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## **Patient-reported outcomes in a phase 2 study of metastatic castration-resistant prostate cancer patients treated with olaparib in combination with abiraterone**

*Fred Saad, Antoine Thiery-Vuillemin, Pawel Wiechno, Boris Alekseev, Nuria Sala, Robert Jones, Ivo Kocak, Vincenzo Emanuele Chiuri, Jacek Jassem, Aude Fléchon, Charles Redfern, Jinyu Kang, Joseph Burgents, Christopher Gresty, Arnold Degboe, Noel Clarke*

Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada (Prof F Saad MD FRCS); Department of Medical Oncology, Centre Hospitalier Universitaire Besançon, Besançon, France (A Thiery-Vuillemin MD PhD); Maria Skłodowska-Curie National Research Institute of Oncology (MSCNRIO), Warsaw, Poland (P Wiechno MD); Herten Moscow Cancer Research Institute, Moscow, Russia (B Alekseev MD); Catalan Institute of Oncology, Hospital Josep Trueta, Girona, Spain (N Sala MD); Velindre Cancer Centre, Cardiff University, Cardiff, UK (R Jones MD); Masaryk Memorial Cancer Institute, Brno, Czech Republic (I Kocak MD); Ospedale Vito Fazzi, Lecce, Italy (E Chiuri MD); Medical University of Gdańsk, Gdańsk, Poland (J Jassem MD); Centre Léon Bérard, Lyon, France (A Fléchon MD); Sharp HealthCare, San Diego, CA, USA (C Redfern MD); AstraZeneca, Gaithersburg, MD, USA (J Kang MD, A Degboe MD); Merck & Co., Inc., Kenilworth, NJ, USA (J Burgents MD); AstraZeneca, Cambridge, UK (C Gresty MSc); The Christie and Salford Royal Hospitals, Manchester, UK (Prof N W Clarke MBBS ChM FRCS)

Correspondence to: Prof Fred Saad, Centre Hospitalier de l'Université de Montréal,  
Montréal, QC, Canada

**fredsaad@videotron.ca**

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## Summary

**Background** A double-blind, phase 2 trial showed patients with metastatic castration-resistant prostate cancer (mCRPC) treated with olaparib plus abiraterone versus placebo plus abiraterone had significantly improved progression-free survival (HR 0.65, 95% CI 0.44–0.97,  $p=0.034$ ). We present exploratory analysis of pain and health-related quality of life (HRQOL).

**Methods** Patients had been treated with docetaxel and up to one additional line of chemotherapy. Patients were randomised (1:1) to olaparib (300 mg bid) or placebo, plus abiraterone (1000 mg od) and prednisone/prednisolone (5 mg bid). They were asked to complete the Brief Pain Inventory-Short Form (BPI-SF), a worst bone pain item, the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and the EuroQol-5 five-dimension five level (EQ-5D-5L) assessment at weeks 4, 8, 12, then every 12 weeks until treatment discontinuation. BPI-SF worst pain, worst bone pain and FACT-P Total and subscale scores were analysed for change from baseline, time to deterioration (TTD). All assessments were analysed for improvement. This trial is registered with Clinicaltrials.gov, number NCT01972217 and is no longer recruiting patients.

**Findings** Between Nov 25, 2014 and July 14, 2015, 171 patients were screened and 71 were randomised to each study arm. Data cut-off: Sept 22, 2017. Questionnaire compliance was generally high. Adjusted mean change in FACT-P Total Score from baseline across all visits was  $-0.60$  with olaparib plus abiraterone and  $-2.09$  with placebo plus abiraterone (difference 1.48 [95% CI  $-3.96$ – $6.92$ ]). TTD in pain and HRQOL was similar in both arms (BPI-SF worst pain [HR 0.90, 95% CI 0.62–1.32];

worst bone pain [HR 0.85, 95% CI 0.59–1.22]; FACT-P Total Score [HR 0.97, 95% CI 0.68–1.40]).

**Interpretation** Patients with mCRPC did not experience a detriment to pain or HRQOL (FACT-P Total Score and subscales) when olaparib was added to abiraterone treatment.

