



First-line talazoparib plus enzalutamide versus placebo plus enzalutamide in men with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: patient-reported outcomes from the randomised, double-blind, placebo-controlled, phase 3 TALAPRO-2 trial

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Summary

Background In the phase 3 TALAPRO-2 trial, talazoparib plus enzalutamide significantly improved radiographic progression-free survival compared with placebo plus enzalutamide in men with metastatic castration-resistant prostate cancer harbouring alterations in genes involved in homologous recombination repair (HRR). We aimed to assess patient-reported outcomes in patients with HRR-deficient metastatic castration-resistant prostate cancer in TALAPRO-2.

Methods TALAPRO-2 is a randomised, double-blind, placebo-controlled, phase 3 trial conducted at 223 hospitals, cancer centres, and medical centres in 26 countries worldwide. Eligible participants were male patients aged 18 years or older (≥ 20 years in Japan) who were receiving ongoing androgen deprivation therapy, had asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer, an Eastern Cooperative Oncology Group performance status of 0 or 1, and had not received previous life-prolonging systemic therapy for castration-resistant prostate cancer or metastatic castration-resistant prostate cancer. Patients with HRR gene alterations were randomly assigned (1:1) using a centralised interactive web response system and a permuted block size of 4 to oral talazoparib 0.5 mg once daily or placebo, plus oral enzalutamide 160 mg once daily, stratified by previous second-generation androgen receptor pathway inhibitor (abiraterone or orteronel) or docetaxel (yes vs no) in the castration-sensitive setting. The sponsor, patients, and investigators were masked to allocation of talazoparib or placebo; enzalutamide was open-label. The primary endpoint was radiographic progression-free survival by blinded independent central review and has been reported previously. Patient-reported outcomes were assessed as secondary outcomes in the patient-reported outcomes population, which comprised patients from the intention-to-treat population with a baseline patient-reported outcome assessment and at least one post-baseline patient-reported outcome assessment. Patient-reported outcomes included time to definitive deterioration in global health status/quality of life (GHS/QoL) per European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and prostate cancer-specific urinary symptoms per EORTC Quality of Life Questionnaire-Prostate (QLQ-PR25), and time to deterioration in pain symptoms per Brief Pain Inventory-Short Form (BPI-SF). Mean change from baseline in GHS/QoL, overall cancer and prostate cancer-specific functioning and symptoms (per EORTC QLQ-C30 and QLQ-PR25), in pain symptoms per BPI-SF, and in general health status per EQ-5D-5L were also patient-reported secondary outcomes. This study is registered with ClinicalTrials.gov, NCT03395197, and is ongoing.

Findings Between Dec 18, 2018, and Jan 20, 2022, 399 patients with HRR-deficient metastatic castration-resistant prostate cancer were enrolled and randomly assigned, of whom 197 assigned to talazoparib plus enzalutamide and 197 assigned to placebo plus enzalutamide were included in the patient-reported outcome population. Median follow-up was 22.2 months (IQR 13.8–27.7) in the talazoparib plus enzalutamide group and 20.2 months (13.5–26.6) for the placebo plus enzalutamide group. Median time to definitive deterioration of GHS/QoL was longer in the talazoparib plus enzalutamide group (27.1 months [95% CI 21.2–non-estimable]) than in the placebo plus enzalutamide group (19.3 months [16.6–23.0]; hazard ratio [HR] 0.69 [95% CI 0.49–0.97]; two-sided $p=0.032$). Median time to definitive deterioration in urinary symptoms was also longer in the talazoparib plus enzalutamide group (non-estimable [95% CI 32.2–non-estimable]) than in the placebo plus enzalutamide group (30.2 months [24.6–non-estimable; HR 0.56 [0.34–0.93]; two-sided $p=0.022$). Median time to deterioration in pain symptoms was non-estimable for both treatment groups (HR 0.58 [0.33–1.01]; two-sided $p=0.051$). Changes from baseline in worst pain in the past 24 h (BPI-SF, question three) and in general health status (EQ-5D-5L) also favoured talazoparib plus enzalutamide versus placebo plus enzalutamide, although the differences were not clinically meaningful. Between-group differences in mean changes from baseline in GHS/QoL, functioning, and symptoms per EORTC QLQ-C30 did not reach the clinically meaningful threshold of 10 or more points, although physical, emotional, and cognitive functioning and pain

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favoured talazoparib plus enzalutamide. Similarly, differences in mean changes from baseline for urinary and bowel symptoms per EORTC QLQ-PR25 favoured talazoparib plus enzalutamide, but were not clinically meaningful.

Interpretation The demonstrated delays in definitive deterioration in GHS/QoL, urinary symptoms, and other functioning and symptom scales with talazoparib plus enzalutamide compared with placebo plus enzalutamide in patients with HRR-deficient metastatic castration-resistant prostate cancer provide insight that might inform clinical decisions for these patients.

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Introduction

Despite the expansion of the treatment landscape for prostate cancer, progression to metastatic castration-resistant prostate cancer can occur and is associated with poor clinical outcomes, with a median overall survival of approximately 2–3 years for chemotherapy-naïve patients.¹ Metastatic castration-resistant prostate cancer thus represents a major therapeutic unmet need.

