bilateral orchiectomy.

The following excluded patients from participation: prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer, or participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo); treatment with hormonal therapy or biologic therapy for prostate cancer (other than approved bone-targeting agents and GnRH agonist/antagonist therapy) within 4 weeks of randomisation; use of an

investigational agent within 4 weeks of randomisation; or, any concurrent disease, infection, or comorbid condition that, in the opinion of the investigator or medical monitor, interfered with the ability of the patient to participate in the trial, placed the patient at undue risk, or complicated the interpretation of data.

Written informed consent, in compliance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice, United States Code of Federal Regulations for Protection of Human Subjects, and local regulations, was obtained from each patient. The Independent Ethics Committee or Institutional Review Board for each study site reviewed the ethical, scientific, and medical appropriateness of the study before it was conducted.

Randomisation and masking

Patients were randomly assigned in a 2:1 (enzalutamide:placebo) ratio to blinded study treatment via interactive voice/web recognition system, which assigned an identification number to each patient and a blinded study-drug bottle number according to the randomisation code. Randomisation was stratified by PSA-doubling time (<6 months *vs* ≥6 months) and baseline use of a bone-targeting agent (yes or no). The investigator, study coordinator(s), patients, sponsor, and sponsor's representatives were blinded to the identity of the randomised drug assignment. Study drug assignment was to be revealed only for reasons relating to patient safety or when critical therapeutic decisions were contingent on knowing the assigned study drug. Study drug accountability was performed to document compliance with the blinded dosing regimen. Patients were asked to bring all used and unused blinded study drug, including packaging, to study visits. Unreturned capsules were considered to have been taken. Treatment compliance was measured by the number of capsules taken during the study divided by the expected number of capsules, multiplied by 100%.

Procedures

The daily dose of enzalutamide/placebo was 160 mg/day given in four capsules (40 mg each) by mouth. Patients self-administered blinded study drug once daily, with or without food, starting on Day 1. Radiographic assessments were approximately every 16 weeks; radiographic progression for soft tissue disease was defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). Patients continued study drug until the appearance of distant metastasis (metastatic bone lesions, but not soft tissue lesions) were confirmed with a second imaging modality. Radiographic metastasis was confirmed by independent central radiology review before stopping radiographic imaging.

Blinded independent central review (BICR) adjudication was not required to enter the protocol. Thus, some patients were randomised but later confirmed by BICR to have metastatic disease before randomisation. These patients were included in the intent-to-treat (ITT) population.

Patients completed PRO assessments at baseline, Week 17, and every 16 weeks thereafter while on treatment. For patients who discontinued study treatment, PRO data continued to be collected every 16 weeks during long-term follow-up for patients who attended these visits. The PROs were collected at the study sites using self-reported forms and were used to evaluate the impact of enzalutamide versus placebo on pain, functioning, prostate cancer-related symptoms, HRQoL, and overall health status.

The Brief Pain Inventory Short Form (BPI-SF) is a validated nine-item questionnaire commonly used to evaluate the severity of and interference from pain.[19] Items 3, 4, 5, and 6 evaluate ‘worst’ pain, ‘least’ pain, and ‘average’ pain in the previous 24 hours and pain ‘now’, respectively, on a scale ranging from 0 (no pain) to 10 (pain as bad as one can imagine). A composite pain severity score was calculated as an average score of these four

items. The interference score assesses the degree to which pain interferes with daily activities, from 0 (no interference) to 10 (complete interference), and is the average of seven scores: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PR25)[20] was developed to assess quality of life in patients with prostate cancer. The questionnaire includes questions to assess the impact of urinary symptoms (eight items), bowel symptoms (four items), and hormonal treatment-related symptoms (six items) over the previous week. Each item in the subscales is scored from 1 to 4 (1='Not at all', 2='A little', 3='Quite a bit', and 4='Very much'), where higher scores reflect a greater impact from symptoms.

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire (version 4)[21] reports 27 cancer-specific items in four domains (physical, social/family, emotional, and functional wellbeing) and 12 prostate cancer-specific items in the prostate cancer subscale to assess function during the previous 7 days. A summary prostate cancer pain subscale and FACT-P total are also calculated. Each item is rated on a Likert-type scale of 0 to 4 (0='Not at all', 1='A little bit', 2='Somewhat', 3='Quite a bit', and 4='Very much'), where higher scores indicate better HRQoL.

The EuroQoL 5 Dimensions 5 Levels health questionnaire visual analogue scale (EQ-VAS)[22] is a standardised questionnaire for measuring generic health status. Patients rate their current health on a vertical scale ranging from 0 (worst imaginable) to 100 (best imaginable).

We previously reported unconfirmed time to deterioration in FACT-P total score for enzalutamide and placebo.[10] Unconfirmed deterioration for total FACT-P was defined as the first time point at which a decrease of ≥10 points was observed. This paper reports the

analysis of confirmed deterioration; two consecutive time points were required for confirmed deterioration.

Outcomes

The primary endpoint was metastasis-free survival (MFS), as reported elsewhere. Secondary endpoints, also previously reported, included time to PSA progression; PSA response rate; time to the first use of subsequent antineoplastic therapy; time to first use of cytotoxic chemotherapy; overall survival; chemotherapy-free, disease-specific-free survival; QoL assessments; and safety.[10] Exploratory endpoints, reported here, included pain progression, longitudinal changes in PRO scores during the study, and time to deterioration in HRQoL.

Statistical analysis

The trial size was calculated based on estimates related to the primary endpoint of MFS, reported previously,[10] and was not specifically powered for the secondary PRO endpoints reported here. A total of 440 MFS events provided 90% power to detect a target hazard ratio (HR) of 0·72 based on a 2-sided log-rank test and an overall significance level of 0·05, and non-uniform accrual of 0·25 patients per month, per site. The trial was stopped after these thresholds were reached. A sample size of approximately 1440 patients was targeted to be randomised. The data from the cut-off date of 28 June 28 2017 was used for analyses summarised in this report.

Analyses were performed on the ITT population (i.e. all patients randomly assigned to study treatment). The completion rate at each planned assessment time point for all questionnaires was calculated as the number of patients returning evaluable forms divided by the total number of patients expected to complete the PRO assessment at the study visit. A form was defined as evaluable if it contained answers to at least the number of items required to

calculate the corresponding scale (FACT-P ≥80% of items completed; EORTC QLQ-PR25 and BPI-SF ≥50%; and 100% of EQ-5D-5L/EQ-VAS items).[19,20,22]

To estimate longitudinal changes from baseline in PRO scores, we used a mixed-effects model for repeated measures (MMRM), controlling for the following baseline covariates: PSA-doubling time; baseline use of a bone-targeting agent; age; Eastern Cooperative Oncology Group performance status; number of prior hormonal therapies; time from initial diagnosis to randomisation; and, baseline PRO score. Time was included in the model as a categorical variable and an unstructured variance-covarience matrix was used to model the covariance structure among each patient's repeated measures. MMRM analyses use all available data and assume that missing observations are missing at random. To address the possibility that missing data were not missing at random, sensitivity analyses using a pattern mixture model (PMM) were also performed.

The primary hypothesis tested the difference between LS mean change from baseline to Week 97. The time point of Week 97 was pre-specified and based on the assumed median MFS for the placebo arm in order to reduce the impact of missing data due to treatment discontinuation. The median MFS for the placebo arm was informed by historical data for this disease segment.[23,24]

Pre-defined thresholds indicating the minimal clinically important differences for patients were used to interpret group differences between the two treatment groups in the longitudinal analyses and to define pain progression, symptom worsening, and HRQoL deterioration (appendix page 12). Time to confirmed pain progression, symptom worsening, and HRQoL deterioration was defined as time from the date of randomisation to date of the first clinically meaningful deterioration in PRO scores of at least 1 threshold unit (appendix page 12) compared with the baseline score and confirmed at the next consecutive visit. Patients who

did not experience a confirmed deterioration were censored at the date of the last questionnaire completion (i.e. date of the last non-missing value). Death was not included in the definition of confirmed deterioration; therefore, patients who died and did not experience confirmed deterioration before death were censored at the last completed assessment. Patients with no baseline assessment were censored at the date of randomisation. Sensitivity analyses using unconfirmed deterioration/progression (i.e. reported at one visit) were also considered.

Time-to-event analyses were estimated using the Kaplan-Meier product limit method. Inferences for time-to-event endpoints were assessed by a log-rank test employing stratification factors at randomisation (e.g. PSA-doubling time and prior or current use of a bone-targeting agent). HRs and associated 95% CIs were determined with a stratified Cox proportional hazards model. Data were analysed with SAS version 9.3 or higher (SAS Institute Inc., Cary, NC, USA). *P*-values of less than 0.05 were judged to be significant; due to the exploratory nature of the analyses, adjustments were not made for multiple comparisons.

PROSPER is registered with ClinicalTrials.gov (NCT02003924). A copy of the trial protocol is available at http://astellasoncologyprotocols.com/PROSPER_final_protocol.

Role of the funding source

This study was funded by Astellas Pharma Inc. and Medivation LLC, a Pfizer Company, the co-developers of enzalutamide. The study sponsors developed the study design in consultation with Professor M Hussain and Dr CN Sternberg, and contributed to: collection, analysis and interpretation of data and writing of the manuscript. The corresponding author had full access to all of the data and the final responsibility to submit for publication. A professional medical writer was paid by the sponsors and assisted in the preparation of the manuscript.

Results

From 26 November 2013 to 28 June 2017, a total of 1401 patients were enrolled and randomised 2:1 to receive enzalutamide (n=933) or placebo (n=468) across 254 study centres. Evaluable baseline BPI-SF, EORTC QLQ-PR25, FACT-P, and EQ-5D-5L forms were completed by 887 (95·1%) of 933 patients in the enzalutamide group and 439 (93·8%) of 468 patients in the placebo group. Completion rates were >85% for all PRO questionnaires in both treatment groups throughout all visits. At Week 97, evaluable BPI-SF and EORTC QLQ-PR25 forms were completed by 366 (94·1%) of 389 patients expected to fill in a PRO assessment in the enzalutamide group and 96 (93·2%) of 103 patients in the placebo group. Similar numbers were observed for the FACT-P and EQ-5D-5L questionnaires: 365 (93·8%) patients in the enzalutamide group completed evaluable forms at Week 97, while 96 (93·2%) and 95 (92·2%) patients in the placebo group completed evaluable forms, respectively.

The median follow-up time for all patients based on reverse Kaplan-Meier estimation was 18·5 months IQR 10·7-29·2 months) in the enzalutamide group and 15·1 months (IQR 7·4-25·9 months) in the placebo group. Median treatment duration was longer in the enzalutamide group than the placebo group (18·4 [IQR 9.7–27·2] months *vs* 11·1 [IQR 6·4–18·7] months). In addition, a greater proportion of patients in the enzalutamide group received at least 24 months of treatment (n=321 [34·5%] *vs* n=60 [12·9%]). The primary reason for treatment discontinuation was disease progression, as reported elsewhere.[10] Of 1401 patients, 249 (17·8%) had at least one PRO assessment post-study drug discontinuation, and PRO data were collected from 194 (13·8%) patients after starting a new antineoplastic treatment (most commonly abiraterone, docetaxel, or bicalutamide).

Demographic characteristics of patients and baseline pain, prostate cancer symptoms, and functional status scores were well balanced between treatment groups, (table 1) and PRO

scores were comparable between treatment arms at baseline. A majority of patients in the enzalutamide and placebo groups were asymptomatic for pain at baseline. Mean BPI-SF scores denoted minimal pain. EORTC QLQ-PR25 scores suggested low symptom burden. FACT-P subscores, FACT-P total score, and EQ-VAS at baseline indicated relatively high functioning and good HRQoL.

BPI-SF scores remained stable (<2 points up to Week 97) in both treatment groups (figure 1A; appendix page 14). The difference between treatment arms in change from baseline in all BPI-SF scores was not statistically significant at any time point (figure 1B; appendix page 14). At Week 97, both treatment arms showed increased pain scores from baseline (≤0·85 points); no statistically significant differences were observed between the groups (table 2). Similar results were observed in the PMM analysis. Time to first confirmed pain progression was not significantly longer for patients receiving enzalutamide compared with placebo for the BPI-SF item 3 and pain interference scores, but a significantly lower hazard ratio in favour of enzalutamide was observed in the pain severity composite score (table 3; appendix page 15). Similar results were observed in the unconfirmed analysis (appendix page 13).

Mean EORTC QLQ-PR25 symptom scores remained stable over the study (figure 3A and 3C; appendix page 18). At all study visits, the difference between treatment arms in change from baseline in urinary and bowel symptoms was not statistically significant (figure 3B and 3D). At Week 97, statistically significant differences were observed in hormonal treatment-related symptoms disfavouring enzalutamide (table 2; appendix page 18); this difference did not meet the clinically meaningful threshold (appendix page 12). Similar results were observed in the PMM analysis. Compared with placebo, enzalutamide significantly delayed the time to first confirmed worsening of urinary symptoms and bowel symptoms (table 3;

figure 2B and 2C). In contrast, time to first confirmed worsening in hormonal treatment-related symptoms was shorter with enzalutamide (table 3; appendix page 15). Similar results were observed in the unconfirmed analysis, with time to deterioration significantly longer for urinary and bowel symptoms and shorter for hormonal treatment-related symptoms (appendix page 13).

FACT-P results indicated that patients in both groups maintained stable HRQoL over time (figure 4A; appendix pages 19−21). At all time points, the difference between treatment groups was not statistically significant (figure 4B). Among the other FACT-P scores, social/family wellbeing (appendix p 19) increased at Week 97. The difference was statistically significant versus placebo (table 2) but not clinically meaningful. No statistically significant or clinically meaningful differences between treatment arms were observed at any time point for the remaining FACT-P scores (appendix pages 19−21). Similar results were observed in the PMM analysis. The time to first confirmed deterioration in FACT-P scores was significantly longer for emotional wellbeing, the prostate cancer subscale, and FACT-P total score (table 3; figure 2; appendix pages 16−17), but not significantly different versus placebo for any other scores. A similar trend was observed in the unconfirmed analysis (appendix page 13).

EQ-VAS results indicated that patients who received enzalutamide maintained their health status over time, as did patients in the placebo group (figure 5A). The difference between treatment arms in change from baseline EQ-VAS was not statistically significant at any time point (figure 5B). At Week 97, patients receiving enzalutamide reported a smaller decrease from baseline in EQ-VAS compared with placebo; the difference was not statistically significant (table 2). Similar results were observed in the PMM analysis. Enzalutamide

significantly delayed time to confirmed deterioration (table 3; figure 2E) and unconfirmed deterioration (appendix page 13) versus placebo.

Discussion

The PROSPER study demonstrated that enzalutamide treatment maintains low baseline pain and high HRQoL and health status scores in patients with non-metastatic castration-resistant prostate cancer. When assessing overall differences between enzalutamide and placebo throughout the study, no clinically meaningful differences were observed. However, when assessing the time to clinically meaningful pain progression (BPI-SF pain severity) and the time to confirmed deterioration in HRQoL, significant differences in favour of enzalutamide were observed in several FACT-P and EORTC QLQ-PR25 scores (except for hormonal treatment-related symptoms) and EQ-VAS. These results, combined with the primary efficacy findings, suggest that in addition to significantly reducing the risk of metastasis (by 71%; HR 0·29; 95% CI 0·24–0·35),[10] enzalutamide also delays pain progression, symptom worsening, and HRQoL deterioration.

Patients enrolled in the PROSPER study were generally asymptomatic for pain or had low symptom burden and reported good HRQoL at baseline. For patients with prostate cancer who do not initially have substantial cancer- or disease-related symptom burden, controlling and delaying the time to symptomatic manifestations of disease are important therapeutic objectives.[13] In this regard, the PROSPER study offered an opportunity to examine the effect of an active antineoplastic therapy on HRQoL in patients not yet burdened by substantial disease-related symptoms.