**Funding** AstraZeneca and Merck Sharp & Dohme.

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## **Research in context panel**

### **Evidence before this study**

This was the first phase 2 trial to demonstrate a statistically significant radiographic progression-free survival (rPFS) benefit with a poly(ADP-ribose) polymerase (PARP) inhibitor in combination with a next-generation hormonal agent (NHA) in the treatment of metastatic castration-resistant prostate cancer. We searched PubMed and the databases of the American Society of Clinical Oncology and the European Society for Medical Oncology from Jan 1, 2012 to Oct 31, 2018 for publications including the search terms “PARP inhibitor”, “prostate cancer”, and “quality of life” or “pain”, using no date or language restrictions. For phase 2 trials in patients with metastatic castration-resistant prostate cancer who had received PARP inhibitor, we identified one poster related to this trial that reported health-related quality of life (HRQOL) that was presented at ASCO-GU in 2019. Two posters were presented at ASCO 2020 that

reported HRQOL and burden of pain data in the phase 3 PROfound trial of olaparib monotherapy versus physician's choice of abiraterone or enzalutamide.

### **Added value of this study**

To our knowledge, these analyses represent the first publication of HRQOL and pain outcomes for patients with metastatic castration-resistant prostate cancer receiving a PARP inhibitor in combination with an NHA. Results indicate that patients with metastatic castration-resistant prostate cancer did not experience a detriment to HRQOL and pain or report worse outcomes when treated with olaparib plus abiraterone compared to placebo plus abiraterone.

### **Implications of all the available evidence**

Data on patient-reported outcomes, such as HRQOL and disease-related symptoms are important to support informed decision-making by patients and clinicians. Analyses from this phase 2 study suggest that combining olaparib with abiraterone did not cause a detrimental effect to patients' HRQOL compared with placebo plus abiraterone. Phase 3 studies are required to validate these results; the ongoing phase 3 PROpel trial (NCT03732820) of olaparib plus abiraterone versus placebo plus abiraterone in the first-line metastatic castration-resistant prostate cancer setting will provide additional insight.

## Introduction

Prostate cancer is the second most common cancer and the fifth largest cause of cancer-related deaths in men worldwide.<sup>1</sup> In unscreened populations approximately 14% of patients present with metastatic disease<sup>2</sup> and up to 40% of patients who present with non-metastatic disease eventually develop metastases despite local therapy.<sup>3</sup> Although next-generation hormonal agents (NHA) such as enzalutamide, abiraterone, apalutamide, and darolutamide have improved treatment outcomes,<sup>4-7</sup> prostate cancer patients develop resistance to hormonal therapy over time and the median overall survival for patients with metastatic castration-resistant prostate cancer in the first-line setting is approximately 3 years.<sup>8</sup> In addition, there is no consensus on how to sequence treatments to deliver the best outcomes for patients. Therefore, in-depth analysis of new therapies, including analysis of health-related quality of life (HRQOL) and patient experience, is essential to facilitate patient and clinician decision-making.

Based on the results of the PROfound trial, the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib has been approved in the USA for the treatment of patients with metastatic castration-resistant prostate cancer with alterations in genes associated with homologous recombination repair (HRR) and whose disease had progressed on prior treatment with an NHA.<sup>9-11</sup> In Europe, olaparib is an approved treatment for patients with *metastatic castration-resistant prostate cancer* and alterations in *BRCA1* or *BRCA2* genes who have had disease progression following prior therapy including NHA.<sup>12</sup>

Preclinical studies suggest that there is a combined anti-tumour effect when PARP inhibitors and NHAs are administered together. This is possibly due to PARP involvement in positive co-regulation of androgen receptor signalling, leading to enhanced androgen receptor (AR) target gene suppression when PARP/AR signalling is inhibited, or by NHAs altering/inhibiting the transcription of some HRR genes, inducing HRR deficiency and increased sensitivity to PARP inhibitors via non-genetic mechanisms.<sup>13-15</sup>

In this randomised, double-blind, placebo-controlled phase 2 trial, the PARP inhibitor olaparib was given in addition to abiraterone to patients with *metastatic castration-resistant prostate cancer* who had previously received docetaxel to test the hypothesis that combining a PARP inhibitor with abiraterone would benefit patients regardless of HRR mutation (HRRm) status. The study showed that treatment with olaparib plus abiraterone compared with placebo plus abiraterone led to a significant radiographic progression-free survival (rPFS) benefit for patients unselected by HRRm status (median rPFS 13.8 [95% CI 10.8–20.4] vs 8.2 months [95% CI 5.5–9.7], respectively; hazard ratio [HR] 0.65 [95% CI 0.44–0.97],  $p=0.034$ ).<sup>16</sup> Most patients (66/71 [93%] in olaparib plus abiraterone arm and 57/71 [80%] in the placebo plus abiraterone arm) experienced at least one adverse event, with grade  $\geq 3$  events reported by 38 of 71 (54%) and 20 of 71 (28%) of patients in the olaparib plus abiraterone and placebo plus abiraterone arms, respectively.<sup>16</sup>