Prostate cancer is a heterogeneous disease, with up to around 30% of patients harbouring somatic or germline alterations, or both, in genes involved in DNA damage response pathways, such as homologous recombination repair (HRR).² Inhibition of poly(ADP-ribose) polymerase (PARP) in the setting of HRR impairment has shown antitumour activity due to synthetic lethality, caused by increased numbers of double-strand DNA breaks that are repaired insufficiently when HRR is compromised.²

Combination therapies of PARP and androgen receptor pathway (AR) inhibitors have been evaluated in several studies in patients with metastatic castration-resistant prostate cancer.^{3–5} TALAPRO-2 is an ongoing phase 3 trial evaluating talazoparib combined with enzalutamide. Recently reported analyses showed that talazoparib plus

enzalutamide significantly improved radiographic progression-free survival compared with placebo plus enzalutamide in patients with metastatic castration-resistant prostate cancer unselected for HRR gene alterations (hazard ratio [HR] 0·63 [95% CI 0·51–0·78]; $p < 0·0001$)⁶ as well as in patients with HRR-deficient metastatic castration-resistant prostate cancer (0·45 [0·33–0·61]; $p < 0·0001$).⁷ The safety profile of talazoparib plus enzalutamide was consistent with the known safety profiles of each of the drugs as monotherapies, apart from the grade and incidence of haematological adverse events, which were higher than with talazoparib alone.^{8,9} The most common grade 3 or 4 adverse events were anaemia and neutropenia,⁶ and no new safety signals were identified among patients with HRR-deficient metastatic castration-resistant prostate cancer.⁷

Metastatic castration-resistant prostate cancer is associated with clinically significant morbidity and worsening of health-related quality of life (HRQoL), characterised by fatigue, problems with urinary and sexual activity and functioning, and substantial pain due to bone metastases.¹⁰ Furthermore, the tolerability and treatment effect on symptoms among the available

Research in context

Evidence before this study

In early 2017, we searched PubMed for relevant preclinical or clinical research published on DNA damage repair, homologous recombination repair, so-called BRCAness, novel hormonal therapies, androgen receptor signalling inhibition, poly(ADP-ribose) polymerase (PARP) inhibitors, and advanced prostate cancer. A recent review of the current literature suggests that combination therapy with androgen receptor pathway inhibitors (formerly known as novel hormonal therapies) and PARP inhibitors might not only improve clinical outcomes but also benefit the overall quality of life and symptom burden of prostate cancer, including pain.

Added value of this study

To our knowledge, the current study is the first phase 3 trial of talazoparib plus enzalutamide to include prespecified assessments of patient-reported outcomes, including pain, overall quality of life, symptoms, and functioning scales using

validated instruments. Based on the results, we hypothesise that durable disease control with talazoparib plus enzalutamide compared with placebo plus enzalutamide contributed to delays in deterioration of symptoms and overall quality of life.

Implications of all the available evidence

The current study, together with other studies reporting on patient-reported outcomes, highlights the substantial symptom burden of metastatic castration-resistant prostate cancer and the disease-specific effect on quality of life. Patient-reported outcome assessments encompass a plethora of important parameters to be evaluated in clinical trials and offer valuable insight towards treatment decisions, as well as enable patient engagement in decision making. The current study provides evidence supporting the combination of talazoparib and enzalutamide as a viable treatment strategy for patients with metastatic castration-resistant prostate cancer, with the potential to improve both clinical outcomes and quality of life.

therapies can vary; it is therefore important to understand how treatment combinations might influence HRQoL. We aimed to describe the prespecified patient-reported outcomes from TALAPRO-2, evaluating the effect of talazoparib plus enzalutamide on HRQoL in patients with metastatic castration-resistant prostate cancer harbouring alterations in genes involved in HRR. We hypothesised that there would be no difference or a slight deterioration in patient-reported outcomes between the triplet and doublet therapy (androgen deprivation therapy plus talazoparib plus enzalutamide vs androgen deprivation therapy plus enzalutamide plus placebo).

Methods

Study design and participants

TALAPRO-2 is a randomised, double-blind, placebo-controlled, phase 3 trial of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment for patients with metastatic castration-resistant prostate cancer.¹¹ The trial was done in 223 hospitals, cancer centres, and medical centres in 26 countries in North America, Europe, Israel, South America, South Africa, and the Asia-Pacific region. Two cohorts were enrolled: patients in cohort 1 (all-comers) were unselected for gene alterations involved in HRR and patients in cohort 2 had gene alterations involved in HRR. Patients with HRR gene alterations from cohort 1 and all patients from cohort 2 were combined for the HRR-deficient population.

Eligible participants were male patients aged 18 years or older (≥ 20 years in Japan) with asymptomatic or mildly symptomatic (per Brief Pain Inventory-Short Form [BPI-SF] question three score < 4) metastatic castration-resistant prostate cancer; had an Eastern Cooperative Oncology Group performance status of 0 or 1; and had a life expectancy of 12 months or longer. Patients included in the HRR-deficient population had one or more alterations in at least one of 12 HRR genes (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *FANCA*, *RAD51C*, *NBN*, *MLH1*, *MRE11A*, and *CDK12*). Trial participants were required to be receiving ongoing androgen deprivation therapy (or have had bilateral orchiectomy) and have progressive disease at study entry (prostate-specific antigen only or imaging-based). Key exclusion criteria included previous treatment for castration-resistant prostate cancer, apart from androgen deprivation therapy and first-generation anti-androgens; previous treatment with a second-generation ARP inhibitor, PARP inhibitors, cyclophosphamide, or mitoxantrone; treatment with opioids for cancer pain within 28 days of randomisation; and clinically significant cardiovascular, kidney, or liver disease. Previous treatment with docetaxel and abiraterone or orteronel for hormone-sensitive disease was allowed. A full list of eligibility criteria is in the appendix (pp 2–4).

The trial conformed to Good Clinical Practice standards, the Declaration of Helsinki, and the International Council on Harmonisation. The protocol received approval from the institutional review board or ethics committee at each site. The trial protocol has been published previously.⁶ Signed informed consent was obtained from all patients. For the TALAPRO-2 trial, comments from patient advocates were reviewed and considered in the final study design, the collection of outcome measures, and aspects of the conduct of the trial. Additionally, patient advocacy groups were engaged to support recruitment efforts and strategies. This study is registered with ClinicalTrials.gov, NCT03395197, and is ongoing.