Treatment with enzalutamide delayed time to clinically meaningful pain progression (BPI-SF item 3 [worst pain] and pain interference) and significantly reduced the risk of pain

progression (BPI-SF pain severity). In patients with metastatic castration-resistant prostate cancer, pain is generally reported alongside poor HRQoL and has been shown to be prognostic of overall and progression-free survival.[14,17] Although pain is not a salient symptom in patients with non-metastatic castration-resistant prostate cancer,[25] pain progression may be associated with disease progression in this population.

Significant but not clinically meaningful differences between enzalutamide and placebo were observed in the EORTC QLQ-PR25 scales. The reported time to confirmed worsening of EORTC QLQ-PR25 urinary and bowel symptoms was significantly longer with enzalutamide treatment compared with placebo. However, the frequency of reported adverse events for urinary and bowel complications (e.g. urinary tract infection, urinary retention, diarrhoea, and constipation) reported with enzalutamide treatment was similar to that with placebo, as previously reported.[10] Patients with prostate cancer have a strong preference to avoid urinary incontinence when choosing treatment,[26] and non-metastatic patients are willing to give up over a year of life to lessen the severity of treatment-related diarrhoea.[27] In patients with non-metastatic castration-resistant prostate cancer, urinary and bowel symptoms are common and negatively affect HRQoL.[25] One plausible explanation for this is that disease may progress locally, aggravating local symptoms before remission or progression. Intervening early with an active treatment may delay local progression and provide an important benefit. EORTC QLQ-PR25 hormonal treatment-related symptoms disfavoured enzalutamide with a significant but not clinically meaningful treatment difference from baseline to Week 97 and a longer time to confirmed worsening of symptoms. The score comprises six items, including hot flushes, sore or enlarged nipples/breasts, swelling in legs/ankles, weight loss, weight gain, and feeling less masculine. As previously reported,[10] the proportion of patients with these symptoms as adverse events in the PROSPER study was <5% in both treatment arms, except for hot flushes (13·0% *vs* 7·7%) and weight loss (5·9% *vs* 1·5%), which were reported by

more patients in the enzalutamide group and may account for the observed EORTC QLQ-PR25 questionnaire results.

We previously reported a similar time to deterioration in FACT-P total score for enzalutamide and placebo in the unconfirmed analysis.[10] Unconfirmed deterioration is defined as the first time point at which a decrease of ≥10 points was observed; two consecutive time points were required for the confirmed deterioration. In the confirmed analysis, reported here, enzalutamide significantly delayed time to deterioration in FACT-P total score compared with placebo. Reported differences in time to deterioration in FACT-P prostate cancer subscale and emotional wellbeing were also significantly in favour of enzalutamide. In contrast, no statistically significant or clinically meaningful differences between treatment arms were observed at any time point for the FACT-P scores, except the social/family wellbeing. Patients with non-metastatic castration-resistant prostate cancer commonly experience an array of emotional impacts, including frustration, anxiety, depression, and stress.[25] Delayed symptom worsening may allow patients to be better equipped to manage treatment- and disease-related symptoms.

In general, data for non-metastatic castration-resistant prostate cancer are scarce, as very few clinical trials have focused on this patient subgroup. SPARTAN, the only other randomised, double-blind trial in this patient population with published results to date, assessed the efficacy and safety of apalutamide relative to placebo.[11] Results of the SPARTAN study are in line with our current findings: FACT-P and EuroQoL 5 Dimensions data indicated that patients who received apalutamide in addition to androgen-deprivation therapy maintained stable overall HRQoL over time (up to 29 months).[11] Taken together, these data suggest that a second-generation androgen receptor inhibitor might provide a valuable therapeutic modality for non-metastatic castration-resistant prostate cancer. Further analyses to identify

potential correlations between objective clinical responses and surrogate markers of efficacy and specific PROs in this population could enhance our understanding of progression in castration-resistant prostate cancer, guide treatment decisions, and improve patient outcomes.

Both the PROSPER and SPARTAN trials were conducted using ^{99m}Tc bone scanning and computed tomography (CT) scanning to detect metastases. These technologies have limited diagnostic accuracy and detect metastatic deposits quite late.[28] This may change rapidly with the widespread use of new imaging technologies (NIT) such as positron emission tomography/CT with prostate specific tracers, including 18F-choline, 68Ga-PSMA, or fluciclovine F18, and whole-body MRI. Incorporating these technologies in the clinic will likely lead to the earlier diagnosis of metastases and reduced overall burden. Indeed, up to one-third of patients diagnosed by NIT will show ≤3 metastases; this offers the opportunity for metastatic-targeted treatment in place of, or in conjunction with, modern systemic therapy.[29] The implication of these NIT on the treatment landscape and clinical trial development was recently reviewed by the EORTC Imaging Group.[30]

Several previous studies show that HRQoL scores can be prognostic for survival in prostate cancer.[16,31-33] The prognostic value of HRQoL may reflect patient experience beyond conventional clinical characteristics. In the current study, evaluable OS data at the time of data cut-off were not yet mature, with only 28% of expected deaths (n=596). Further analyses exploring the association between OS and HRQoL changes will be conducted at a later date. Ultimately, the identification of prognostic HRQoL factors for survival could contribute to the modification of treatment regimens and help identify patient groups for interventions.

A key strength of our analysis was the pre-specified evaluation of the effects of enzalutamide treatment, in addition to standard of care (androgen-deprivation therapy), on HRQoL in a large randomised, double-blind, placebo-controlled clinical trial. Additionally, both generic

(BPI-SF and EuroQoL 5 Dimensions) and prostate cancer-specific (FACT-P and EORTC QLQ-PR25) questionnaires were used.

Our analysis had some limitations that should be considered when interpreting the results. While this study enrolled patients more likely to develop overt disease rapidly (PSA-doubling time of ≤10 months), further study is needed to identify whether or not patients with even more aggressive tumours at baseline (PSA-doubling time of <3 months *vs* 3−10 months) would benefit from enzalutamide with respect to HRQoL. Due to the abnormal distribution of patients with PSA-doubling time ≤10 months in the PROSPER population, the sample sizes would not be large enough to draw meaningful conclusions.

In addition, patients were enrolled in the study based on documentation submitted by sites at the time of enrolment. However, after these "eligible patients" were enrolled, BICR identified PSA-doubling time values (>10 months) for seven (0.49%) of 1401 patients that were not reported on the initial case report forms. Therefore, these seven patients became “not eligible.” However, these patients were included in the ITT population and in the PRO analyses reported herein.

Since several PRO measures were collected at different time points, multiplicity could be an issue; repeated-measures analyses were used to adjust for this over time. Patient numbers were low on some assessments, particularly beyond Week 97. Overall, a higher proportion of enzalutamide patients completed self-rating questionnaires than did placebo patients; this difference was mainly due to disease progression occurring earlier in patients given placebo, at which time the study drug was discontinued and PRO data collection continued only for patients attending clinic visits. Moreover, because some patients who continued attending clinic visits upon treatment discontinuation also initiated secondary treatments, it is possible that secondary treatments benefited placebo in the comparison against the enzalutamide arm.

However, many different secondary treatments were used, making it difficult to clearly assess their impact on HRQoL.

The absence of HRQoL data after treatment discontinuation is a well-established drawback of clinical studies incorporating PROs as secondary or exploratory endpoints. This pattern of attrition makes data interpretation difficult and can lead to overestimation of HRQoL at later time points. To address this imbalance, the MMRM analysis of longitudinal data was limited to 97 weeks; it has been shown that MMRM works well when there is unbalanced withdrawal.[34,35] Lastly, because there are no established cut points for clinically meaningful change for the EORTC QLQ-PR25, a distribution-based approach using a threshold of 0·5 standard deviations was used. While this approach is sample dependent, it has shown consistency with other methods.[36]

In conclusion, the PROSPER study demonstrated that, in addition to significantly increased MFS,[10] enzalutamide treatment maintained HRQoL while delaying clinically meaningful pain progression and symptom worsening compared with placebo.

Contributors

BT contributed to the literature search, study design, data analysis, data interpretation, and writing of the manuscript. FS contributed to the study design, data collection, data interpretation, and writing of the manuscript. MN contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript. CNS contributed to the literature search, figures, study design, data collection, data analysis, data interpretation, and writing of the manuscript. DP contributed to data interpretation. RM and KR contributed to data analysis, data interpretation, and writing of the manuscript. CI contributed to data analysis and data interpretation. GA contributed to provision of study

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Declaration of interests

Dr. Tombal reports personal fees from Astellas, during the conduct of the study; grants and personal fees from Bayer, grants and personal fees from Janssen, grants and personal fees from Sanofi, grants, personal fees and non-financial support from Ferring, personal fees from Amgen, outside the submitted work. Dr. Saad reports grants and personal fees from Astellas, grants and personal fees from Janssen, during the conduct of the study; grants and personal fees from Sanofi, grants and personal fees from Bayer, outside the submitted work. Dr. Penson reports grants and personal fees from Astellas, grants and personal fees from Medivation, during the conduct of the study; grants and personal fees from Dendreon, outside the submitted work. Dr. Hussain reports other from Genentech/Roche, other from Abbvie, other from Bayer, other from Onclive, other from Pfizer, other from PCCTC, other from AstraZeneca, outside the submitted work. In addition, Dr. Hussain has a patent SYSTEMS AND METHODS FOR TISSUE IMAGING, 3676 pending to see comments, a patent

METHOD OF TREATING CANCER pending to see comments, and a patent Dual Inhibition of MET and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases. Applicant/Proprietor Exelexis, Inc. pending to see comments. Dr. Sternberg reports personal fees from Janssen, personal fees from Astellas, personal fees from Clovis Oncology, personal fees from AstraZeneca, personal fees from Sanofi, personal fees from Bayer, personal fees from Pfizer, outside the submitted work. Dr. Morlock reports personal fees from Astellas, during the conduct of the study; personal fees from Abbot Medical Optics, personal fees from Ironwood, personal fees from Genentech, outside the submitted work. Dr. Ramaswamy reports other from Pfizer Inc, during the conduct of the study; other from Johnson & Johnson, outside the submitted work. Dr. Ivanescu reports I am an employee of IQVIA which received funding from Astellas to conduct the statistical analyses for this work under consultancy contract. Dr. Attard reports personal fees and non-financial support from Astellas, personal fees and non-financial support from Medivation/Pfizer, during the conduct of the study, grants, personal fees, and non-financial support from Janssen, personal fees from Veridex, personal fees and non-financial support from Roche/Ventana, personal fees from Novartis, personal fees from Millenium Pharmaceuticals, personal fees and non-financial support from Abbott Laboratories, personal fees and non-financial support from Essa Pharmaceuticals, personal fees and non-financial support from Bayer Healthcare Pharmaceuticals, personal fees from Takeda, personal fees from Sanofi-Aventis, grants from AstraZeneca, grants from Arno Therapeutics, grants from Innocrin Pharma, and is on The Institute of Cancer Research (ICR) rewards to inventors scheme for abiraterone acetate, outside the submitted work.

Data sharing

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the USA and/or EU or (2) in programmes that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Table 1: **Baseline characteristics and PRO scores**

Category	**Enzalutamide (n=933)**		**Placebo (n=468)**	
	n*		n*	
Median age, years (range)	933	74 (50–95)	468	73 (53–92)
Age group				
<75 years	933	489 (52·4%)	468	267 (57·1%)
≥75 years		444 (47·6%)		201 (43·0%)
Geographical region				
Europe	933	458 (49·1%)	468	232 (49.6%)
North America		141 (15·1%)		63 (13·5%)
Other		334 (35.8%)		173 (37·0%)
Disease status†				
Non-metastatic	933	910 (97·5%)	468	454 (97·0%)
Metastatic		23 (2·5%)		14 (3·0%)
ECOG performance status				
0	932	747 (80·2%)	467	382 (81·8%)
1		185 (19·9%)		85 (18·2%)
PSA doubling time§				
<6 months	933	719 (77·1%)	468	361 (77·1%)
≥6 months		214 (22·9%)		107 (22·9%)

Prior/current use of bone-targeting agents[§]				
Yes	933	96 (10·3%)	468	49 (10·5%)
No		837 (89·7%)		419 (89·5%)
Pain at baseline (item 3 of BPI-SF)				
Asymptomatic (score: 0)	887	580 (65·4%)	439	303 (69·0%)
Mildly symptomatic (score: 1–4)		206 (23·2%)		101 (23·0%)
Moderately symptomatic (score: 5–6)		72 (8·1%)		20 (4·6%)
Severely symptomatic (score: 7–10)		29 (3·3%)		15 (3·4%)
BPI-SF scores, mean (SD)				
Item 3: pain at its worst	887	1·24 (2·09)	439	1·01 (1·94)
Pain severity	887	0·93 (1·50)	439	0·71 (1·35)
Pain interference	887	0·75 (1·47)	439	0·59 (1·43)
EORTC QLQ-PR25, mean (SD)				
Bowel symptoms and function	884	5·14 (8·39)	439	4·65 (7·70)
Hormonal treatment-related symptoms	884	14·92 (12·50)	439	15·79 (13·30)
Urinary symptoms and problems	884	20·69 (17·55)	439	20·02 (17·68)
FACT-P, mean (SD)				
Physical wellbeing	887	25·02 (3·32)	439	25·28 (3·23)
Functional wellbeing	887	19·99 (5·17)	439	20·14 (5·15)
Emotional wellbeing	887	19·18 (3·54)	439	19·16 (3·64)

Social/family wellbeing	887	20·69 (5·57)	439	20·73 (5·12)
Prostate cancer subscale	887	34·67 (6·13)	439	35·47 (5·73)
Prostate cancer pain subscale	887	13·16 (3·44)	439	13·56 (3·15)
FACT-P total score	887	119·54 (17·75)	439	120·79 (16·73)
EQ-5D-5L, mean (SD)				
EQ-VAS	884	76·17 (16·92)	439	77·53 (15·97)

Data are n (%) unless specified otherwise. BPI-SF=Brief Pain Inventory Short Form; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=European Quality of Life 5 Dimensions 5 Levels health questionnaire; EQ-VAS=EuroQoL 5 Dimensions 5 Levels health questionnaire visual analogue scale; FACT-P=Functional Assessment of Cancer Therapy-Prostate; PRO=patient-reported outcome; PSA=prostate-specific antigen; SD=standard deviation.

*Number of patients with non-missing data. Percentages are calculated based on the number of patients with non-missing data.

†Patients may have been determined by the blinded independent central review to be metastatic following entry into the study.

§Data were collected from Interactive Voice/Web Recognition System (IxRS); previously published data[10] were collected from case report forms.