Considered alone, efficacy and safety results do not provide a comprehensive description of patient experience. Collection and analysis of patient-reported outcomes (PROs) can help to address this knowledge gap and support informed decision-making by patients and clinicians regarding type and timing of treatment. For



example, if a treatment does not affect a patient's HRQOL then there may be potential for it to be used earlier in the treatment sequence.<sup>17,18</sup> In order to understand the impact of combining olaparib with abiraterone on patient experience, predefined exploratory objectives of this trial were to investigate the impact of treatment on pain, HRQOL and health state utility. These were assessed using the Brief Pain Inventory-Short Form (BPI-SF), a worst bone pain item, the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire; and the EuroQol-5 five-dimension five level (EQ-5D-5L) index.

## **Methods**

### **Study design and participants**

The study design has previously been reported.<sup>16</sup> In brief, the study was a randomised, double-blind, placebo-controlled phase 2 trial at 41 sites in 11 countries across Europe and North America. Eligible patients were aged  $\geq 18$  years with histologically or cytologically proven metastatic castration-resistant prostate cancer defined as an increasing prostate-specific antigen concentration or other signs of disease progression despite androgen-deprivation therapy and serum testosterone levels at castrate levels ( $\leq 50$  ng/dL), and at least one metastatic lesion on bone scan, computed tomography scan, or magnetic resonance imaging, and who had received prior treatment with docetaxel and up to one additional prior line of chemotherapy.

All patients provided written informed consent and the study protocol was approved by the institutional review board or ethics committee at all participating institutions. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and the AstraZeneca Policy on Bioethics.

### **Randomisation and masking**

As previously reported,<sup>16</sup> patients were enrolled by the investigators at each individual site and were randomly assigned (1:1) to receive either olaparib plus abiraterone or placebo plus abiraterone using a centralised interactive voice or web response system, without stratification. Investigators contacted the centralised interactive voice response system by telephone or online for allocation of the randomised treatment Kit ID number, which were assigned sequentially to each patient as they became eligible.

Patients, those giving the interventions, data collectors, and study personnel were masked to treatment allocation. Individuals involved in data analysis remained masked to treatment allocation until the time of the primary analysis and all investigators and patients remained masked until verification and closure of the study database, with the exception of medical emergencies in which knowledge about treatment group was required for appropriate patient management.

## **Procedures**

As previously reported,<sup>16</sup> the trial comprised an open-label safety run-in dose-escalation phase (during which time an initial cohort of up to six patients was given an initial dose of olaparib 200 mg twice daily plus abiraterone 1000 mg once daily and if well tolerated was increased to 300 mg twice daily, and if this higher dose was well tolerated, then olaparib 300 mg twice daily was used in the next phase of the study) followed by a randomised, double-blind treatment phase. In this randomised phase patients received either olaparib (300 mg twice daily) plus abiraterone (1000 mg once daily) and prednisone or prednisolone (5 mg twice daily) or placebo plus abiraterone (1000 mg once daily) and prednisone or prednisolone (5 mg twice daily) while continuing with standard androgen-ablation therapy with luteinising hormone-releasing hormone agonists, antagonists, or surgical castration. Treatment was continued until disease progression or lack of clinical benefit (investigator-assessed), and patients were permitted to discontinue either olaparib or placebo, or abiraterone individually at the discretion of the investigator.

## Outcomes

The primary endpoint of the randomised phase of the study was investigator-assessed radiographic progression-free survival (RECIST v1.1 or PCWG2). Key secondary endpoints were safety and tolerability, time to second progression and overall survival. A full list of endpoints has been described previously.<sup>16</sup> Exploratory PROs are reported here.

The impact of treatment on pain, HRQOL, health state utility and other cancer-related symptoms were assessed using the BPI-SF worst pain and a single item question on worst bone pain, FACT-P and EQ-5D-5L questionnaires. These questionnaires were selected because they are well established as instruments to measure disease symptoms and HRQOL, and they consider the most relevant symptoms in patients with prostate cancer.<sup>19-21</sup> Patients were asked to complete paper-based versions of the BPI-SF, a worst bone pain item, the FACT-P and EQ-5D-5L questionnaires at baseline, at patient visits at weeks 4, 8, and 12 and then every 12 weeks until treatment discontinuation. If patients discontinued treatment for reasons other than disease progression, they were assessed 30 days after discontinuation and then every 12 weeks until progression.