Randomisation and masking

Patients with HRR gene alterations were randomly assigned (1:1) to receive talazoparib plus enzalutamide or placebo plus enzalutamide. Randomisation was carried out by personnel on site using a centralised interactive web response system and a permuted block size of 4. Randomisation was stratified by previous treatment with second-generation ARP inhibitor (abiraterone or orteronel) or docetaxel (yes or no) for castration-sensitive prostate cancer.^{6,7} A randomisation number was generated, and a dispensable unit or container number assigned to each patient. The sponsor, patients, and investigators were masked to the allocation of talazoparib or placebo, whereas the treatment assignment of enzalutamide was not masked. Placebo capsules, which did not contain talazoparib, were identical in appearance to each dosage strength of talazoparib capsules and provided by the sponsor.

Procedures

Before randomisation, patients were required to prospectively have their tumour assessed for alterations in HRR-related genes (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *FANCA*, *RAD51C*, *NBN*, *MLH1*, *MRE11A*, and *CDK12*) by next-generation sequencing of a blood sample using FoundationOne Liquid CDx (Foundation Medicine, Cambridge, MA, USA) or the most recent tumour tissue biopsy using FoundationOne CDx.

Patients received talazoparib 0.5 mg as two 0.25 mg capsules (or 0.35 mg as one 0.25 mg and one 0.1 mg capsule if moderate renal impairment was present) taken orally once daily with or without food, plus enzalutamide 160 mg as four 40 mg capsules taken orally once daily at the same time as talazoparib, or placebo plus enzalutamide both once daily. Study treatment continued until radiographic progression by blinded independent central review, an adverse event leading to permanent discontinuation, patient decision to discontinue treatment, or death. After radiographic progression, treatment could be continued if the investigator determined benefit was still being derived.⁶ The dose of talazoparib or placebo could be reduced sequentially to

See Online for appendix

0·35 mg, 0·25 mg, and 0·1 mg or interrupted to manage adverse events. Dose modifications of enzalutamide could occur according to the local label instructions.

Imaging scans (CT of chest, CT or MRI of abdomen and pelvis, and whole-body bone scan) were conducted every 8 weeks through to week 25 and every 12 weeks thereafter until radiographic progression was determined by investigator and blinded independent central review.¹¹ Soft tissue responses were confirmed by a follow-up radiographic assessment at least 4 weeks later with no evidence of confirmed bone disease progression on repeated bone scans at least 6 weeks apart per Prostate Cancer Working Group 3 criteria. Clinical laboratory evaluations and safety assessments were done at screening and at scheduled visits, every 2 weeks up to week 17, every 4 weeks up to week 53, every 8 weeks thereafter while on study drug, then 28 days after discontinuation of all study treatments or before initiation of a new antineoplastic or investigational therapy, whichever occurred first.

For patient-reported outcomes, the last assessment performed on or before the date of the first dose of study treatment (or before randomisation for patients randomly assigned but not receiving study drug) served as the baseline assessment. Patient-reported outcome assessments were completed electronically by patients at study visits before any other study activities, starting at baseline; then every 4 weeks through to week 53 or radiographic progression; next every 8 weeks after week 53 until radiographic progression, when no such progression had previously been documented; and finally, every 12 weeks after radiographic progression until the end of the study, using validated patient-reported outcome instruments.¹¹

Cancer-specific global health status/quality of life (GHS/QoL), functioning scales (physical, role, cognitive, emotional, and social), and cancer-specific symptoms scales (including fatigue, pain, and nausea or vomiting scales) were evaluated according to the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30).¹² Responses on 4-point and 7-point Likert scales were converted to a 0–100 scale, on which higher scores represent better functioning or quality of life (functional scales) or more extreme symptoms (symptom scales).

Patient-reported prostate cancer-specific urinary, bowel, and hormone treatment-related symptoms and incontinence aid, and functioning scales (sexual activity and sexual function) were assessed according to EORTC Quality of Life Questionnaire-Prostate (QLQ-PR25).¹³ Responses were collected on a 4-point scale and scored similarly to the EORTC QLQ-C30.

Worst pain experienced in the past 24 h and patient-reported pain symptoms were evaluated per BPI-SF. Worst pain (BPI-SF, question three) was assessed for 7 consecutive days before study visits and on study visit days based on a numeric rating scale between 0 and 10, with 0 meaning no pain and 10 meaning the worst imaginable pain;¹⁴ scores were averaged for each visit.

General health status was reported using the EQ-5D-5L, which includes a visual analogue scale item for measuring general health status.

Study sites were instructed that patients should self-report both ethnicity and race, with ethnicity being asked before race. If the patient refused to provide either their ethnicity or race, or if local laws prohibited collection of these data, the study sites were to record these data as not reported. Sex data were reported from the case report form by the clinical investigator at the screening or enrolment visit.

Outcomes

The primary endpoint was radiographic progression-free survival assessed by blinded independent central review per Response Evaluation Criteria in Solid Tumors (version 1.1; soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease) criteria. Efficacy and safety have been previously reported.⁶

Patient-reported outcomes were evaluated as secondary endpoints as specified in the protocol. Patient-reported outcomes included estimated mean change from baseline in cancer-specific GHS/QoL, functioning, and symptoms per EORTC QLQ-C30; prostate cancer-specific functioning and symptom scales per EORTC QLQ-PR25; pain symptoms per BPI-SF; and general health status per EQ-5D-5L. Time to definitive deterioration in GHS/QoL per EORTC QLQ-C30 and in prostate cancer-specific urinary symptoms per EORTC QLQ-PR25, and time to deterioration in pain symptoms per BPI-SF were also patient-reported secondary endpoints.