Table 2: **Mean change in PRO scores from baseline to Week 97 (MMRM)**

Questionnaire	**LS mean (95% CI)**		**LS mean difference (95% CI)**	***P*-value**
	Enzalutamide	Placebo	Enzalutamide *vs* placebo	
BPI-SF				
Item 3: pain at its worst	0·52 (0·27 to 0·77)	0·73 (0·31 to 1·16)	−0·21 (−0·66 to 0·24)	0.353
Pain severity	0·49 (0·30 to 0·69)	0·55 (0·23 to 0·87)	−0·06 (−0·40 to 0·29)	0.746
Pain interference	0·65 (0·45 to 0·84)	0·85 (0·53 to 1·16)	−0·20 (−0·53 to 0·13)	0.237
EORTC QLQ-PR25				
Bowel symptoms and function	2·28 (1·34 to 3.23)	1·42 (−0·14 to 2·99)	0·86 (−0·80 to 2·52)	0.309
Hormonal treatment-related symptoms	1·55 (0·26 to 2·83)	−1·83 (−3·86 to 0·20)	3·38 (1·24 to 5·51)	0.002
Urinary symptoms and problems	3·07 (1·31 to 4·83)	3·93 (1·08 to 6·77)	−0·86 (−3·89 to 2·18)	0.579
FACT-P				
Physical wellbeing	−2·26 (−2·71 to −1·81)	−2·00 (−2·71 to −1·29)	−0·26 (−1·00 to 0·49)	0.499
Social/family wellbeing	0·30 (−0·25 to 0·85)	−0·64 (−1·51 to 0·24)	0·94 (0·02 to 1·85)	0.045
Emotional wellbeing	−0·24 (−0·63 to 0·14)	−0·58 (−1·19 to 0·03)	0·34 (−0·30 to 0·98)	0.303
Functional wellbeing	−2·44 (−2·98 to −1·90)	−2·57 (−3·44 to −1·70)	0·13 (−0·78 to 1·05)	0.774

Prostate cancer subscale	−2·61 (−3·24 to −1·99)	−3·32 (−4·31 to −2·32)	0·70 (−0·35 to 1·75)	0.189
Prostate cancer pain subscale	−0·93 (−1·28 to −0·59)	−1·06 (−1·62 to −0·51)	0·13 (−0·46 to 0·71)	0.668
FACT-P total	−7·17 (−8·98 to −5·35)	−9·20 (−12·05 to −6·36)	2·04 (−0·97 to 5·04)	0.184
EQ-5D-5L				
EQ-VAS	−4·57 (−6·36 to −2·77)	−5·29 (−8·17 to −2·41)	0·72 (−2·30 to 3·75)	0.639

BPI-SF=Brief Pain Inventory Short Form; CI=confidence interval; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=European Quality of Life 5 Dimensions 5 Levels health questionnaire; EQ-VAS=EuroQoL 5 Dimensions 5 Levels health questionnaire visual analogue scale; FACT-P=Functional Assessment of Cancer Therapy-Prostate; LS=least squares; MMRM=mixed-model repeated measures; PRO=patient-reported outcome. A negative number contrast favours enzalutamide over placebo for BPI-SF scores and bowel symptoms and function, hormonal treatment-related symptoms, and urinary symptoms and problems, while a positive number contrast favours enzalutamide over placebo for FACT-P scores, and EQ-VAS.

Table 3: **Time to confirmed pain progression and HRQoL deterioration**

Questionnaire	**Median time, months (95% CI)**		**HR (95% CI) Enzalutamide *vs* placebo**	***P*-value**
	Enzalutamide	Placebo		
BPI-SF				
Item 3	34·69 (29·73–36·86)	30·52 (22·11–NYR)	0·82 (0·66–1·03)	0.085
Pain severity	36·83 (34·69–NYR)	NYR	0·75 (0·57–0·97)	0.028
Pain interference	33·15 (29·54–NYR)	30·52 (22·11–NYR)	0·94 (0·76–1·18)	0.602
EORTC QLQ-PR25				
Bowel symptoms and function	33·15 (29·50–NYR)	25·89 (18·43–29·67)	0·72 (0·59–0·89)	0.002
Hormonal treatment-related symptoms	33·15 (29·60–NYR)	36·83 (29·47–NYR)	1·29 (1·02–1·63)	0.035
Urinary symptoms and problems	36·86 (33·35–NYR)	25·86 (18·53–29·47)	0·58 (0·46–0·72)	<0.001
FACT-P				
Physical wellbeing	18·56 (16·82–22·18)	19·35 (18·33–25·79)	1·15 (0·96–1·38)	0.135
Social/family wellbeing	34·04 (29·60–NYR)	29·50 (25·79–NYR)	0·87 (0·71–1·08)	0.219
Emotional wellbeing	36·73 (33·12–38·21)	29·47 (22·18–33·15)	0·69 (0·55–0·86)	<0.001
Functional wellbeing	18·60 (18·20–22·14)	18·37 (14·78–18·66)	0·94 (0·79–1·13)	0.524
Prostate cancer subscale	18·43 (14·85–18·66)	14·69 (11·07–16·20)	0·79 (0·67–0·93)	0.004

Prostate cancer pain subscale	25·76 (22·11–29·47)	22·11 (18·40–30·52)	0·94 (0·78–1·14)	0.521
FACT-P total	22·11 (18·63–25·86)	18·43 (14·85–9·35)	0·83 (0·69–0·99)	0.037
EQ-5D-5L				
EQ-VAS	22·11 (18·46–25·66)	14·75 (11·07–18·17)	0·75 (0·63–0·90)	0.001

BPI-SF=Brief Pain Inventory Short Form; CI=confidence interval; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=European Quality of Life 5 Dimensions 5 Levels health questionnaire; EQ-VAS=EuroQoL 5 Dimensions 5 Levels health questionnaire visual analogue scale; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HR=hazard ratio; HRQoL=health-related quality of life; NYR=not yet reached.

Figure legends

Figure 1: **Patient-reported changes in BPI-SF item 3 score by (A) study visit and (B)* treatment difference in change from baseline (MMRM)**

BPI-SF=Brief Pain Inventory Short Form; CI=confidence interval; LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation.

*Difference was not statistically significant or clinically meaningful.

Figure 2: **Kaplan-Meier estimates of time to confirmed pain progression and HRQoL deterioration: (A) BPI-SF item 3, (B) EORTC QLQ-PR25 urinary symptoms, (C) EORTC QLQ-PR25 bowel symptoms, (D) FACT-P total score, and (E) EQ-VAS**

BPI-SF=Brief Pain Inventory Short Form; CI=confidence interval; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS=EuroQoL 5 Dimensions 5 Levels health questionnaire visual analogue scale; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HR=hazard ratio.

Figure 3: **Patient-reported changes in EORTC QLQ-PR25 scores by study visit and treatment difference in change from baseline (MMRM) for urinary symptoms (A and B,* respectively) and bowel symptoms (C and D,* respectively)**

CI=confidence interval; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation.

*Difference was not statistically significant or clinically meaningful.

Figure 4: **Patient-reported changes in FACT-P total score by (A) study visit and (B)* treatment difference in change from baseline (MMRM)**

CI=confidence interval; FACT-P=Functional Assessment of Cancer Therapy-Prostate; LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation.

*Difference was not statistically significant or clinically meaningful.

Figure 5: **Patient-reported changes in EQ-VAS by (A) study visit and (B)* treatment difference in change from baseline (MMRM)**

CI=confidence interval; EQ-VAS=EuroQoL 5 Dimensions 5 Levels health questionnaire visual analogue scale; LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation.

*Difference was not statistically significant or clinically meaningful.

Figure 1A and B

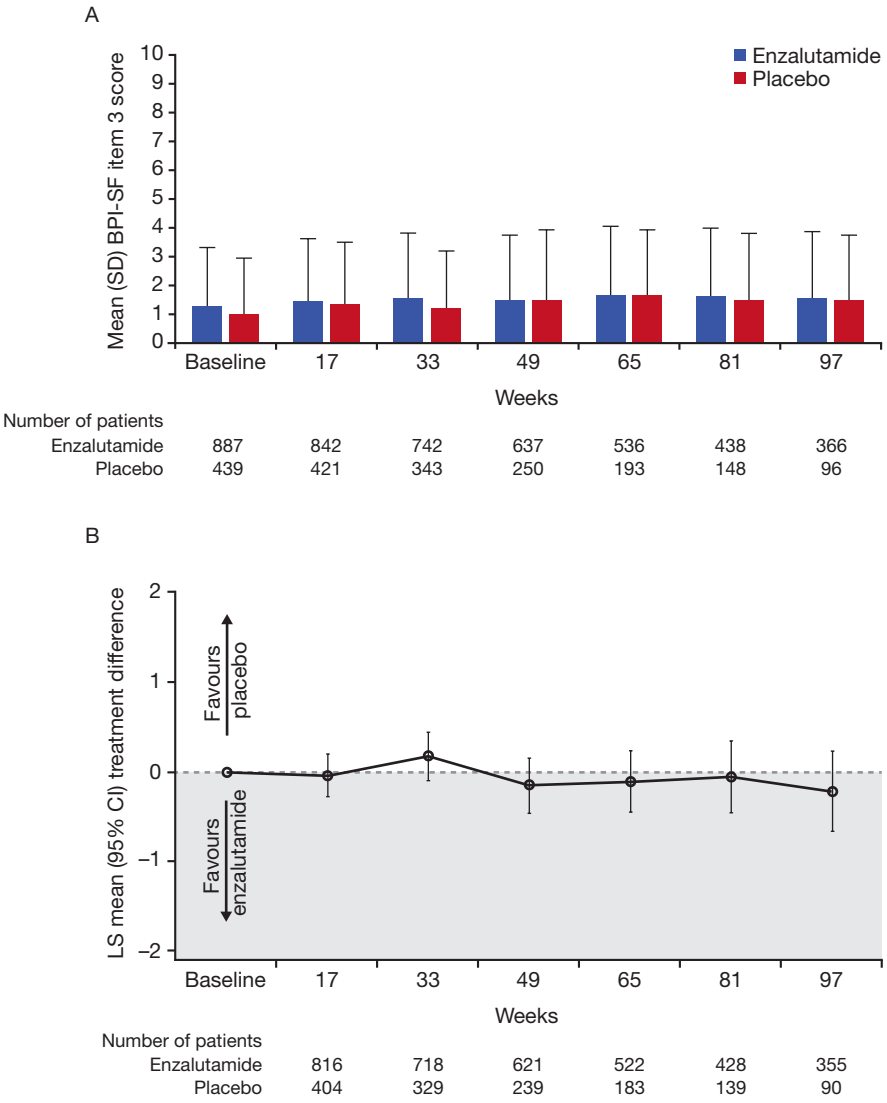
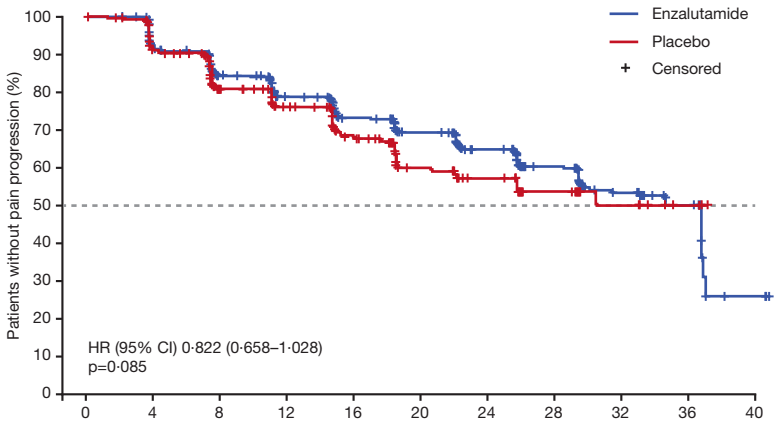


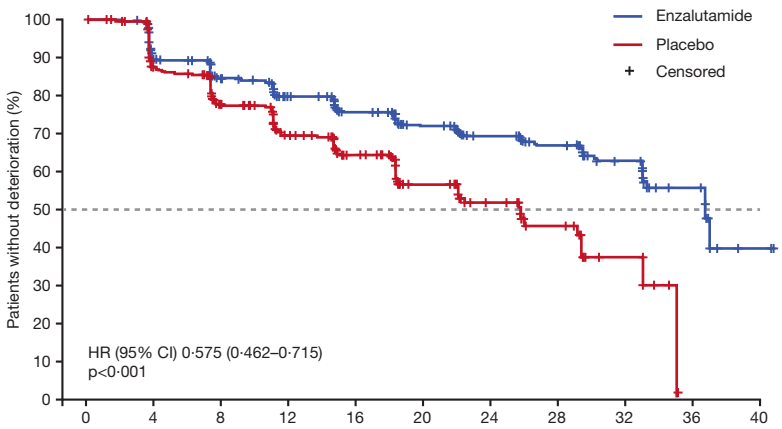
Figure 2A-E

A



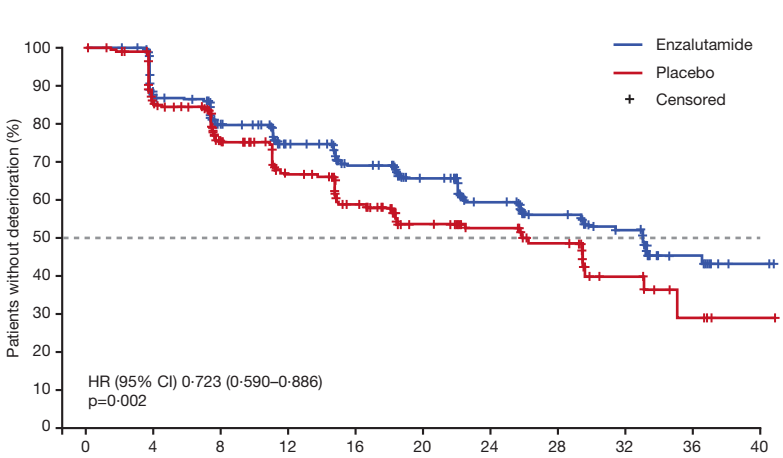
Number at risk (number censored)											
Enzalutamide	933 (0)	699 (168)	572 (241)	451 (325)	364 (382)	287 (442)	209 (503)	140 (559)	73 (613)	20 (664)	3 (675)
Placebo	468 (0)	328 (106)	224 (175)	170 (217)	120 (251)	72 (287)	53 (303)	28 (325)	14 (338)	3 (349)	0 (352)

B



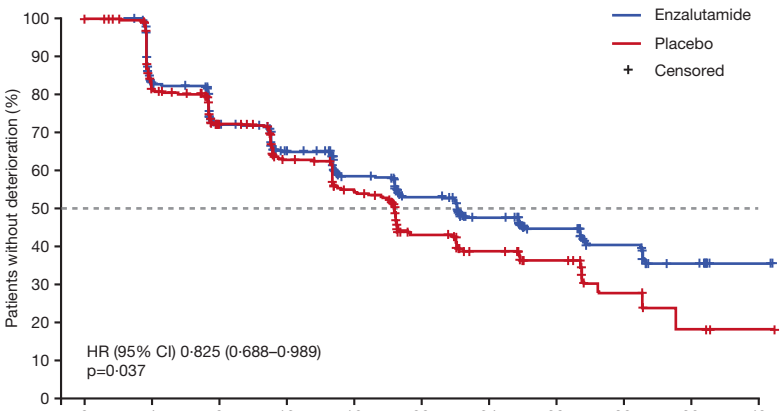
Number at risk (number censored)											
Enzalutamide	933 (0)	685 (163)	565 (245)	448 (333)	361 (399)	282 (462)	216 (519)	156 (572)	80 (641)	26 (688)	2 (708)
Placebo	468 (0)	308 (110)	214 (173)	154 (212)	107 (249)	66 (279)	46 (294)	23 (313)	8 (325)	0 (331)	