The BPI-SF contains 15 items measuring two domains (pain severity and pain interference). Each item is rated on an 11-point number rating scale, ranging from 'no pain' (0) to 'worst imaginable' pain (10) but our analysis focused on the 'worst pain' item of the pain severity scale only. In addition, a worst bone pain item was developed for this study as 90% of patients with metastatic castration-resistant prostate cancer have bone metastases.<sup>22</sup> The worst bone pain item has a similar format to the BPI-SF

worst pain item and patients are asked to rate their worst bone pain on an 11-point number rating scale ranging from 'no pain' (0) to 'worst imaginable' pain (10). Reported scores were used to evaluate change from baseline, time to deterioration (TTD) and time to improvement for both scales. A clinically meaningful worsening or deterioration in pain was defined as an increase in score of  $\geq 2$  points from baseline, and clinically meaningful improvement was defined as a decrease in score of  $\geq 2$  points from baseline.<sup>23</sup>

The FACT-P questionnaire includes four subscales regarding physical, emotional, functional, and social/family wellbeing, plus a 12-item Prostate Cancer Symptoms (PCS) subscale. The questionnaire is used to calculate FACT-P Total Score (range 0–156), FACT-P Treatment Outcome Index (TOI; range 0–104), FACT advanced prostate symptom index-8 (FAPSI-8; range 0–32), FACT advanced prostate symptom index-6 (FAPSI-6; range 0–24), PCS (range 0–48), Functional Wellbeing (FWB; range 0–28) and Physical Wellbeing (PWB; range 0–28). In all subscales a higher score indicates a higher HRQOL.

The FACT-P Total Score was analysed for change from baseline, TTD and time to improvement. In addition, the FACT-P subscales were analysed for best response. A clinically meaningful improvement (increase) or worsening/deterioration (decrease) in score was defined as a change of  $\geq 6$  points for FACT-P Total Score,  $\geq 5$  points for TOI,  $\geq 3$  points for FAPSI-8, FAPSI-6 and PCS, and  $\geq 2$  points for FWB and PWB.<sup>24</sup>

The impact of treatment and disease state on health state utility was evaluated using the EQ-5D-5L, a standardised instrument developed to measure HRQOL in a wide range of health conditions and treatments.<sup>21</sup> The instrument comprises two sections:

the EQ-5D-5L descriptive system and the EQ visual analogue scale (VAS). In the EQ-5D descriptive system five dimensions are assessed: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients are asked to rate each dimension on a scale ranging from 'no problems' (1) to 'unable to/ extreme problems' (5). The VAS is a vertical scale ranging from 0 to 100 where 0 indicates worst imaginable health and 100 indicates best imaginable health. The pain/discomfort dimension was of particular interest in this study due to its relation to symptoms, and so this score was analysed for improvement.

Predefined outcomes included change from baseline in BPI-SF worst pain, single-item worst bone pain and FACT-P scales scores; TTD in BPI-SF worst pain and worst bone pain; and assessment of EQ-5D-5L health state utility index. Improvement and best response analyses for these variables were post hoc.

### **Statistical analyses**

We calculated that we needed to enrol approximately 140 patients (70 per treatment group) in the randomised phase to give 80% power to detect a statistically significant difference between treatment groups at a one-sided significance level of 10%, assuming a true HR of 0.65. A hierarchical multiple testing strategy was prespecified for the primary analysis of rPFS and the key secondary endpoints of overall survival and investigator-assessed time to second progression (PFS2). The final analysis was planned to be conducted after 100 rPFS events had occurred. If statistical significance was shown for rPFS, PFS2 was then compared between the treatment groups. If the null hypothesis of no difference between treatment groups was rejected for PFS2, overall survival was tested as part of the multiple-testing procedure; however, all

planned analyses were done, and p values determined outside of the multiple testing strategy should be considered nominal.

All PRO and health state utilities data were analysed using the Full Analysis Set (FAS) that includes all randomised patients, as well as patients who were randomised but did not subsequently go on to receive study treatment, with the exception of mean baseline and total change from baseline analyses that used the population who had a valid baseline and at least one post-baseline assessment.