Definitive deterioration in GHS/QoL, functional scales, and symptom scales was defined as a decrease of 10 points or more (GHS/QoL and functional scales) or an increase of 10 points or more (symptom scales) from baseline, with deterioration (≥ 10 points) observed for all subsequent observations by the EORTC QLQ-C30.^{15,16} The same threshold of 10 or more points for definitive deterioration in functional and symptoms scales of the EORTC QLQ-PR25 was applied. Deterioration in pain symptoms per BPI-SF was defined as an increase of 2 points or more from baseline for two consecutive periods 4 weeks or more apart.¹⁷ Between-group differences of 10 points or more for EORTC QLQ-C30 and EORTC QLQ-PR25 scales and of 2 points or more for BPI-SF scales were considered clinically meaningful.

Statistical analysis

For the primary comparison in the HRR-deficient population of TALAPRO-2, it was estimated that a sample of 380 patients with HRR-deficient metastatic castration-resistant prostate cancer was required to observe 224 radiographic progression-free survival events based on blinded independent central review, providing 85% power to detect an HR of 0·64 using a one-sided stratified log rank test at a significance level of 0·0125. The primary results from the HRR-deficient population of

TALAPRO-2 have been published previously.⁷ The HRR-deficient, patient-reported outcome population of TALAPRO-2 had at least one HRR gene alteration, a baseline patient-reported outcome assessment, and at least one post-baseline patient-reported outcome assessment before the end of the study. Missing items were handled according to the scoring manuals of each instrument, and death was treated as a censoring event.

Mean changes from baseline in GHS/QoL, functional scales and symptoms, and general health status were calculated using a longitudinal repeated measures mixed-effects model. For the mixed-effects regression models, the assessments linked to specific on-treatment visits were used in the change from baseline analysis. Time to (definitive) deterioration analyses were summarised using the Kaplan–Meier method, and the median value and 95% CI were determined using the Brookmeyer-Crowley method. Time to definitive deterioration of EORTC QLQ-C30 functional and symptom scales were assessed post hoc. Patients without a definitive deterioration or without observed pain progression at the time of analysis were censored at the date of the last assessment using that instrument. In addition, to avoid worsening of pain events caused by reduction in pain management rather than clinical pain progression, pain observations associated with a reduction in analgesic use as per WHO criteria were censored when conducting this analysis. Between-group comparisons and statistical significance were obtained using a stratified log-rank test, and HR (95% CI) were obtained from a Cox proportional hazards model. Most of the analyses reported here were prespecified in the trial statistical analysis plan, unless otherwise mentioned. None of the patient-reported outcome analyses were in the testing hierarchy or adjusted for multiplicity. Adjustments for multiple comparisons were not made. Two-sided *p* values were generated and a threshold of 0·05 was used to identify differences. SAS version 9·4 statistical software was used for analyses.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, and data interpretation. The funder of the study was also responsible for the review and approval of the manuscript for submission and provided funding for medical writing support.

Results

Between Dec 18, 2018, and Jan 20, 2022, 399 patients with HRR-deficient metastatic castration-resistant prostate cancer were enrolled and randomly assigned: 200 in the talazoparib plus enzalutamide group and 199 in the placebo plus enzalutamide group. Of these, 394 (99%) had a baseline patient-reported outcome assessment followed by at least one post-baseline patient-reported outcome assessment (talazoparib plus enzalutamide *n*=197 and placebo plus enzalutamide *n*=197), and were included for analysis. Three patients in the talazoparib plus

enzalutamide group and two patients in the placebo plus enzalutamide group were not evaluable for patient-reported outcomes. The number of patients who completed the patient-reported outcome assessments by visit and baseline scores are shown in the appendix (pp 5–7). Overall, patient demographics including age, geographical region, race and ethnicity, and physical characteristics (including weight and BMI) were similar across treatment groups for the patient-reported outcome population (table). The median age of HRR-deficient patients with available patient-reported outcome data was 70 years (IQR 64–76) and 268 (68%) of 394 patients were White (table). Median follow-up was 22·2 months (IQR 13·8–27·7) in the talazoparib plus enzalutamide group and 20·2 months (13·5–26·6) in the placebo plus enzalutamide group. Subsequent systemic therapies for the all-comers intention-to-treat population have been previously published.⁶ Data on subsequent systemic therapies for the HRR-deficient population are not currently available.

Median time to definitive deterioration in GHS/QoL as measured by the EORTC QLQ-C30 was 27·1 months

	Talazoparib plus enzalutamide (n=197)	Placebo plus enzalutamide (n=197)	Total (n=394)
Age, years			
Median	70 (65–76)	71 (64–75)	70 (64–76)
<65	47 (24%)	53 (27%)	100 (25%)
65 to <75	91 (46%)	88 (45%)	179 (45%)
≥75	59 (30%)	56 (28%)	115 (29%)
Geographical region			
North America	22 (11%)	27 (14%)	49 (12%)
EU and Great Britain	91 (46%)	99 (50%)	190 (48%)
Asia	44 (22%)	36 (18%)	80 (20%)
Rest of the world	40 (20%)	35 (18%)	75 (19%)
Race			
White	134 (68%)	134 (68%)	268 (68%)
Black or African American	6 (3%)	5 (3%)	11 (3%)
Asian	45 (23%)	39 (20%)	84 (21%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	1 (1%)	1 (1%)	2 (1%)
Multiracial	0	1 (1%)	1 (<1%)
Not reported	10 (5%)	17 (9%)	27 (7%)
Unknown	1 (1%)	0	1 (<1%)
Ethnicity			
Hispanic, Latino, or of Spanish origin	20 (10%)	25 (13%)	45 (11%)
Not Hispanic, Latino, or of Spanish origin	163 (83%)	151 (77%)	314 (80%)
Not reported	14 (7%)	21 (11%)	35 (9%)
Baseline weight, kg	80·8 (72·3–91·6)	83·9 (73·2–93·8)	81·8 (72·6–93·8)
Baseline BMI, kg/m ² *	27·2 (24·1–29·9)	27·8 (24·6–31·0)	27·4 (24·4–30·6)
Data are median (IQR) or <i>n</i> (%). * <i>n</i> =196 in the talazoparib plus enzalutamide group, <i>n</i> =194 in the placebo plus enzalutamide group, and total <i>n</i> =390.			
Table: Patient demographics of the homologous recombination repair-deficient patient-reported outcome population			