C



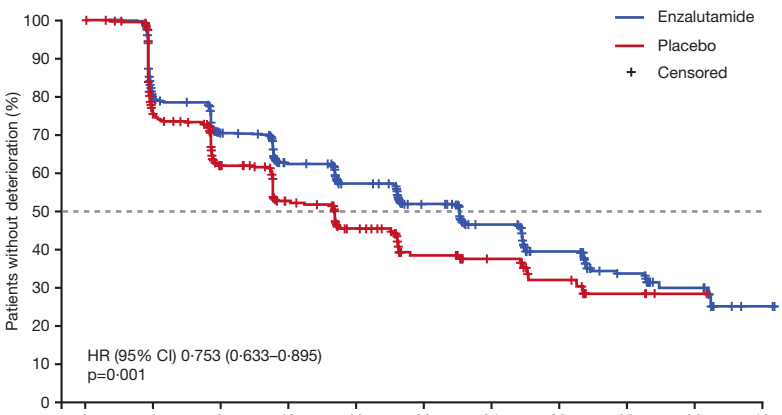
Number at risk (number censored)											
Enzalutamide	933 (0)	669 (164)	538 (238)	429 (316)	343 (371)	273 (426)	201 (475)	139 (527)	76 (582)	21 (630)	2 (648)
Placebo	468 (0)	307 (103)	218 (160)	155 (200)	106 (233)	66 (265)	51 (279)	30 (297)	14 (309)	4 (317)	1 (320)

D



Number at risk (number censored)											
Enzalutamide	933 (0)	645 (152)	506 (207)	396 (270)	309 (319)	234 (368)	164 (416)	108 (463)	61 (502)	14 (543)	2 (555)
Placebo	468 (0)	298 (97)	208 (156)	152 (187)	107 (214)	62 (239)	44 (251)	26 (267)	11 (278)	3 (284)	1 (286)

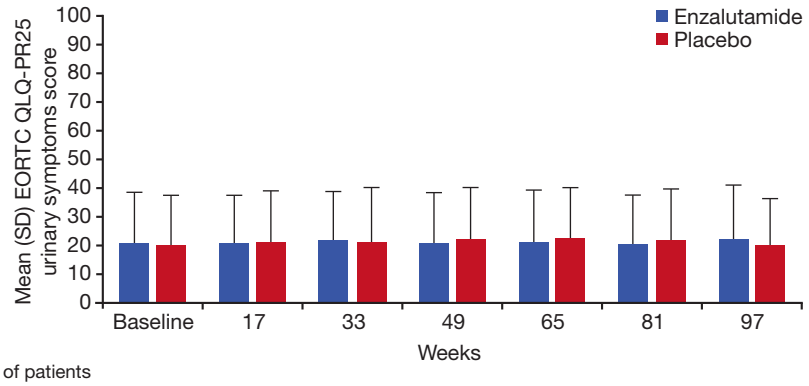
E



Number at risk (number censored)											
Enzalutamide	933 (0)	617 (150)	486 (213)	374 (272)	300 (317)	224 (367)	156 (414)	101 (448)	50 (488)	20 (514)	2 (530)
Placebo	468 (0)	280 (91)	184 (141)	128 (171)	81 (202)	48 (225)	37 (235)	20 (248)	8 (258)	1 (265)	0 (266)

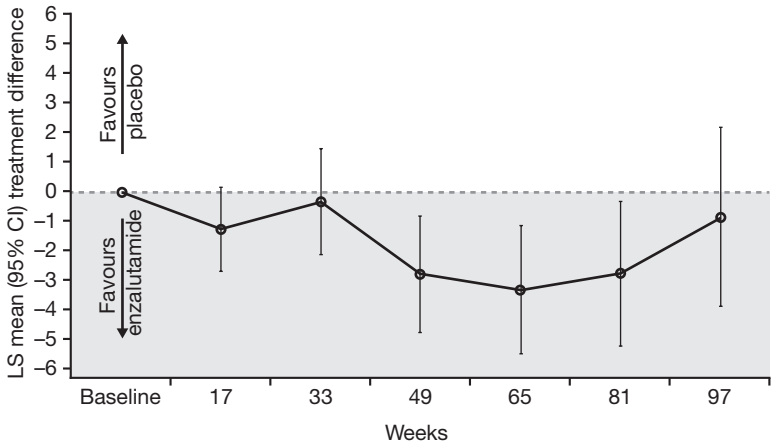
Figure 3A-D

A



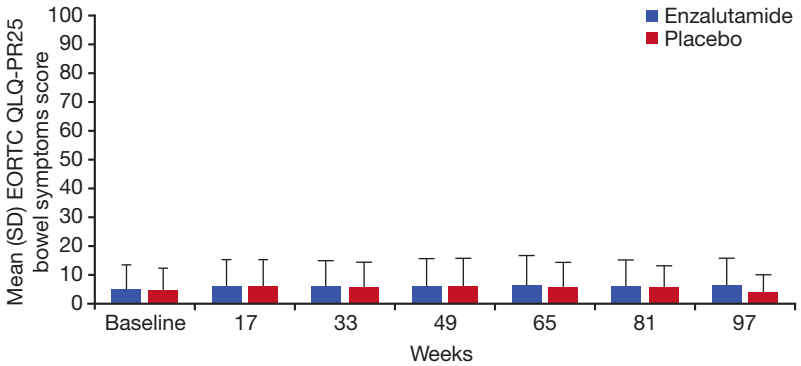
Number of patients							
Enzalutamide	884	839	737	635	536	434	365
Placebo	439	419	341	250	193	148	95

B



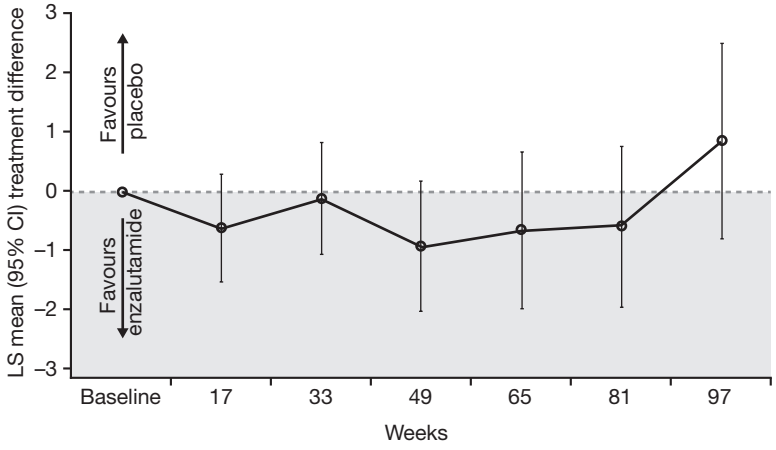
Number of patients						
Enzalutamide	811	711	618	520	422	353
Placebo	402	328	239	183	139	89

C



Number of patients							
Enzalutamide	884	839	737	635	536	434	365
Placebo	439	419	341	250	193	148	95

D



Number of patients						
Enzalutamide	811	711	618	520	422	353
Placebo	402	328	239	183	139	89

Figure 4A and B

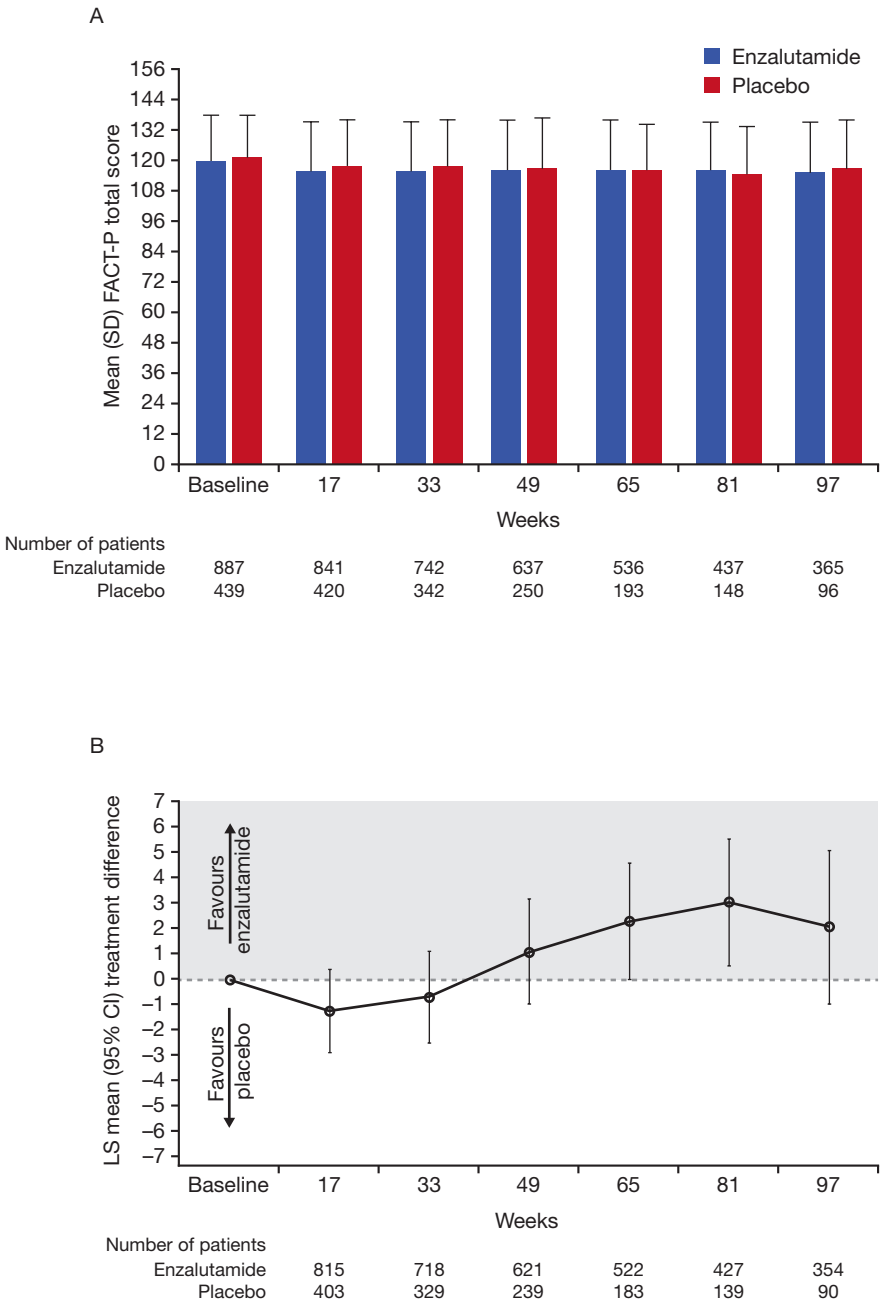
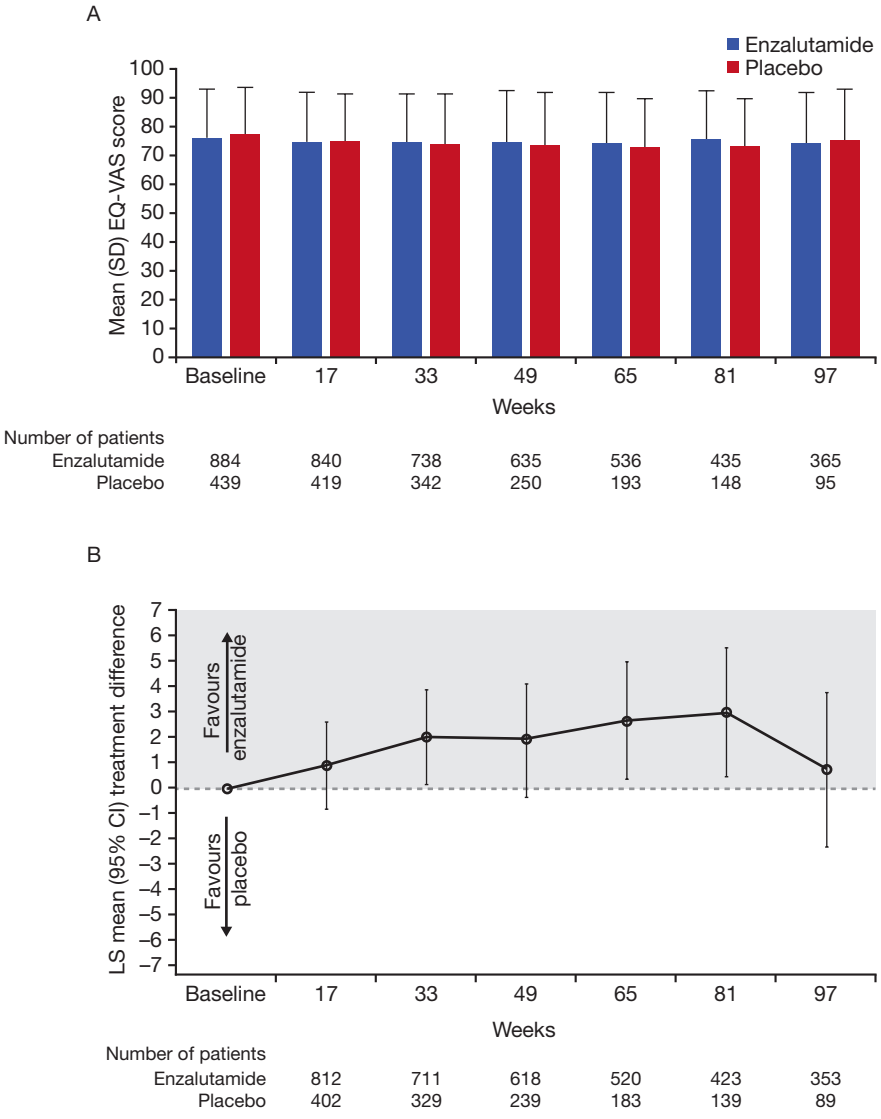


Figure 5A and B



Supplementary appendix

Table of Contents

PROSPER patient recruitment sites, principal investigators and patients recruited by site*

Country	Site #	Study centre	Principal investigator	# patients randomised
Denmark	421	Herlev Hospital	Per Rathenborg	40
Brazil	992	Hospital das Clinicas da Faculdade de Ciencias Medicas da UNICAMP	Ubirajara Ferreira	22
Canada	110	Cross Cancer Institute	Michael Kolinsky	19
Brazil	988	Centro de Estudos e Pesquisas em Hematologia e Oncologia (CEPHO)	Daniel Cubero	18
Ukraine	791	Kyiv City Clinical Hospital #3, Department of Urology	Petro Ivashchenko	18
Denmark	426	Vejle Sygehus	Bettina Norby	17
Italy	459	Laboratorio Farmaci Antiblastici; U.O. Oncologia Medica; UO Radiologia	Ugo De Giorgi	17
Denmark	420	Copenhagen Prostate Cancer Center	Peter Iversen	15
Greece	280	General Hospital of Athens "Alexandra", Therapeutic Clinic	Eleni Efstathiou	15
Greece	286	General Hospital "Papageorgiou", B' Univ. Urology Clinic	Evangelos Ioannidis	14
Korea	870	Severance Hospital, Yonsei University Health System	Young Deuk Choi	14
Poland	550	Wojewodzki Szpital Specjalistyczny im. Janusza. Korczaka	Jacek Olubiec	14
Slovakia	705	IZOTOPCENTRUM, s.r.o.; Jessenjus-diagnosticke centrum, a.s.; UROEXAM spol. s r.o. urologicka ambulancia	Jozef Marko	14
Canada	108	CHU de Quebec	Louis Lacombe	13
Ukraine	793	CI Dnipropetrovsk I.I. Mechnykov RCH, Department of Urology #2, SI Dnipropetrovsk Medical Academy of MoH of Ukraine	Viktor Stus	13
Australia	804	Austin Health, Austin Hospital Olivia Newton-John Cancer & Wellness Centre	Andrew Weickhardt	12
Canada	113	London Regional Cancer Program & Urology Research - Victoria Hospital, London Health Sciences Centre (LHSC)	Eric Winquist	12
Finland	432	Helsingin yliopistollinen keskussairaala, Meilahden sairaala	Kimmo Taari	12
France	315	Institut Bergonie & Institut Bergonie – Centre regional de Lutte contre le Cancer	Guilhem Roubaud	12
Korea	872	Samsung Medical Center	Hyun Moo Lee	12
Russian Federation	771	SBEI HPE "First Pavlov State Medical University of St. Petersburg" & Saint-Petersburg State Budgetary Healthcare Institution "Hospital for Veterans of War"	Salman Al-Shukri	12
United States	140	Urology San Antonio Research	Daniel Saltzstein	12
Australia	814	Sunshine Hospital	Shirley Wong	11
Australia	839	Icon Cancer Care; Icon Cancer Centre Southport; Icon Cancer Foundation	Michael Slancar	11
Brazil	987	Hospital de Clinicas de Porto Alegre	Pedro Liedke	11
China	526	Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine	Jun Qi	11
France	300	Institut Gustave Roussy	Karim Fizazi	11
Korea	871	Asan Medical Center	Choung-Soo Kim	11