Compliance rate for completion of each questionnaire was calculated for each assessment visit, including baseline, using the number of patients with an evaluable form at that time point divided by number of patients expected to complete forms at that visit.

Comparison of change from baseline in BPI-SF worst pain and single item worst bone pain was analysed using a mixed model for repeated measures (MMRM) with visit, treatment by visit interaction, baseline score, and score by visit interaction as fixed effects.

TTD in BPI-SF worst pain and single-item worst bone pain was defined as the time from the date of randomisation to the date of first assessment of worsening of pain (an increase of pain score of  $\geq 2$  points from baseline on the 0–10 scale), or death. If a patient was too heavily affected by symptoms of disease under investigation to complete the assessment, this was also considered a clinically important deterioration. TTD was analysed by log-rank test.

An improvement in BPI-SF worst pain and worst bone pain was defined as a decrease of  $\geq 2$  points from baseline on the 0–10 scale and time to improvement in pain was analysed by log-rank test.

For the FACT-P Total Score, adjusted mean changes in FACT-P Total Score from baseline were analysed using a MMRM methodology using treatment, visit, treatment-by-visit interaction, baseline FACT-P Total Score and baseline score-by-visit interaction as fixed effects. The corresponding 95% CIs by visit for each treatment group were calculated. TTD in FACT-P Total Score was defined as the time from randomisation to the first assessment of worsened (decrease of  $\geq 6$  points) without an improvement in the next 12 weeks or death and was analysed by log-rank test. Time to improvement in FACT-P Total Score was defined as the time from randomisation to the first assessment of improved (increase of  $\geq 6$  points) and was analysed by log-rank test.

Best response for the FACT-P Total Score, FAPSI-8, FAPSI-6, TOI, PCS, FWB and PWB subscales was categorised as 'improved', 'no change', 'deterioration', and 'other' with a conservative approach according to the following criteria: 'improved' – two visit responses of 'improved' sustained for at least 21 days with no intervening response of 'deterioration' or 'no change' – two visit responses of either 'no change' or 'improved' and 'no change' at least 21 days apart with no intervening response of 'deterioration'; 'deterioration' – a visit response of 'deterioration' without a response of 'improved' or 'no change' within 21 days; 'other' – patients that did not meet the criteria for 'improved', 'no change' or 'deterioration'. If less than half of the subscale items are missing from a returned questionnaire, the subscale score will be calculated by



replacing the missing items with the mean of the non-missing items in the scale. If 50% or more of the items are missing, that visit will be treated as missing.

Improvement in the EQ-5D-5L pain/discomfort scale was defined as a decrease from baseline score.

All statistical analyses were done using SAS version 9.4. There was no data monitoring committee for this study.

This trial is registered with ClinicalTrials.gov, number NCT01972217.

### **Role of the funding source**

The study sponsor, AstraZeneca, was involved in the study design, data collection, data analysis, and data interpretation, and gave approval to submit for publication. Merck & Co, Inc, which is co-developing olaparib, provided input into data interpretation. Both AstraZeneca and Merck & Co, Inc, had a role in the writing of the report through funding of medical writing support. All authors had full access to all the data in the study and were involved in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Nov 25, 2014, and July 14, 2015, 171 patients were enrolled in the randomised phase and assessed for eligibility, of whom 142 patients were randomly assigned to receive olaparib plus abiraterone (the olaparib group; 71 patients) or placebo plus abiraterone (the placebo group; 71 patients). All patients (71 in the olaparib group and 71 in the placebo group) were included in the efficacy and safety sets. The clinical cut-off date for the final analysis was Sept 22, 2017. At data cut-off, seven (10%) of 71 patients were still receiving olaparib plus abiraterone, and eight (11%) of 71 were still receiving placebo plus abiraterone. Patients in the olaparib plus abiraterone and the placebo plus abiraterone arms had a median age of 70 years (interquartile range [IQR] 65–75) and 67 years (IQR 62–74), respectively. There were discreet imbalances between the arms with respect to baseline prostate-specific antigen (PSA) and bone metastases. The median PSA concentration ( $\mu\text{g/L}$ ) was 86 (IQR 23–194) in the olaparib plus abiraterone arm and 47 (IQR 21–199) in the placebo plus abiraterone arm, and the number of bone metastases in patients treated with olaparib plus abiraterone was higher than in the placebo plus abiraterone arm.<sup>16</sup> A full list of the baseline characteristics reported previously can be found in the appendix (table S1). At the start of the study, 18.3% (13/71) of patients randomised to olaparib plus abiraterone and 9.9% (7/71) of patients randomised to placebo plus abiraterone had back pain. Hypertension and diabetes were the most common comorbidities (42.3% [30/71] in each study arm had hypertension and 15.5% [11/71] vs 14.1% [10/71] of olaparib plus abiraterone vs placebo plus abiraterone patients had diabetes, respectively).