(95% CI 21.2–non-estimable) in the talazoparib plus enzalutamide group and 19.3 months (16.6–23.0) in the placebo plus enzalutamide group. The observed stratified HR was 0.69 (95% CI 0.49–0.97; two-sided $p=0.032$;

figures 1A and 2A). Definitive deterioration in GHS/QoL was reported by 64 (32%) of 197 men in the talazoparib plus enzalutamide group and 71 (36%) of 197 men in the placebo plus enzalutamide group. In the post-hoc

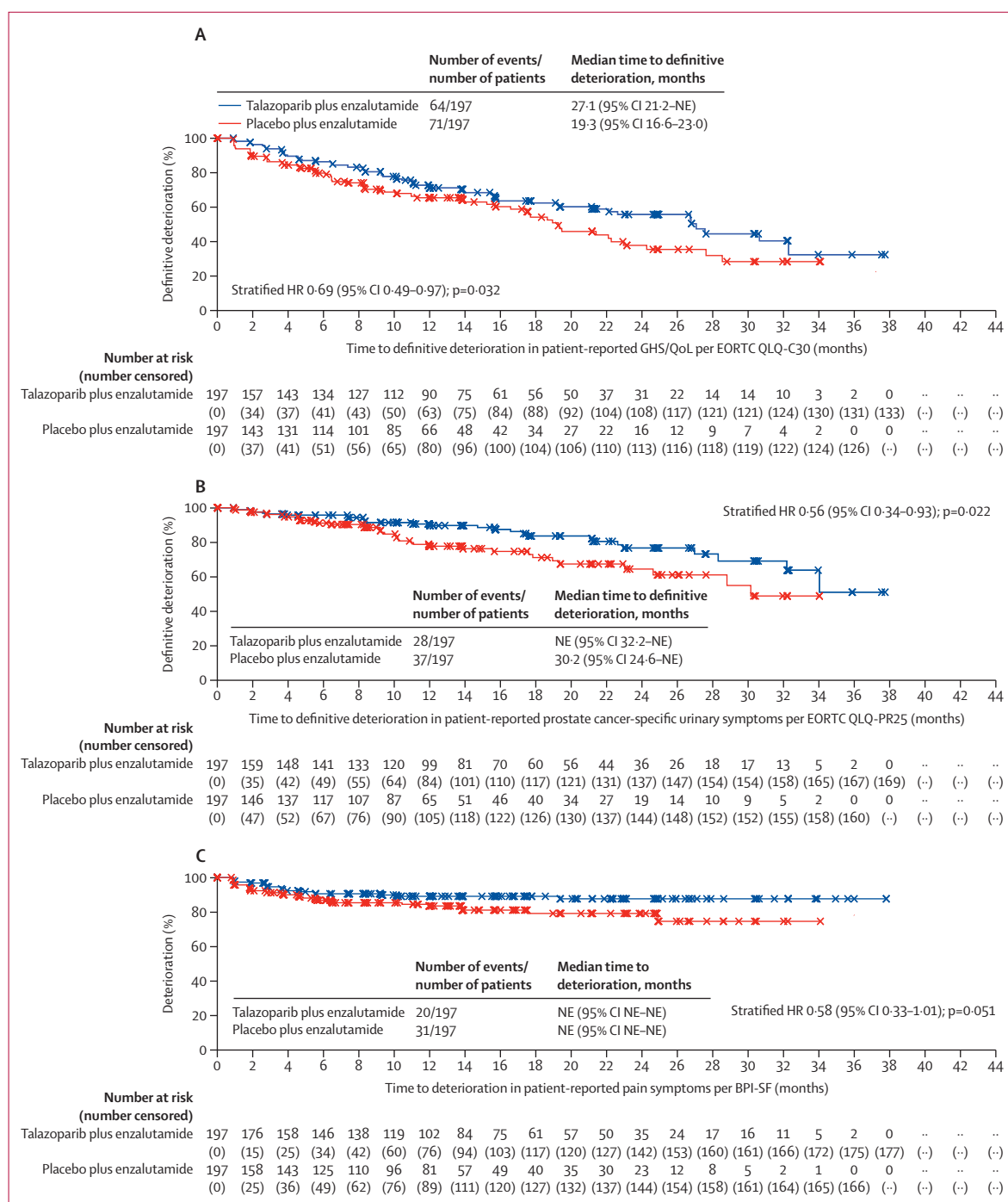


Figure 1: Time to deterioration in patient-reported outcomes

(A) Time to definitive deterioration in GHS/QoL per EORTC QLQ-C30. (B) Time to definitive deterioration in urinary symptoms per EORTC QLQ-PR25. (C) Time to deterioration in pain symptoms per BPI-SF. The reasons for censoring are shown in the appendix pp 8–9. BPI-SF=Brief Pain Inventory-Short Form. EORTC=European Organisation for Research and Treatment of Cancer. GHS=global health status. HR=hazard ratio. NE=non-estimable. QLQ-C30=Core Quality of Life Questionnaire. QLQ-PR25=Quality of Life Questionnaire-Prostate. QoL=quality of life.