New Zealand	844	Greenlane Clinical Centre; Regional Blood and Cancer Services	Peter Fong	11
United Kingdom	652	University College Hospitals NHS Trust, University College London Hospital & University College Hospital Macmillan Cancer Centre	Heather Payne	11
Canada	105	University Health Network- Princess Margaret Cancer Centre	Neil Fleshner	10
China	519	Fudan University Shanghai Cancer Center	Dingwei Ye	10
France	302	Centre Leon Berard	Aude Flechon	10
Sweden	722	Apoteket AB Kliniska Provningar Molnlycke; Klinisk Fysiologi Sahlgrenska Universitetssjukhuset; Urologmottagningen Kliniska Provningsenheten	Jan-Erik Damber	10
Turkey	384	Istanbul Universitesi Cerrahpasa Tip Fakultesi	Mustafa Ozguroglu	10
United Kingdom	662	University Hospitals Bristol NHS Foundation Trust - Bristol Haematology & Oncology Centre & Bristol Royal Infirmary	Amit Bahl	10
Canada	112	Centre Hospitalier de l'Universite de Montreal	Fred Saad	9
China	518	Jiangsu Cancer hospital	Qing Zou	9
Finland	430	Tampereen yliopistollinen Sairaala	Teuvo Tammela	9
Poland	552	Uniwersyteckie Centrum Kliniczne	Jacek Jassem	9
Spain	624	Hospital Clinico Universitario de Santiago de Compostela Servicio de Oncologia Radioterapica	Antonio Caamano	9
Taiwan	891	Taichung Veterans General Hospital	Yen-Chuan Ou	9
United Kingdom	656	Belfast Health and Social Care Trust, Northern Ireland Cancer Trials Centre, Belfast City Hospital	Suneil Jain	9
Australia	820	Sydney Adventist Hospital	Gavin Marx	8
Australia	831	Calvary Mater Newcastle	Antonino Bonaventura	8
Australia	834	The Canberra Hospital	Paul Craft	8
Brazil	982	Liga Paranaense de Combate ao cancer / Hospital Erasto Gaertner	Fabricio Martinelli De Oliveira	8
Brazil	983	Associacao Hospital de Caridade de Ijui	Fabio Andre Franke	8
Brazil	985	Hospital da Cidade de Passo Fundo	Nicolas Lazaretti	8
Brazil	989	CLINIONCO - Clinica de Oncologia de Porto Alegre Ltda.	Ernani Rhoden	8
Brazil	993	Hospital Sao Rafael	Alvaro Edson Lessa	8
Chile	950	Centro de Investigaciones Clinicas; Instituto Oncologico Ltda.	Pablo Gonzalez Mella	8
France	309	Clinique Victor Hugo	Eric Voog	8
Italy	478	Fondazione IRCCS Istituto Nazionale dei Tumori (Farmacia Studi Clinici e Sperimentali, S.C. Diagnostica Radiologica 2, S.C. di Oncologia Medica 1)	Giuseppe Procopio	8
New Zealand	845	Palmerston North Hospital	Claire Hardie	8
Slovakia	702	Bratislavske radiodiagnosticke centrum, a.s.; CUIMED, s.r.o., Urologicka ambulancia; GAMMALAB, spol. s.r.o., Oddelenie nuklearnej mediciny Poliklinka Druzba	Frederico Goncalves	8
Sweden	720	Apoteket AB Kliniska Provningar Molnlycke; Diagnostiskt centrum for bild- och	Anders Bjartell	8

		funktionsmedicin Skanes Universitetssjukhus, Malmo; Urologiska Kliniken		
Thailand	920	Songklanagarind Hospital Div of Uro, Dept of Sur, Fac of Med, Prince of Songkla University	Choosak Pripatnanont	8
Ukraine	794	CI Zaporizhzhia Regional Clinical Hospital, Dep. Of Urology, Institution Zaporizhzhia Medical Academy of Post- graduate Education	Olexiy Lyulko	8
Ukraine	797	Central City Clinical Hospital, City Oncological Center, State Higher Educational Institution Uzhgorod National University	Yevhen Hotko	8
United Kingdom	651	The Christie NHS Foundation Trust, Christie Hospital	Paul Elliott	8
United Kingdom	654	University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Queen Elizabeth Hospital	Nicholas James	8
United States	138	Michigan Institute of Urology	Kenneth Kernen	8
United States	139	Vanderbilt University Medical Center, Dept. of Urologic Surgery & The Urologic Clinic	David Penson	8
Australia	822	APHS Pharmacy; Adelaide Cancer Centre; Ashford Cancer Centre Research; Cancer Care SA Pty Ltd	Francis Parnis	7
Australia	824	Cabrini Hospital - Brighton & Malvern and Education & Research Project	Jeremy Shapiro	7
Australia	840	HPS Pharmacies;Tasman Oncology Research Pty Ltd	Andrew Hill	7
Canada	102	Vancouver Prostate Centre - Gordon & Leslie Diamond Health Care Centre	Martin Gleave	7
China	513	Peking University Third Hospital	Lulin Ma	7
Denmark	423	Aarhus University Hospital	Michael Borre	7
France	314	Hopital Europeen Georges Pompidou	Stephane Oudard	7
France	322	Hopitaux Universitaires de Strasbourg - Hopital Civil Service Oncologie & Hematologie	Philippe Barthelemy	7
Slovakia	706	Institut nuklearnej a molekularnej mediciny; Vychodoslovensky onkologicky ustav, a.s. Oddelenie radiacnej onkologie & Radiologicke oddelenie	Pavol Dubinsky	7
Spain	623	Hospital Universitario 12 de octubre	Alfredo Rodriguez Antolin	7
Taiwan	886	China Medical University Hospital	His-Chin Wu	7
Taiwan	887	National Taiwan University Hospital	Yeong-Shiau Pu	7
United Kingdom	657	Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital	Danish Mazhar	7
United States	134	Clinical Research Solutions; SouthWest Urology	Lawrence Gervasi	7
Australia	801	Icon Cancer Care; Icon Cancer Care Chermside; Icon Cancer Care South Brisbane; Icon Cancer Care Wesley; Icon Cancer Foundation; River City Pharmacy - APHS	Paul Austin Vasey	6
Australia	802	The Tweed Hospital	Ehtesham Abdi	6
Australia	807	Westmead Hospital	Howard Gurney	6
Australia	823	Monash Cancer Centre; Monash Medical Centre; Southern Urology	David Pook	6
China	517	Peking University First Hospital	Jie Jin	6
France	308	Institut de Cancerologie de I'Ouest - Rene Gauducheau	Emmanuelle Bompas	6
France	311	Institut de Cancerologie de l'Ouest - Paul Papin	Remy Delva	6

Greece	281	University General Hospital of Larissa, Urology Department	Vassilios Tzortzis	6
Greece	282	University General Hospital of Patras, Oncology Department, Internal Medicine Clinic	Haralabos Kalofonos	6
Hong Kong	846	Prince of Wales Hospital	Chi Fai NG	6
Italy	475	Istituto Oncologico Veneto (IOV) (Farmacia, IRCCS UOC Oncologia Medica 1, Medicina Nucleare, UOC Radiodiagnostica Oncologica)	Umberto Basso	6
Italy	477	Ospedale Santa Chiara (U.O. Farmacia, U.O. Radiologia, U.O. di Oncologia Medica)	Orazio Caffo	6
Italy	479	AUSL di Ravenna (Servizio di Farmacia, Servizio di Radiologia, U.O. di Oncologia); Ospedale Civile Degli Infermi (U.O. di Oncologia, U.O. di Radiologia); Ospedale Civile Umberto I (U.O. di Oncologia, U.O. di Radiologia)	Francesco Carrozza	6
Poland	561	Lexmedica	Zenona Jablonska	6
Serbia	712	Clinical Center "Dr Dragisa Misovic -Dedinje", Clinic of Urology	Dejan Kojic	6
Slovakia	700	Univerzitna nemocnica Martin Klinika nuklearnej mediciny	Jan Kliment	6
Slovakia	704	Alfamedis, s.r.o.; MILAB s.r.o., UROCENTRUM	Ivan Mincik	6
Spain	609	Hospital Universitario Parc Tauli	Enrique Gallardo Diaz	6
Taiwan	892	Kaohsiung Veterens General Hospital	Tong-Lin Wu	6
Taiwan	895	Chang-Gung Memorial Hospital at Linkuo	Yung-Chang Lin	6
United Kingdom	659	Oxford university Hospitals NHS Trust, Churchill Hospital	Andrew Protheroe	6
United States	014	Duke University Medical Center Duke Cancer Center Cary; Duke Women's Cancer Care Raleigh; Duke Raleigh Hospital	William Berry	6
United States	018	Adult and Pediatric Urology, P.C; GU Research Network	Luke Nordquist	6
United States	130	University of Michigan Health System	David Smith	6
United States	147	Kansas City Urology Care, PA	Son Nguyen	6
Argentina	908	Centro de Urologia	Luis Montes de Oca	5
Australia	827	Australian Clinical Trials SAN Clinic	Henry Woo	5
Australia	835	Princess Alexandra Hospital	Elizabeth McCaffrey	5
Brazil	981	Fundacao Dr. Amaral Carvalho	Ederson Mattos	5
Canada	107	Sunnybrook Health Sciences Centre	Laurence Klotz	5
China	529	Wuxi People's Hospital	Qiang Hu	5
China	536	Chongqing Cancer Hospital	Hong Luo	5
Finland	433	Docrates Syopasairaala	Timo Joensuu	5
France	310	Institut Curie	Philippe Beuzeboc	5
France	313	CHU Poitiers - Hopital la Milertie	Jean-Marc Tourani	5
France	336	Centre Paul Strauss; Clinique Sainte Anne; Societe MIM, Clinique Sainte Anne	Youssef Tazi	5
Italy	450	Azienda Ospedaliera S. Camillo Forlanini, UOC per il governo clinico in Oncologia Medica; Farmacia, Ospedale Forlanini	Cora Sternberg	5

Korea	875	Gangnam Severance Hospital, Yonsei University Health System	Byung-Ha Chung	5
Netherlands	505	Catharina Ziekenhuis	Michel De Wildt	5
Russian Federation	770	Federal State Budgetary Institution "N.N. Blokhin Russian Cancer Research Center"	Vsevolod Matveev	5
Spain	612	Hospital Clinic de Barcelona	Antonio Alcaraz Asensio	5
Spain	627	Hospital Universitario de la Princesa	Almudena Zapatero	5
Sweden	725	Apoteket AB Kliniska Provningar Molnlycke; Nuklearmedicin, BDC; Urologmottagningen	Ulf Norming	5
Ukraine	795	CHI V.I.Shapoval RCC of Urology and Nephrology, Dep. Of Urology #4 KhMAPE	Igor Antonyan	5
United Kingdom	673	The Royal Marsden NHS Foundation Trust, The Royal Marsden Hospital	Gerhardt Attard	5
United States	031	Oregon Urology Institute	Bryan Mehlhaff	5
Australia	813	Sydney Cancer Centre, Concord Repatriation General Hospital	Martin Stockler	4
Australia	832	Epic Pharmacy; North Coast Cancer Institute	Adam Boyce	4
Austria	204	Krankenhaus Barmherzige Schwestern Linz, Abteilung Radiologie & Abteilung Urologie; St. Vincent's Hospital, PET - CT Center	Wolfgang Loidl	4
Belgium	256	Algemeen Ziekenhuis Groeninge	Patrick Werbrouck	4
Canada	119	Urology South Shore Research	Lorne Aaron	4
Canada	120	Capital District Health Authority; Queen Elizabeth II Health Sciences Centre	Ricardo Rendon	4
Canada	121	McGill University Health Centre	Armen Aprikian	4
China	515	Shanghai First People's Hospital	Shujie Xia	4
China	525	Huashan Hospital Fudan University	Haowen Jiang	4
Denmark	427	Odense University Hospital Depts of Nuclear Medicine, Radiology, & Urology	Steen Carlsson	4
Finland	434	Satakunnan keskussairaala	Antti Kaipia	4
France	317	Centre de Medecine Nucleaire LUMEN; Hopital Edouard Herriot – CHU Lyon	Marc Colombel	4
Italy	454	AOU San Luigi Gonzaga (Farmacia Ospedaliera, SCDU Oncologia Medica II Pad, SCDU Radiodiagnostica, SS Medicina Nucleare)	Giorgio Vittorio Scagliotti	4
Italy	456	Azienda Socio Sanitaria Territoriale di Cremona (Farmacia, Medicina Nucleare, Servizio di Radiologia, Struttura Complessa di Oncologia)	Rodolfo Passalacqua	4
Korea	878	Chonnam National University Hwasun Hospital	Dong-deuk Kwon	4
Korea	879	Seoul National University Hospital	Cheol Kwak	4
Korea	880	Gachon University Gil Medical Center	Han Jung	4
Malaysia	851	University Malaya Medical Centre	Adlinda Alip	4
New Zealand	842	Canterbury Regional Cancer & Blood Service	Benjamin Hindson	4
New Zealand	843	Waikato Urology Research Ltd	Michael Holmes	4
Poland	570	WRO MEDICA	Katarzyna Madziarska	4
Serbia	710	Clinical Center "Bezanijska Kosa", Department of Urology	Zoran Filipovic	4

Slovakia	707	Fakultna nemocnica s poliklinikou Zilina, Urologicke oddelenie; KK MED s.r.o.; UVN SNP - FN Ruzomberok, Pracovisko Nuklearnej mediciny CCSR Klinika nuklearnej mediciny	Juraj Mikulas	4
Spain	610	Complejo Hospitalario Universitario A Coruna Urology Department	Jose Ignacio Rodriguez Gomez	4
Spain	613	ALTAHIA. Xarxa Assistencial Universitaria de Manresa	Montserrat Domenech Santasusana	4
Sweden	723	Apoteket AB Kliniska Provningar Molnlycke; Karolinska Universitetssjukhuset Solna - Rontgenkliniken Solna & Urologiska Kliniken	Mats Olsson	4
United States	019	Urological Associates of Southern Arizona, PC	Curtis Dunshee	4
United States	020	Lancaster Urology	Paul Sieber	4
United States	023	Carolina Urologic Research Center	Neal Shore	4
United States	045	Ronald Reagan UCLA Medical Center Dept of Pharmaceutical Services; UCLA Clark Urology Center	Allan Pantuck	4
United States	137	Yale New Haven-Hospital Smilow Cancer Center & Yale Diagnostic Radiology; Yale University School of Medicine	Daniel Petrylak	4
Argentina	911	Centro Medico Austral(OMI)	Silvia Carraro	3
Australia	803	Epic Pharmacy Port Macquarie base hospital; Mid North Coast Cancer Institute	Stephen Begbie	3
Australia	821	Box Hill Hospital (Eastern Health) & Eastern Clinical Research Unit (Eastern Health)	Ian Davis	3
Australia	837	Border Medical Oncology Research Unit & Ramsay Health Care Australia Pty Ltd, Albury Wodonga Regional Cancer Centre	Craig Underhill	3
Australia	838	Macquarie Universite Hospital	Howard Gurney	3
Austria	201	Diagnosezentrum Meidling GesmbH; Isotopix, Ambulatorium fuer Nuklearmedizin; Medizinische Universitaet Wien, Universitaetsklinik fuer Innere Medizin I	Michael Krainer	3
Belgium	253	Clinique Universitaire de Bruxelles Hopital Erasme	Thierry Roumeguere	3
Belgium	258	Universitaire Ziekenhuizen Leuven	Steven Joniau	3
Brazil	986	Hospital Universitario Pedro Ernesto - UERJ	Ronaldo Damiao	3
Canada	111	Manitoba Prostate Centre - CancerCare Manitoba	Darrel Drachenberg	3
Canada	124	The Male/Female Health and Research Centre	Joseph Zadra	3
China	511	Office of Hongqian Guo	Hongqian Guo	3
China	514	Beijing Hospital	Jianye Wang	3
China	522	The Second Affiliated Hospital of Zhejiang University School of Medicine	Chuanjun Du	3
Finland	431	Oulun yliopistollinen sairaala	Hanna-Leena Ronkainen	3
France	331	Hopital Calude Huriez - CHU Lille	Arnauld Villers	3
France	333	Institut Claudius Regaud	Loic Mourey	3
France	341	ICM Val D'Aurelle	David Azria	3
Netherlands	508	Albert Schweitzer Ziekenhuis	Joan van den Bosch	3