analysis, median time to definitive deterioration in physical, emotional, and cognitive functioning, as well as in symptoms of nausea and vomiting, pain, appetite loss, and constipation favoured talazoparib plus enzalutamide compared with placebo plus enzalutamide ($p < 0.05$ for all comparisons; figure 2A). However, no difference was seen in time to definitive deterioration for role and social functioning, and for fatigue, dyspnoea, insomnia, and diarrhoea symptoms. Differences in mean scores over time for physical, emotional, and cognitive functioning, as well as pain, were also observed, which favoured talazoparib plus enzalutamide versus placebo plus enzalutamide. However, these differences did not reach the clinically meaningful threshold of 10 or more points (figure 3A, B; appendix pp 10–11). The mean change in score for sexual activity was similar between patients in the two groups (HR -0.8 [95% CI -3.1 to 1.4]; two-sided $p = 0.46$; figure 3A, appendix pp 10–11). Because low numbers of patients were sexually active over the previous 4 weeks and thereby eligible to answer the question on sexual function (talazoparib plus enzalutamide, $n = 20$; placebo plus enzalutamide, $n = 14$ at baseline), assessment of sexual functioning was omitted from the analysis.

Median time to definitive deterioration in urinary symptoms was non-estimable (95% CI 32.2 –non-estimable) in the talazoparib plus enzalutamide group and 30.2 months (24.6 –non-estimable) in the placebo plus enzalutamide group. The observed stratified HR was 0.56 (95% CI 0.34 – 0.93 ; two-sided $p = 0.022$; figures 1B, 2B). Definitive deterioration in urinary symptoms was reported for 28 (14%) of 197 patients in the talazoparib plus enzalutamide group and 37 (19%) of 197 patients in the placebo plus enzalutamide group. Time to definitive deterioration in bowel, hormone treatment-related symptoms, and incontinence aid were similar in the talazoparib plus enzalutamide group and the placebo plus enzalutamide group (figure 2B). Differences in mean changes from baseline for urinary and bowel symptoms were not clinically meaningful (these did not reach the threshold of ≥ 10 points difference; figure 3C, appendix pp 10–11).

Patients reported less pain with talazoparib plus enzalutamide versus placebo plus enzalutamide (estimated mean difference in scores -0.6 [95% CI -0.9 to -0.3]; two-sided $p = 0.0005$; appendix pp 10–11) on the scale of the worst pain in the last 24 h of the BPI-SF instrument. However, this difference in scores was not clinically meaningful (these did not reach the threshold of ≥ 2 points). The median time to deterioration in pain symptoms was non-estimable for both treatment groups (stratified HR 0.58 [95% CI 0.33 to 1.01]; two-sided $p = 0.051$; figure 1C).

General health status as measured by the EQ-ED-5L index favoured talazoparib plus enzalutamide versus placebo plus enzalutamide, although the estimated mean difference over the treatment period was 0.0 (95% CI 0.0 – 0.1 ; two-sided $p = 0.0077$; appendix p 11).

A EORTC QLQ-C30

	Number of events/number of patients			Hazard ratio (95% CI)	p value
	Talazoparib plus enzalutamide	Placebo plus enzalutamide			
GHS/QoL	64/197	71/197	●	0.69 (0.49–0.97)	0.032
Physical functioning	60/197	82/197	●	0.57 (0.41–0.80)	0.0010
Role functioning	67/197	69/197	●	0.77 (0.55–1.08)	0.12
Emotional functioning	39/197	57/197	●	0.48 (0.32–0.72)	0.0004
Cognitive functioning	66/197	73/197	●	0.70 (0.50–0.97)	0.033
Social functioning	61/197	68/197	●	0.75 (0.53–1.06)	0.10
Fatigue	88/197	88/197	●	0.85 (0.63–1.14)	0.27
Nausea and vomiting	24/197	32/197	●	0.56 (0.33–0.95)	0.030
Pain	52/197	74/197	●	0.56 (0.39–0.79)	0.0011
Dyspnoea	45/197	50/197	●	0.68 (0.45–1.02)	0.063
Insomnia	39/197	40/197	●	0.77 (0.50–1.21)	0.26
Appetite loss	52/197	64/197	●	0.60 (0.41–0.87)	0.0061
Constipation	33/197	48/197	●	0.52 (0.34–0.82)	0.0037
Diarrhoea	19/197	21/197	●	0.61 (0.32–1.15)	0.12

B EORTC QLQ-PR25

Urinary symptoms	28/197	37/197	●	0.56 (0.34–0.93)	0.022
Bowel symptoms	16/197	21/197	●	0.54 (0.28–1.05)	0.064
Hormonal treatment-related symptoms	43/197	41/197	●	0.78 (0.50–1.20)	0.25
Incontinence aid	16/197	14/197	●	1.16 (0.56–2.41)	0.69

0 1 2 3
Favours talazoparib plus enzalutamide Favours placebo plus enzalutamide

Figure 2: Forest plot of time to definitive deterioration in functioning and symptoms by treatment group (A) Time to definitive deterioration in functional and symptoms scales per EORTC QLQ-C30. (B) Time to definitive deterioration in symptoms per EORTC QLQ-PR25. Functional scales for EORTC QLQ-PR25 are not reported here owing to small sample size. EORTC=European Organisation for Research and Treatment of Cancer. GHS=global health status. QLQ-C30=Core Quality of Life Questionnaire. QLQ-PR25=Quality of Life Questionnaire-Prostate. QoL=quality of life.