Russian Federation	563	SBEI of HPE "Bashkir State Medical University" of MoH of the RF based on Clinic of Bashkir State Medical University	Adel Izmailov	3
Russian Federation	780	P. Hertsen Moscow Oncology Research Institute - branch of the National Medical Research Radiological Centre of the MoH of RF	Boris Alekseev	3
Spain	622	MD Anderson Cancer Center	Jose Angel Arranz Arija	3
Spain	625	ICO Girona-Hospital Universitari de Girona Dr. Josep Trueta	Nuria Sala Gonzalez	3
Taiwan	888	Chang Gung Medical Fundation, Chiayi Branch (Chiayi Chang Gung Memorial Hospital)	Chih-Shou Chen	3
Taiwan	889	Kaohsiung Medical University Chung-Ho Memorial Hospital	Shu-Pin Huang	3
Taiwan	896	Taipei Veterans General Hospital	Wayne Yen-Hwa Chang	3
Thailand	924	King Chulalongkorn Memorial Hospital, Chulalongkorn University Division of Urology, Department of Surgery, Faculty of Medicine	Julin Opanuraks	3
United Kingdom	650	The Royal Marsden NHS Foundation Trust, The Royal Marsden Hospital	Gerhardt Attard	3
United Kingdom	658	The Newcastle upon Tyne Hospitals NHS Foundation Trust, Northern Centre for Cancer Care, Freeman Hospital	Ian Pedley	3
United States	132	Chesapeake Urology Research Associates	Jayant Uberoi	3
United States	160	Urology of Indiana, LLC	Ronald Suh	3
Argentina	914	Hospital Italiano de Buenos Aires	Oscar Damia	2
Australia	826	Peter MacCallum Cancer Centre	Guy Toner	2
Brazil	980	Associacao de Pesquisa Clinica; Oncologia Rede D'Or	Daniel Herchenhorn	2
Brazil	984	Hospital Sao Lucas da PUCRS	Carlos Cairoli	2
Canada	101	Tom Baker Cancer Centre	Joseph Ruether	2
Canada	122	McMaster Institute of Urology @ St. Joseph's Healthcare Hamilton	Bobby Shayegan	2
Canada	123	Urology Associates / Urologic Medical Research	Russell Egerdie	2
Chile	955	Fundacion Arturo Lopez Perez	Christian Caglevic Medina	2
Chile	956	Instituto Clinico Oncologico del Sur (ICOS)	Eduardo Yanez Ruiz	2
China	535	Qingdao Municipal Hospital	Sichuan Hou	2
France	316	Centre Hospitalier Lyon Sud	Sophie Tartas	2
France	337	Hopital Nord	Marjorie Baciuchka-Palmaro	2
France	338	Centre Regional de lutte Contre le Cancer Georges Francois Leclerc	Sylvain Ladoire	2
Germany	350	Charite, Campus Benjamin Franklin Klinik fuer Urologie	Kurt Miller	2
Germany	355	Martini-Klinik am UKE GmbH	Petra Stroelin	2
Germany	357	Universitaetsklinikum Carl Gustav Carus Dresden an der technischen Universitaet Dresden lnstitut und Poliklinik fuer Radiologische Diagnostik & Klinik und Poliklinik fuer Urologie	Manfred P Wirth	2
Hong Kong	847	Tuen Mun Hospital	Ka Chai Lee	2
Hong Kong	848	Queen Mary Hospital	Hok Leung James Tsu	2

Italy	453	Azienda Ospedaliero-Universitaria Policlinico di Modena (Farmacia Interna, Medicina Nucleare)	Roberto Sabbatini	2
Malaysia	853	Sarawak General Hospital	Teh Chou	2
Malaysia	856	Universiti Kebangsaan Malaysia Medical Centre	Fuad Ismail	2
Netherlands	503	University Medical Center Groningen Dept of Urology	Igle de Jong	2
Netherlands	506	University Hospital Maastricht (MUMC)	Cees van de Beek	2
Poland	565	UROMEDYK, Poradnia Urologiczna	Mateusz Obarzanowski	2
Serbia	714	Clinical Center Zemun Department of Urology	Bora Cvetkovic	2
Singapore	862	National Cancer Centre Singapore	Ravindran Kanesvaran	2
Slovakia	701	Fakultna nemocnica s poliklinikou F.D. Roosevelta II. Urologicka klinika SZU; Radiologicke oddelenie; Institut nuklearnej a molekularnej mediciny pracovisko Banska Bystrica	Vladimir Balaz	2
Sweden	721	Apoteket AB Kliniska Provningar Molnlycke; Rontgenkliniken Universitetssjukhuset Orebro; Urologmottagningen universitetssjukhuset orebro	Ove Andren	2
Taiwan	894	Chang Gung Memorial Hospital, Keelung Branch (Keelung Chang Gung Memorial Hospital)	Chun-Te Wu	2
Thailand	923	Maharaj Nakorn Chiang Mai Hospital Division of Urology, Dept of Surgery, Faculty of Medicine Chiang Mai University	Supon Sriplakich	2
Turkey	382	Izmir Bozyaka Egitim Arastirma Hastanesi	Tansu Degirmenci	2
United States	049	University of California, Irvine Medical Center	Edward Uchio	2
United States	133	Urology of Virginia, PLLC	Robert Given	2
United States	141	Brooklyn Urology Research Group	Ivan Grunberger	2
United States	143	IU Health Arnett Cancer Care	Bamidele Adesunloye	2
United States	148	Carolina Urology Partners, PLLC; Caramont Health; Gaston Medical Associates	Robert Waterhouse	2
United States	152	Urology Associates, P.C.	Barrett Cowan	2
Argentina	912	Instituto De Oncologia De Rosario	Luis Fein	1
Argentina	913	COIBA (Centro de Oncologia e Investigacion Buenos Aires)	Mirta Varela	1
Australia	833	Royal North Shore Hospital	Alexander Guminski	1
Belgium	259	Centre Hospitalier Universitaire de Liege, Site du Sart-Tilman	David Waltregny	1
Belgium	271	Vzw Algemeen Ziekenhuis Maria Middelares	Filip Ameye	1
Brazil	994	Hospital Israelita Albert Einstein	Oren Smaletz	1
China	510	Shanghai Changhai Hospital	Yinghao Sun	1
China	512	Peking Union Medical College Hospital	Hanzhong Li	1
China	527	Jiangsu Province Hospital	Lixin Hua	1
China	528	The Second Hospital of Tianjin Medical University	Yong Xu	1
China	530	Zhongnan Hospital of Wuhan University	Tongzu Liu	1
China	533	The First Affiliated Hospital of Guangzhou Medical University	Jian Yuan	1
China	538	The First Affiliated Hospital of Wenzhou University	Zhiliang Weng	1
France	335	Centre Hospitalier d'Avignon - Hopital Henri Duffaut Service de Medecine Nucleaire;	Lysian Cartier	1

		Institut Sainte Catherine (Service de Radiologie & Laboratoire Chaperon Tarbouriech)		
France	343	CHU Brest Hopital Morvan	Friederike Schlurmann-Constans	1
Germany	353	Hannover Medical School Department of Diagnostic and lnterventional Radiology & Institute for Radiology; Medizinische Hochschule Hannover Klinik fuer Nuklearmedizin & Klinik fuer Urologie und Urulogische Onkologie	Christoph-Alexander von Klot	1
Germany	356	Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim; Universitaetsklinikum Mannheim	Manuel Ritter	1
Germany	370	Gemeinschaftspraxis Dr. H. Fritz, S. Berger	Susan Feyerabend	1
Greece	283	General Hospital of Athens "Korgialeneio-Benakeio EES" Urology Clinic	Nikolaos Ferakis	1
Serbia	713	Clinical Center Of Serbia, Clinic of Urology	Nebojsa Bojanic	1
Singapore	860	National University Hospital Singapore	Edmund Chiong	1
Spain	621	Hospital de Navarra	Nuria Lainez Milagro	1
Sweden	724	Apoteket AB Kliniska Provningar Molnlycke; Norrlands Universitetssjukhus Bild-och Funktionsmedicin Vasterbotten & Urologkliniken	Borje Ljungberg	1
Taiwan	890	Chang Gung Medical Fundation, Kaohsiung (Kaohsiung Chang Gung Memorial Hospital)	Po-Hui Chiang	1
Taiwan	893	Chi Mei Medical Centre	Kun-Hung Shen	1
Thailand	922	Rajavithi Hospital	Nattapong Wongwattanasatien	1
Turkey	380	Hacettepe Universitesi Tip Fakultesi Sihhiye	Haluk Ozen	1
Turkey	381	Cukurova Universitesi Tip Fakultesi Balcali Hastanesi	Mustafa Tansug	1
United States	142	Urology Associates of San Luis Obispo, a Medical Group, Inc	Craig Canfield	1
United States	146	GU Research Network/ Wichita Urology Group	Fadi Joudi	1
United States	150	Premier Medical Group of the Hudson Valley	Jaspreet Singh	1

*As of 25 October 2017

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Table S1. Pre-defined thresholds for defining clinically meaningful changes in patient-reported outcomes

	Thresholds	
	Reference	Primary analysis
BPI-SF		
Item 3: pain at its worst	2*[1,2]	2
Pain severity	2*[1,2]	2
Pain interference	1*[1,2]	1
EORTC QLQ-PR25		
Bowel symptoms and function	N/A	4§
Hormonal treatment-related symptoms	N/A	6§
Urinary symptoms and problems	N/A	9§
FACT-P		
Physical wellbeing	2–3‖[3,4]	3
Social/family wellbeing	2–3‖[3,4]	3
Emotional wellbeing	2–3‖[3,4]	3
Functional wellbeing	2–3‖[3,4]	3
Prostate cancer subscale	2–3‖[3,4]	3
Prostate cancer pain subscale	1–2‖	2
FACT-P total	6–10‖	10
EQ-5D-5L		
EQ-VAS	7[5]	7

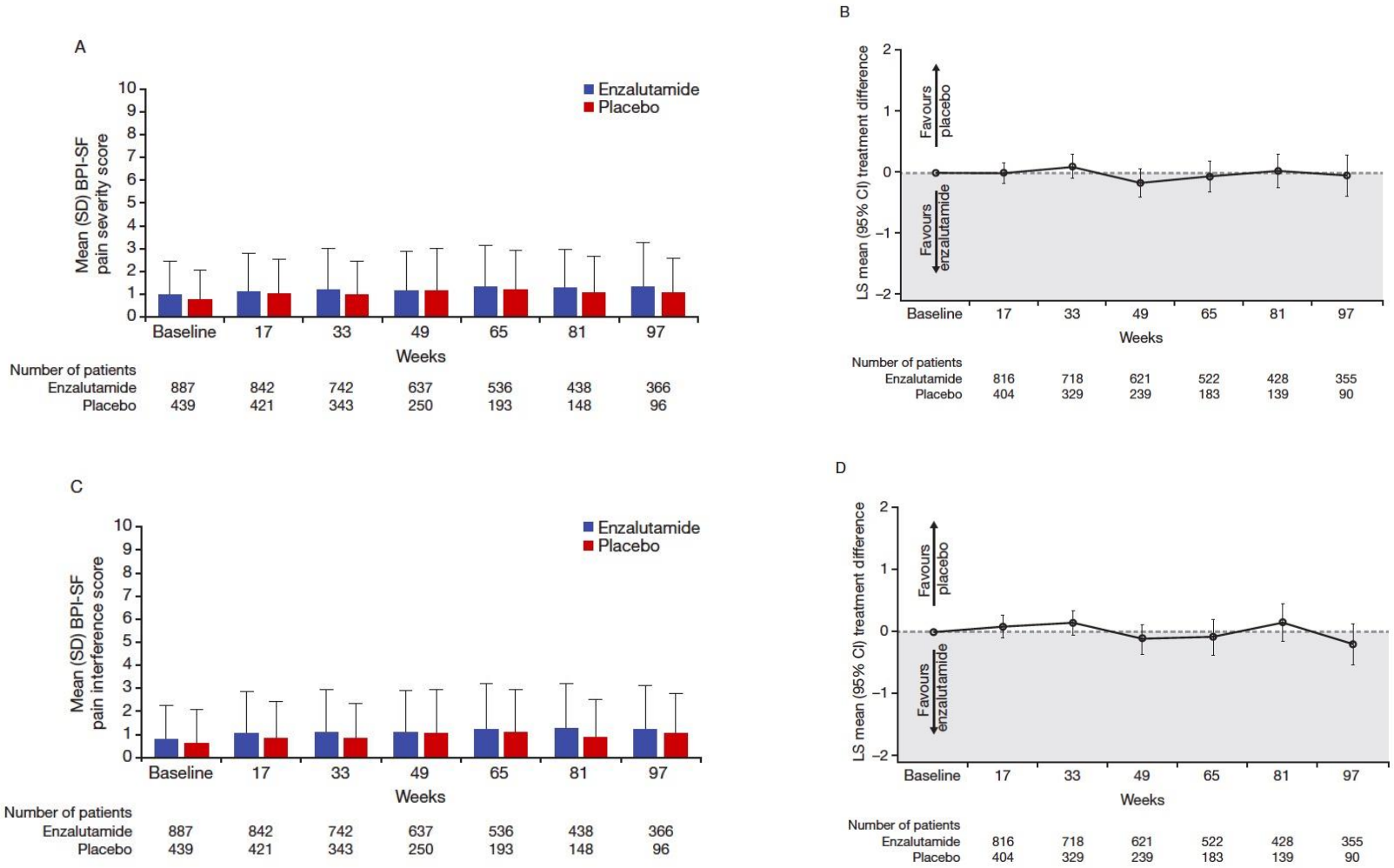
BPI-SF=Brief Pain Inventory Short Form; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=European Quality of Life 5 Dimensions 5 Levels health questionnaire; EQ-VAS=EuroQoL 5 Dimensions 5 Levels health questionnaire visual analogue scale; FACT-P=Functional Assessment of Cancer Therapy-Prostate. *Based on clinically reported important improvements in cancer-breakthrough pain and chronic pain states. §Thresholds are one-half the baseline mean standard deviation pooled over the two treatment groups. ‖The upper limit was used to define change on a patient level and the lower limit was used to interpret group changes (within and between treatment arms).

Table S2. Time to unconfirmed pain progression and HRQoL deterioration

Instrument	Median time, months (95% CI)		HR (95% CI) Enzalutamide *vs* placebo	*P*-value
	Enzalutamide	Placebo		
BPI-SF				
Item 3	18·46 (18·30–22·11)	18·53 (14·78–25·79)	0·98 (0·82–1·18)	0·838
Severity	29·54 (25·86–36·83)	25·79 (18·56–NYR)	0·88 (0·71–1·08)	0·223
Interference	18·43 (14·88–22·11)	22·01 (18·46–29·47)	1·18 (0·97–1·43)	0·096
EORTC QLQ-PR25				
Bowel symptoms and function	18·27 (14·75–18·63)	11·30 (11·07–14·78)	0·80 (0·67–0·95)	0·012
Hormonal treatment-related symptoms	14·75 (11·34–18·50)	24·18 (18·53–30·75)	1·31 (1·08–1·59)	0·006
Sexual activity	NYR	NYR	1·04 (0·83–1·31)	0·711
Urinary symptoms and problems	29·41 (22·11–33·08)	18·33 (14·69–22·11)	0·72 (0·60–0·87)	<0·001
FACT-P				
Physical wellbeing	7·85 (7·46–11·07)	11·53 (11·11–14·75)	1·28 (1·08–1·50)	0·004
Social/family wellbeing	18·43 (14·78–22·18)	14·82 (11·07–18·60)	0·88 (0·74–1·05)	0·153
Emotional wellbeing	25·79 (21·98–29·41)	18·37 (14·72–8·60)	0·84 (0·70–1·01)	0·070
Functional wellbeing	10·97 (7·52–11·07)	11·07 (10·68–14·55)	1·07 (0·91–1·25)	0·419
Prostate cancer subscale	7·75 (7·46–11·07)	7·72 (7·43–11·07)	0·85 (0·73–0·99)	0·036
Prostate cancer pain subscale	11·53 (11·07–14·75)	11·14 (11·04–14·78)	0·98 (0·83–1·16)	0·812
FACT-P total	11·11 (11·04–14·69)	11·14 (11·07–14·69)	0·97 (0·82–1·14)	0·700
EQ-5D-5L				
EQ-VAS	11·07 (7·82–11·17)	7·46 (7·39–10·97)	0·83 (0·71–0·97)	0·019

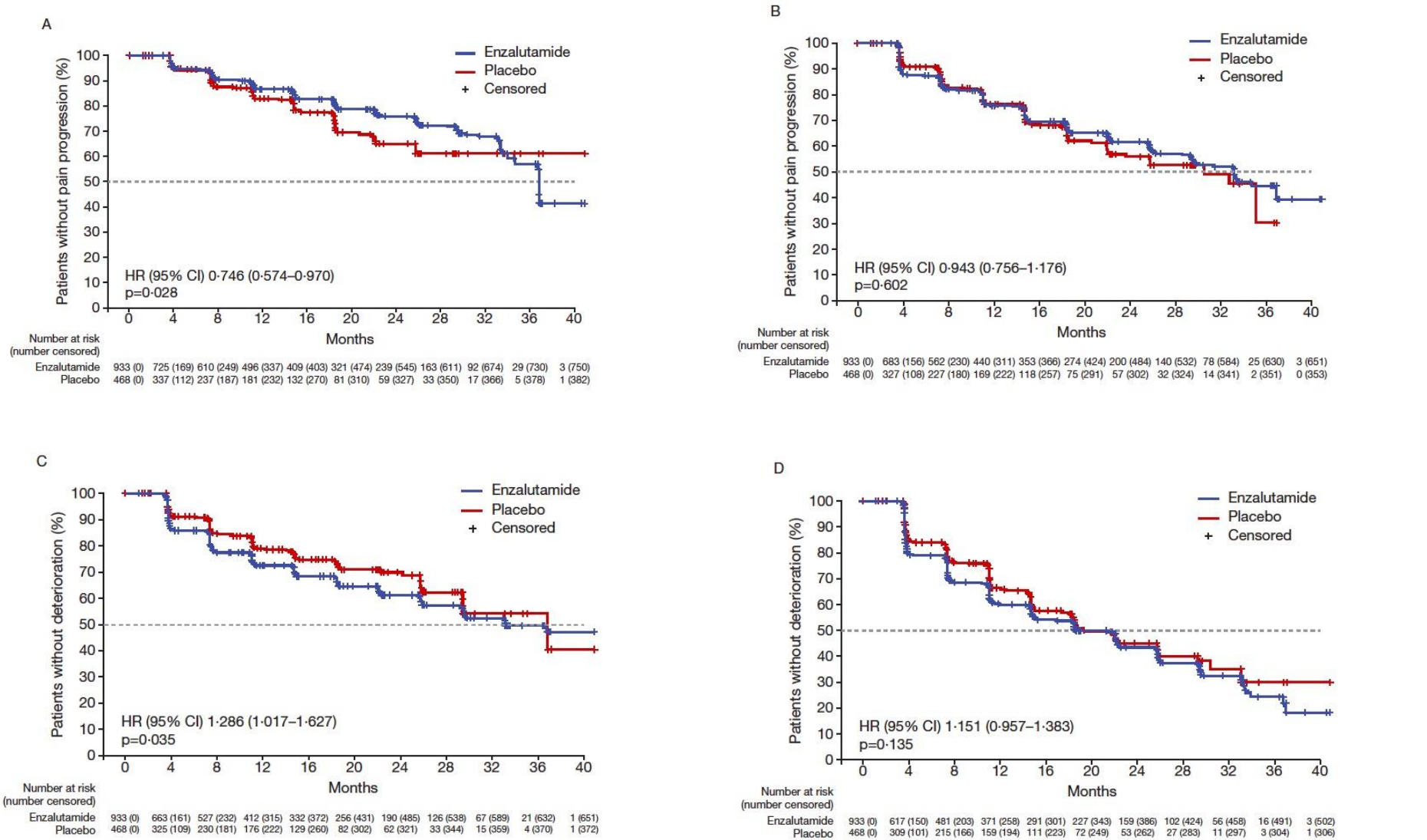
BPI-SF=Brief Pain Inventory Short Form; CI=confidence interval; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=European Quality of Life 5 Dimensions 5 Levels health questionnaire; EQ-VAS=EuroQoL 5 Dimensions 5 Levels health questionnaire visual analogue scale; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HR=hazard ratio; HRQoL=health-related quality of life; NYR=not yet reached.

Figure S1. Patient-reported changes in BPI-SF scores by study visit and treatment difference in change from baseline (MMRM) for pain severity (A and B*, respectively) and pain interference (C and D*, respectively)



BPI-SF=Brief Pain Inventory Short Form; CI=confidence interval; LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation. *Difference was not statistically significant (*P*=0·746 for pain severity; *P*=0·237 for pain interference) or clinically meaningful.

Figure S2. Kaplan-Meier estimates of time to confirmed pain progression and HRQoL deterioration: BPI-SF (A) pain severity and (B) pain interference; EORTC QLQ-PR25 (C) hormonal treatment-related symptoms; FACT-P (D) physical wellbeing, (E) social/family wellbeing, (F) emotional wellbeing, (G) functional wellbeing, (H) prostate cancer subscale, and (I) prostate cancer pain subscale



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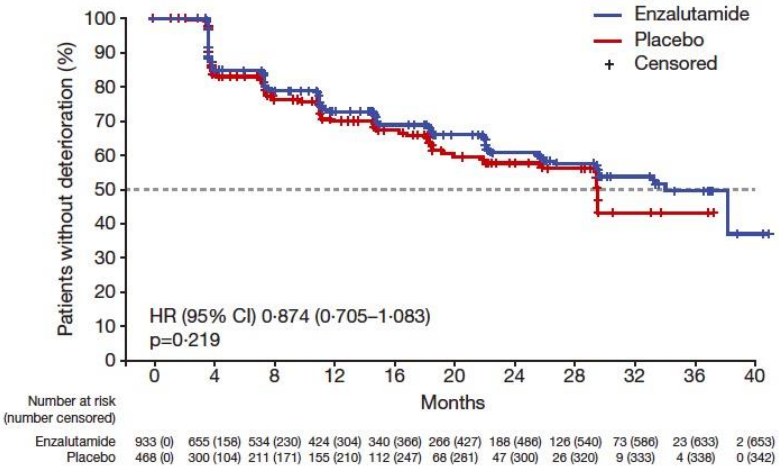
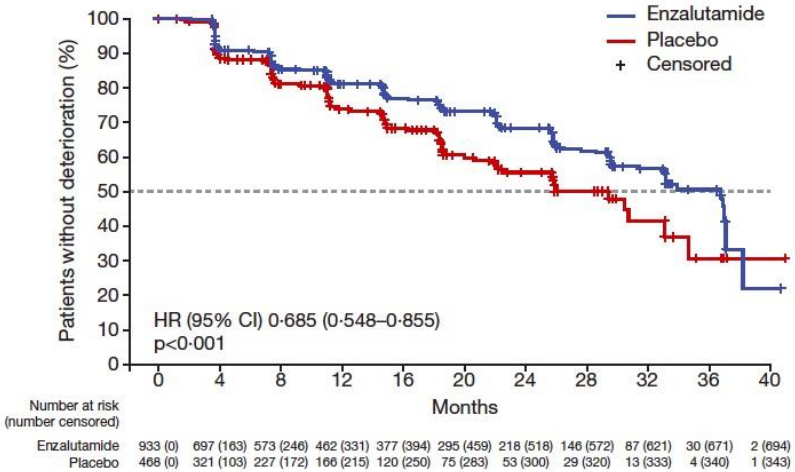


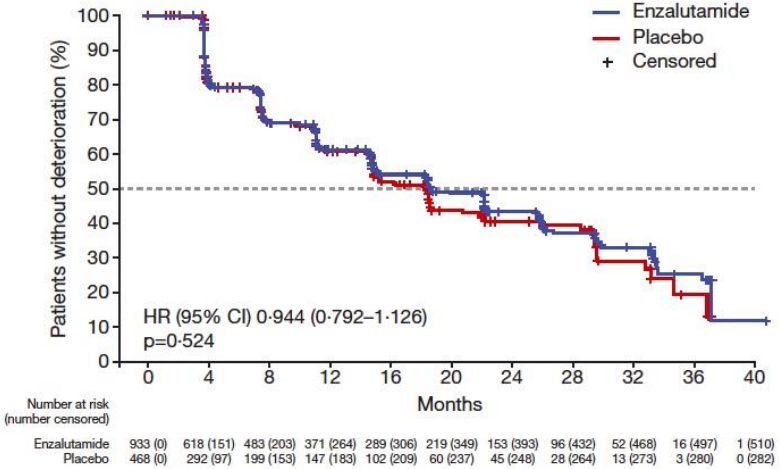
Number at risk (number censored)												
Enzalutamide	933 (0)	655 (158)	534 (230)	424 (304)	340 (366)	266 (427)	188 (486)	126 (540)	73 (586)	23 (633)	2 (653)
Placebo	468 (0)	300 (104)	211 (171)	155 (210)	112 (247)	68 (281)	47 (300)	26 (320)	9 (333)	4 (338)	0 (342)

F



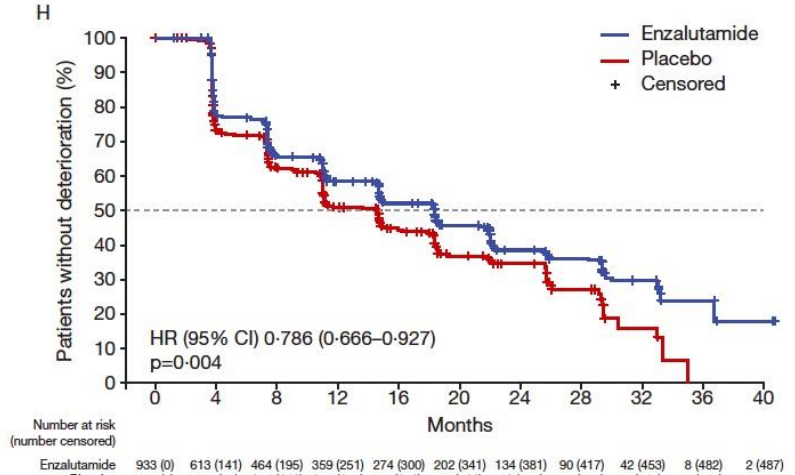
Number at risk (number censored)												
Enzalutamide	933 (0)	697 (163)	573 (246)	462 (331)	377 (394)	295 (459)	218 (518)	146 (572)	87 (621)	30 (671)	2 (694)
Placebo	468 (0)	321 (103)	227 (172)	166 (215)	120 (250)	75 (283)	53 (300)	29 (320)	13 (333)	4 (340)	1 (343)

G

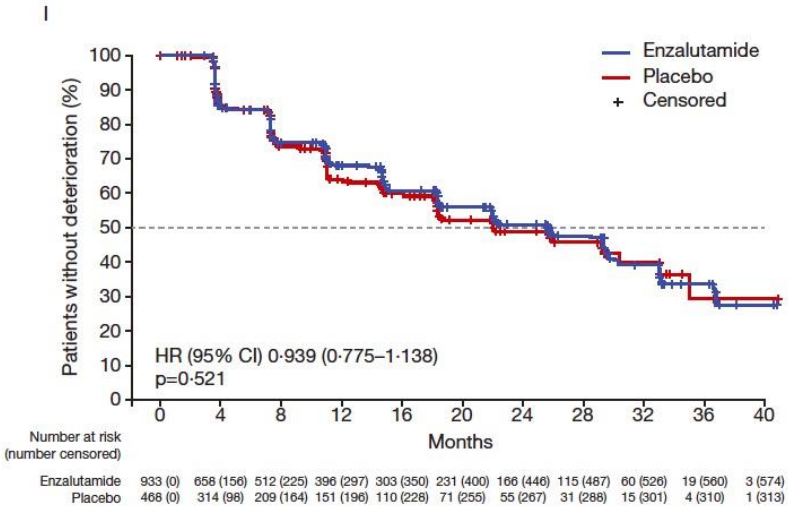


Number at risk (number censored)												
Enzalutamide	933 (0)	618 (151)	483 (203)	371 (264)	289 (306)	219 (349)	153 (393)	96 (432)	52 (468)	16 (497)	1 (510)
Placebo	468 (0)	292 (97)	199 (153)	147 (183)	102 (209)	60 (237)	45 (248)	28 (264)	13 (273)	3 (280)	0 (282)