Discussion

In addition to the previously reported improvements in efficacy outcomes for talazoparib plus enzalutamide in patients with HRR-deficient metastatic castration-resistant prostate cancer,⁷ this analysis suggests that talazoparib plus enzalutamide is also associated with improvements in quality of life and patient-reported outcomes compared with placebo plus enzalutamide. In the current analysis, definitive deterioration in GHS/QoL, physical, emotional, and cognitive functioning, pain, nausea and vomiting, appetite loss, and constipation per EORTC QLQ-C30, as well as in urinary symptoms per EORTC QLQ-PR25, was delayed with talazoparib plus enzalutamide versus placebo plus enzalutamide. Worst pain in the past 24 h on the BPI-SF scale and some functioning and symptoms scales also favoured talazoparib plus enzalutamide; however, the differences between treatment groups were not clinically meaningful. The treatment effect for time to definitive deterioration in GHS/QoL per EORTC QLQ-C30 is consistent with patient-reported outcome results from the TALAPRO-2 all-comers population (cohort 1).¹⁸ However, in the

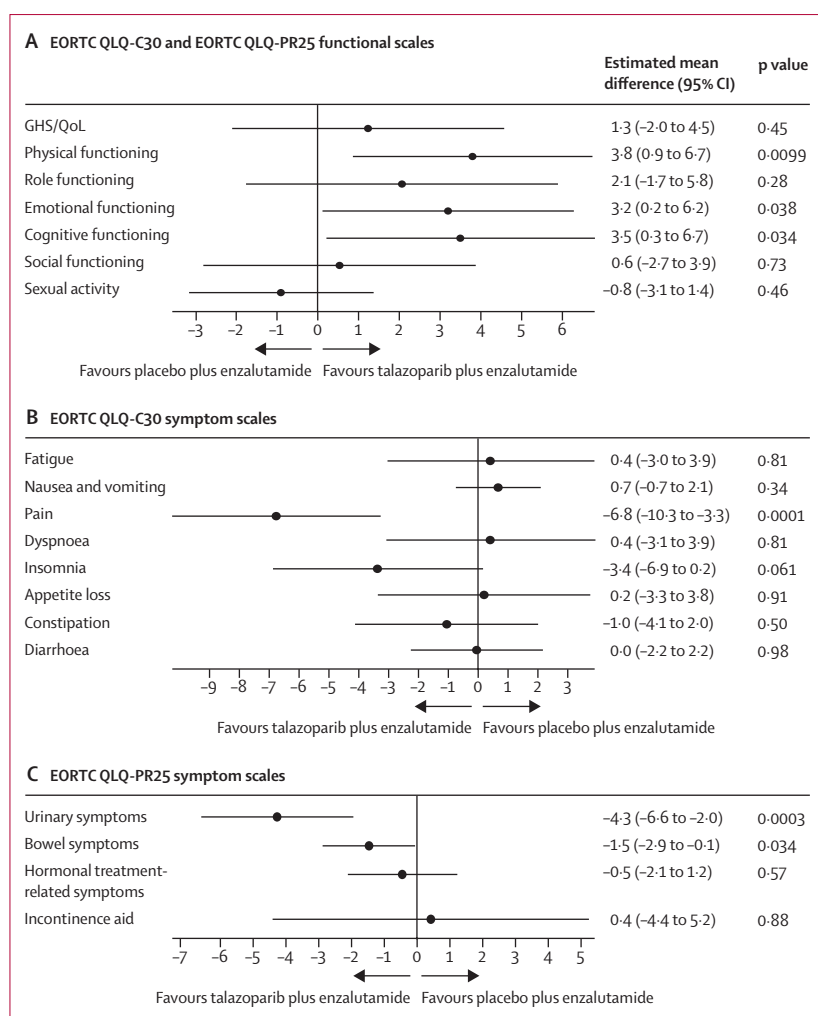


Figure 3: Estimated mean treatment differences in functional and symptom scales

(A) Estimated mean treatment differences in EORTC QLQ-C30 and EORTC QLQ-PR25 functional scales. (B) Estimated mean treatment differences in EORTC QLQ-C30 symptom scales. (C) Estimated mean treatment differences in EORTC QLQ-PR25 symptom scales. Estimated mean differences were obtained by subtracting the mean change from baseline with placebo plus enzalutamide from the mean change from baseline with talazoparib plus enzalutamide. For GHS/QoL, functional scales, and sexual activity, larger values correspond to better outcomes or functioning. For symptom scales, larger values correspond to worse outcomes. As per the QLQ-PR25 instrument, only patients who wore an incontinence aid were asked to complete the question about incontinence aids. EORTC=European Organisation for Research and Treatment of Cancer. GHS=global health status. QLQ-C30=Core Quality of Life Questionnaire. QLQ-PR25=Quality of Life Questionnaire-Prostate. QoL=quality of life.

HRR-deficient population, there was also a favourable outcome in delaying worsening of several functional and symptom scales per EORTC QLQ-C30 and urinary symptoms per EORTC QLQ-PR25, attributed to talazoparib plus enzalutamide. We hypothesise that a more durable disease control with talazoparib plus enzalutamide compared with placebo plus enzalutamide led to a delay in deterioration of symptoms and overall quality of life.

Although comparisons with results from other trials evaluating combination therapies with PARP inhibitors and ARP inhibitors should be treated with caution given major differences in patient characteristics and the

patient-reported outcome instruments used, no clinically significant differences in HRQoL were observed with niraparib plus abiraterone versus placebo plus abiraterone in patients with metastatic castration-resistant prostate cancer harbouring gene alterations associated with HRR who were enrolled in the phase 3 MAGNITUDE trial.¹⁹ Similarly, no clinically meaningful differences in time to pain progression, symptomatic skeletal events, or change in HRQoL based on the BPI-SF and Functional Assessment of Cancer Therapy-Prostate questionnaires were observed with olaparib plus abiraterone versus placebo plus abiraterone in the phase 3 PROpel trial evaluating first-line treatment for patients with metastatic castration-resistant prostate cancer.²⁰ The addition of olaparib to abiraterone also did not negatively affect HRQoL compared with placebo plus abiraterone in a phase 2 trial of patients with metastatic castration-resistant prostate cancer who were previously treated with docetaxel.²¹ Interestingly, in the CARD study,²² cabazitaxel improved pain response, and delayed pain progression and symptomatic skeletal events more than abiraterone or enzalutamide in patients with metastatic castration-resistant prostate cancer. Going beyond PARP inhibitors and ARP inhibitors, in addition to improving radiographic progression-free survival and overall survival, the prostate-specific membrane antigen (PSMA)-targeted radioligand therapy [¹⁷⁷Lu]Lu-PSMA-617 plus standard of care also delayed time to deterioration in HRQoL and time to skeletal events compared with standard of care alone.²³

Overall, patient-reported outcome assessments highlight the substantial morbidity and pain associated with genitourinary symptoms and metastases to the bones among patients with metastatic castration-resistant prostate cancer. Bone-related parameters (such as absent to mild pain) and no previous skeletal-related events among patients with bone metastases represent prognostic factors for overall survival and underscore the importance of symptomatic relief and the use of bone-protecting agents for the prevention of skeletal events.²⁴⁻²⁷ Additionally, locoregional urinary symptoms (such as haematuria, dysuria, and pelvic pain caused by the primary tumour) might be associated with worse overall survival and require active management throughout the course of the disease to alleviate symptoms and reduce overall tumour burden.²⁸ Furthermore, patients diagnosed with metastatic castration-resistant prostate cancer tend to be older and therefore their overall health and fitness status should guide treatment strategies. Patient-reported outcome analyses, such as those in the current study, emphasise the importance of physicians obtaining their patients' perspective regarding quality of life parameters and offering patients with metastatic castration-resistant prostate cancer a role in decisions regarding their treatment strategy, enabling shared decision making.

This analysis is limited by the absence of adjustment for multiple comparisons and the potential for informative

missing data and selection bias. Another limitation is that increases in pain management were not considered when evaluating time to deterioration in pain.

The TALAPRO-2 patient-reported outcomes data suggest that combination treatment with talazoparib plus enzalutamide represents an appropriate treatment strategy for patients with metastatic castration-resistant prostate cancer harbouring HRR gene alterations, showing improvements versus placebo plus enzalutamide in overall quality of life of patients in addition to a previously reported benefit in radiographic progression-free survival.

Contributors

All authors contributed to the conception and design of the study. APF, KF, NM, AAA, FS, UDG, JYJ, PCCF, RJJ, SZ, JO, NDS, CD, JCa, and NA were trial investigators, and responsible for the compilation of resources and collection of data. PC did the data analysis. All authors contributed to the interpretation of data and reviewed and critically edited the manuscript. NA and PC accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

APF reports honoraria from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, and Roche; a consulting or advisory role for Bayer, Ipsen, Janssen, MSD, Novartis, Pfizer, and Roche; stock or stock options in Brazilian Information Oncology; research funding from AstraZeneca, Bristol Myers Squibb, CAPES–CNPq, Foundation Medicine, Ipsen, MSD, and Roche; and travel, accommodation, or expenses from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, and Roche. KF reports honoraria (institution) for participation in advisory boards and talks from Advanced Accelerator Applications/Novartis, Amgen, Astellas Pharma, AstraZeneca, Bayer, Clovis Oncology, Daiichi Sankyo, Janssen, MSD, Novartis, Pfizer, and Sanofi; and honoraria (personal) for participation in advisory boards from Arvinas, CureVac, MacroGenics, and Orion. NM reports honoraria (personal) from Sanofi; research funding (institution) from Amgen, Astellas Pharma, AstraZeneca, Bayer, Chugai Pharma, Eisai, Janssen, Lilly, MSD, Pfizer, PRA Health Science, Roche, Seagen, Taiho, and Takeda; and travel, accommodation, or expenses (personal) from Pfizer. AAA reports honoraria from Aculeus Therapeutics, Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Ipsen, Janssen, MSD, Merck Serono, Novartis, Noxopharm, Pfizer, Sanofi, Telix, and Tolmar; consulting fees from Aculeus Therapeutics, Astellas, Janssen, and Novartis; participation on advisory boards for Amgen, Astellas, AstraZeneca, Arvinas, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Ipsen, Janssen, MSD, Merck Serono, Novartis, Noxopharm, Pfizer, Sanofi, Telix, and Tolmar; participation on a data safety monitoring board for OncoSec; research funding (institution unless stated otherwise) from Astellas (investigator), AstraZeneca (investigator), Merck Serono (investigator), Astellas, Aptevo Therapeutics, AstraZeneca, Bayer, Bionomics, Bristol Myers Squibb, Eli Lilly, Exelixis, GlaxoSmithKline, Gilead Sciences, Hinova, Ipsen, Janssen, MedImmune, MSD, Merck Serono, Novartis, Pfizer, Sanofi Aventis, and SYNthorx; receiving medical writing services from Astellas Pharma, Exelixis, and Pfizer; travel and accommodation fees from Amgen, Astellas, Bayer, Janssen, Merck Serono, Novartis, Pfizer, and Tolmar; speakers bureau activities for Amgen, Astellas, Bayer, Bristol Myers Squibb, Ipsen, Janssen, Merck Serono, and Novartis; being a member of steering committees for Astellas, AstraZeneca, Exelixis, Janssen, and Pfizer; and Chair of the Urologic Oncology Group for the Clinical Oncology Society of Australia, and Chair of the Translational Research Subcommittee and on the Scientific Advisory Committee for the ANZUP Cancer Trials Group. FS reports honoraria from Astellas Pharma, AstraZeneca, Bayer, Janssen Oncology, and Sanofi; a consulting role for Astellas Pharma, AstraZeneca/MedImmune, Janssen Oncology, and Sanofi; and institutional funding from Astellas Pharma, AstraZeneca, Bayer, Janssen Oncology, and Sanofi. UDG reports a consulting or advisory role for Amgen, Astellas Pharma,

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Data sharing

On request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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