H

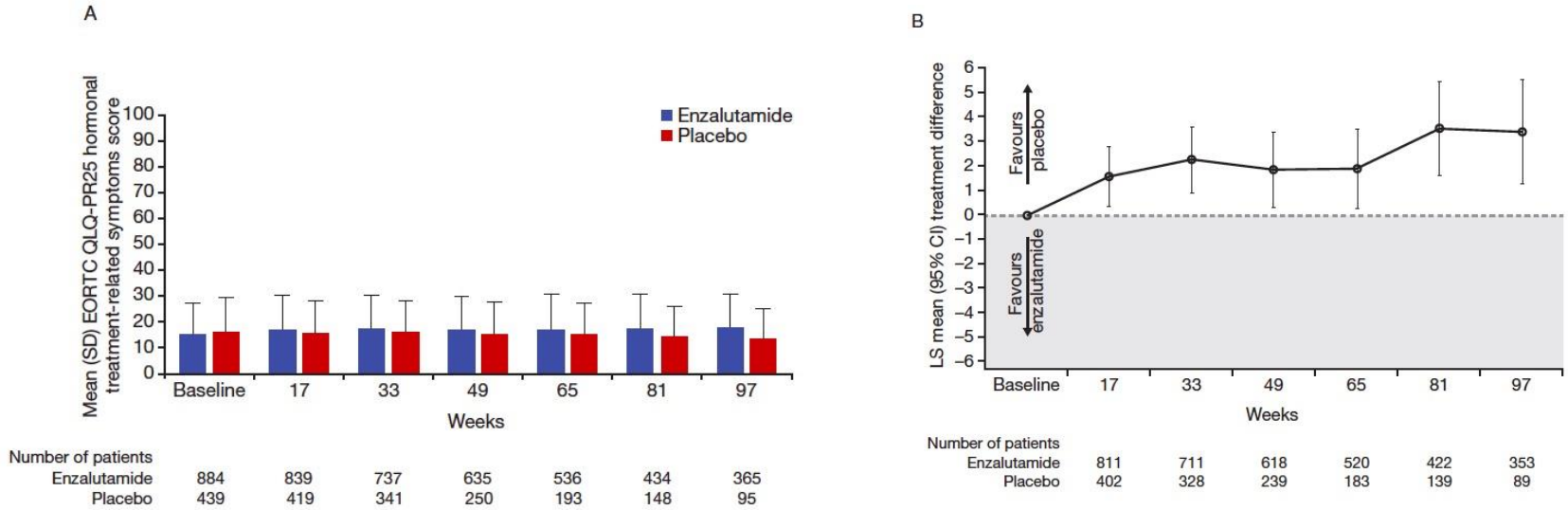


Number at risk (number censored)												
Enzalutamide	933 (0)	613 (141)	464 (195)	359 (251)	274 (300)	202 (341)	134 (381)	90 (417)	42 (453)	8 (482)	2 (487)
Placebo	468 (0)	272 (90)	184 (141)	126 (167)	89 (191)	55 (211)	41 (222)	22 (233)	6 (243)	0 (246)	



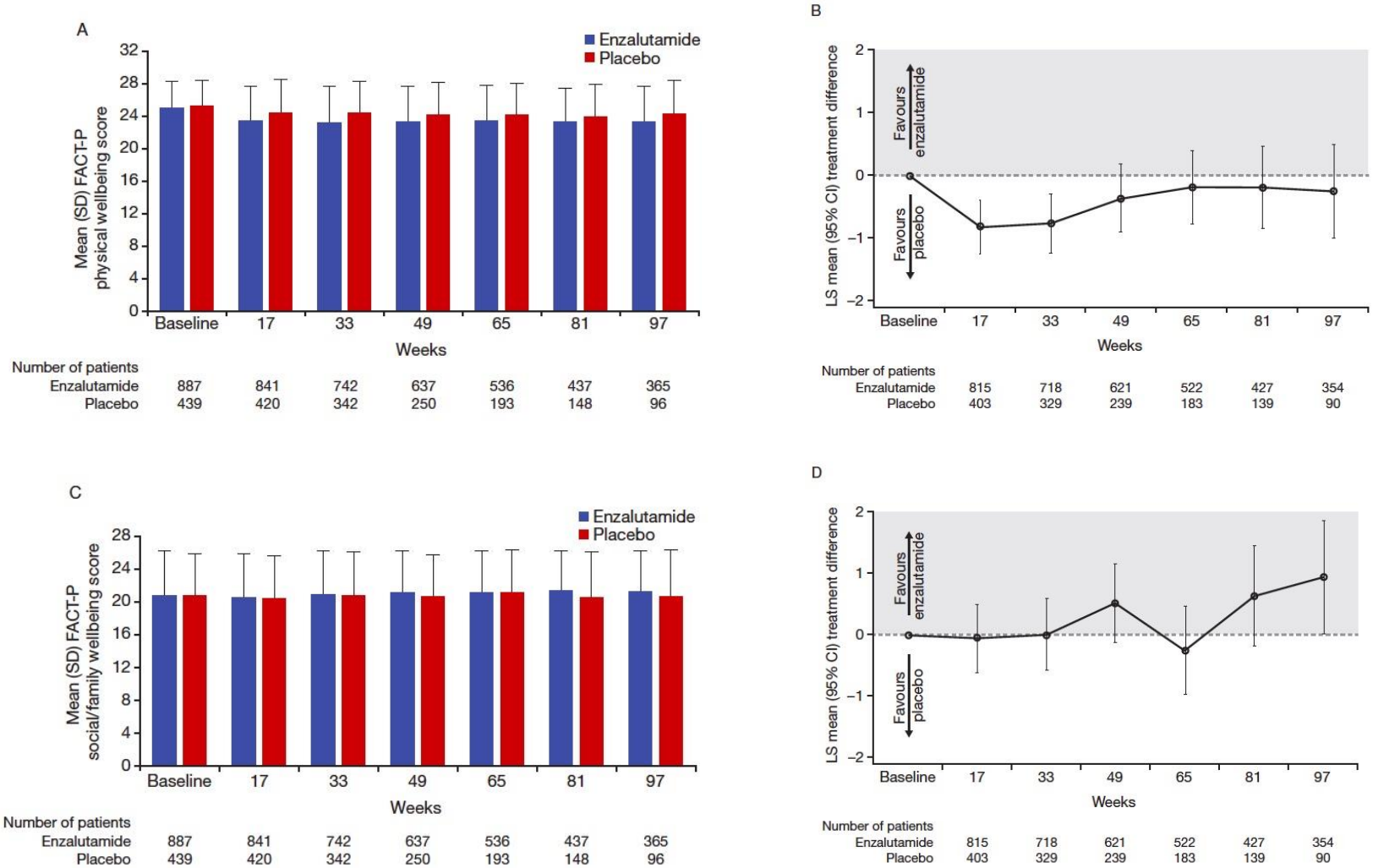
BPI-SF=Brief Pain Inventory Short Form; CI=confidence interval; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-P=Functional Assessment of Cancer Therapy-Prostate; HR=hazard ratio; HRQoL=health-related quality of life.

Figure S3. Patient-reported changes in EORTC QLQ-PR25 hormonal treatment-related symptoms by (A) study visit and (B)* treatment difference in change from baseline (MMRM)



CI=confidence interval; EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation.
*Difference was statistically significant (*P*=0·002) but not clinically meaningful.

Figure S4. Patient-reported changes in FACT-P scores by study visit and treatment difference in change from baseline (MMRM) for physical wellbeing (A and B,* respectively), social/family wellbeing (C and D,† respectively), emotional wellbeing (E and F,* respectively), functional wellbeing (G and H,* respectively), prostate cancer subscale (I and J,* respectively) and prostate cancer pain subscale (K and L,* respectively)



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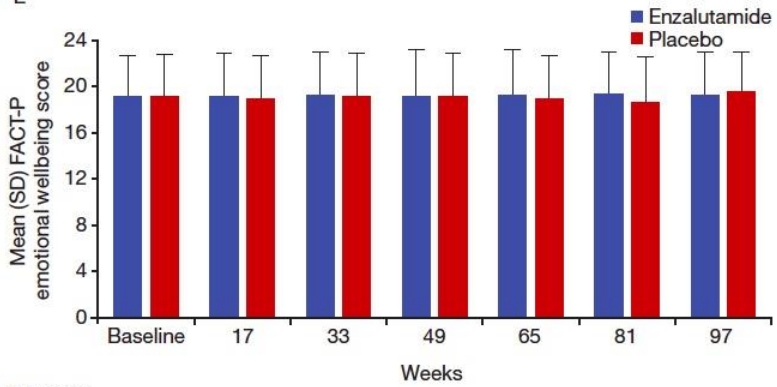
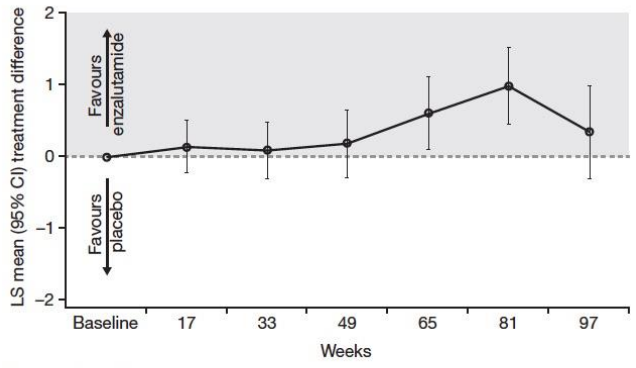


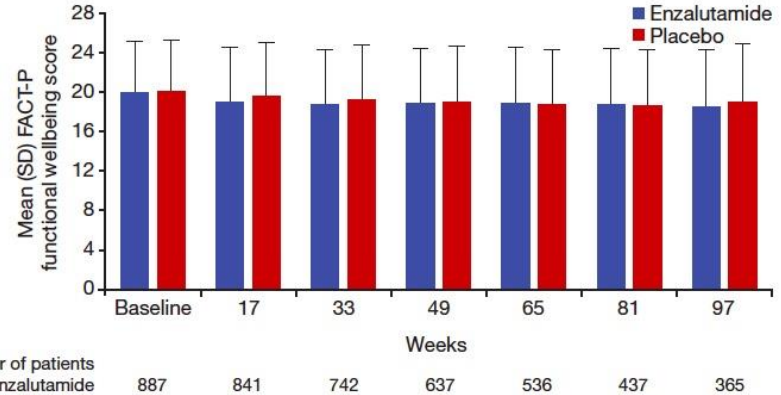
Number of patients							
Enzalutamide	887	841	742	637	536	437	365
Placebo	439	420	342	250	193	148	96

F



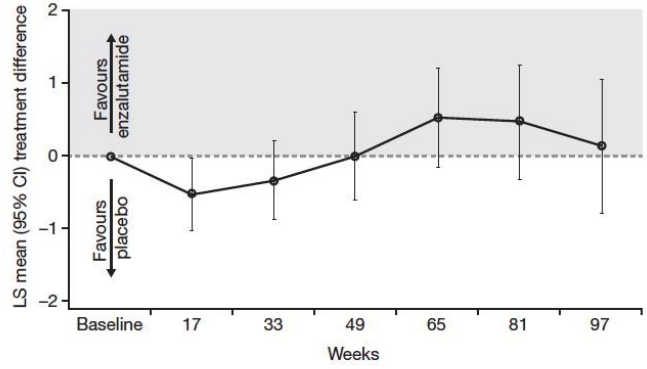
Number of patients							
Enzalutamide	815	718	621	522	427	354	
Placebo	403	329	239	183	139	90	

G

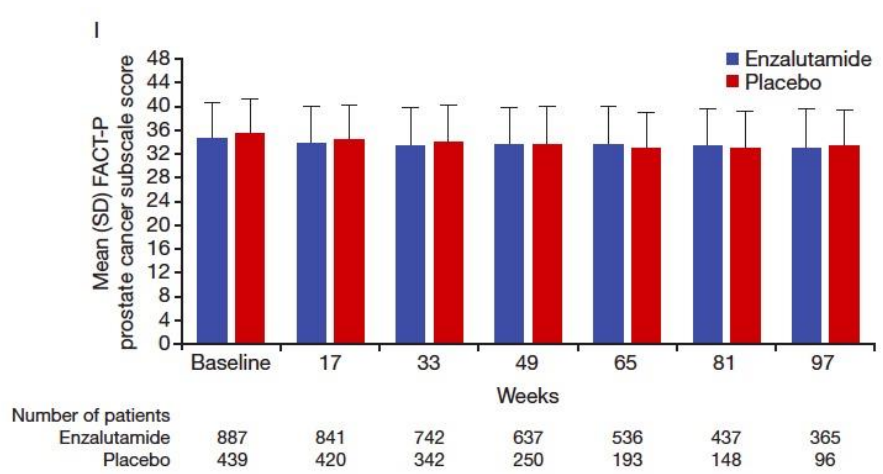


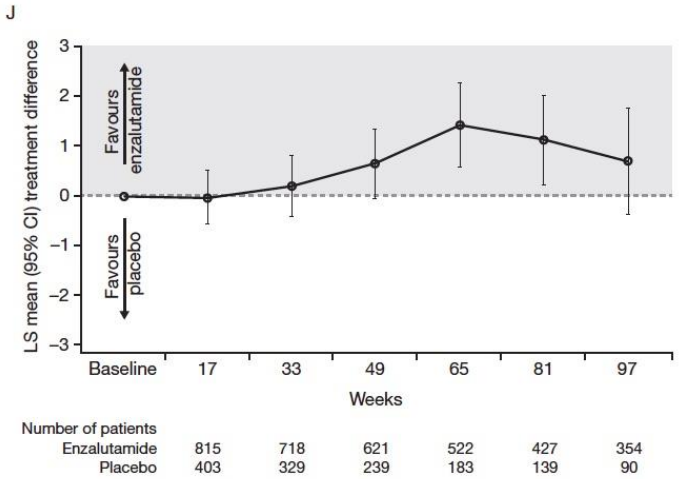
Number of patients							
Enzalutamide	887	841	742	637	536	437	365
Placebo	439	420	342	250	193	148	96

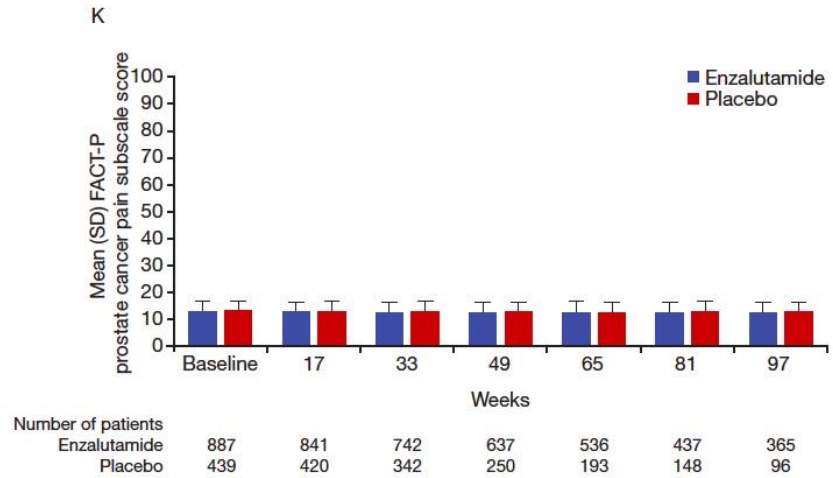
H

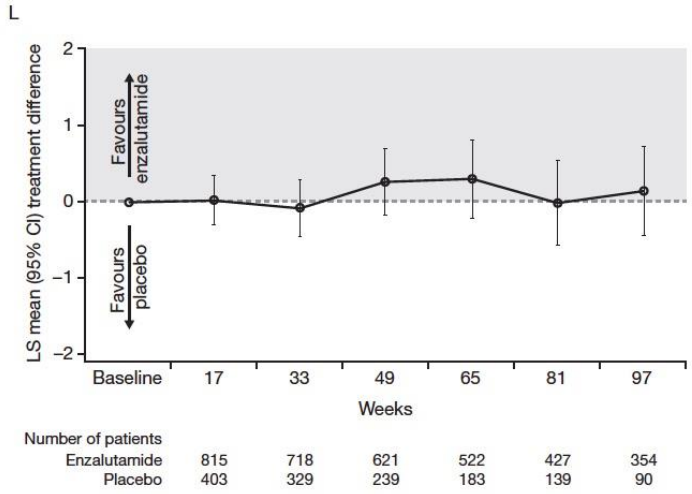


Number of patients							
Enzalutamide	815	718	621	522	427	354	
Placebo	403	329	239	183	139	90	









CI=confidence interval; FACT-P=Functional Assessment of Cancer Therapy-Prostate; LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation. *Difference was not statistically significant (P=0·499 for physical wellbeing, P=0.303 for emotional wellbeing; P=0·774 for functional wellbeing; P=0·189 for prostate cancer subscale; P=0·668 for prostate cancer pain subscale) or clinically meaningful. †Difference was statistically significant (P=0·045) but not clinically meaningful.

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