Mean baseline scores for FACT-P Total Score were 101.1 (SD 19.4) in the olaparib plus abiraterone arm, and 106.4 (SD 19.1) in the placebo plus abiraterone arm (full details of baseline scores can be found in the appendix table S2). Mean baseline BPI-SF worst pain and single-item worst bone pain were 3.5 (SD 2.7) and 2.8 (SD 2.6) , respectively, in the olaparib plus abiraterone arm and 3.3 (SD 2.9) and 2.5 (SD 2.8), respectively, in the placebo plus abiraterone arm.

At the data cut-off for the primary analysis, the median duration of follow-up was 15.9 months (IQR 8.1–25.5) in the olaparib and abiraterone group compared with 24.5 months (8.1–27.6) in the placebo and abiraterone group.

Compliance rates were generally high (appendix table S3).

Least-squares mean changes from baseline in BPI-SF worst pain and single-item worst bone pain remained relatively stable across all visits for patients in both treatment arms (figure 1A and 1B).

Based on Kaplan–Meier estimates, the median TTD in BPI-SF worst pain was similar in both treatment arms (8.1 months in the olaparib plus abiraterone arm vs 7.6 months in the placebo plus abiraterone arm [HR 0.90, 95% CI 0.62–1.32, 1-sided p=0.302]). There was also no difference in median TTD in worst bone pain (8.7 months vs 8.2 months [HR 0.85, 95% CI 0.59–1.22, 1-sided p=0.181]) (figure 2A and B).

For BPI-SF worst pain, 30 of 71 patients (42.3%) in the olaparib plus abiraterone arm had improvement events, versus 23 of 71 patients (32.4%) in the placebo plus abiraterone arm. Time to BPI-SF worst pain improvement was unchanged between treatment arms (5.5 months [95% CI 2.8–13.9] in the olaparib plus abiraterone arm

and 3.0 months [95% CI 1.8–not calculable] in the placebo plus abiraterone arm [HR 0.92, 95% CI 0.53–1.60; 1-sided  $p=0.390$ ]).

There was no difference in time to improvement in single-item worst bone pain between treatment arms (2.9 months [95% CI 1.9–10.0] in the olaparib plus abiraterone arm and 2.8 months [95% CI 1.0–5.6] in the placebo plus abiraterone arm [HR 0.91, 0.51–1.62]). Twenty-nine of 71 patients (40.8%) in the olaparib plus abiraterone arm had improvement events compared with 20 of 71 patients (28.2%) in the placebo plus abiraterone arm.

The overall adjusted mean change in FACT-P Total Score from baseline across all visits was  $-0.60$  (95% CI  $-4.17$ – $-2.97$ ) in the olaparib plus abiraterone arm and  $-2.09$  (95% CI  $-6.13$ – $-1.97$ ) in the placebo plus abiraterone arm (difference  $1.48$  [95% CI  $-3.96$ – $6.92$ ];  $p=0.590$ ). Analysis of least-squares mean changes from baseline for each visit shows that HRQOL was relatively stable over the course of the study (figure 3).

For the FACT-P Total Score, 60 of 71 patients (85%) in the olaparib plus abiraterone arm versus 57 of 71 patients (80%) in the placebo plus abiraterone arm had deterioration in HRQOL (decrease in FACT-P score of  $\geq 6$  points from baseline).

The TTD in FACT-P Total Score (based on Kaplan–Meier estimates) was similar in each treatment arm (median 5.7 [95% CI 2.8–11.2] months in the olaparib plus abiraterone arm, and 6.0 [95% CI 1.9–11.2] months in the placebo plus abiraterone arm [HR 0.97, 95% CI 0.68, 1.40; nominal  $p=0.89$ ]) (figure 4).

For the FACT-P Total Score, 35 of 71 patients (49.3%) in the olaparib plus abiraterone arm versus 30 of 71 patients (42.3%) in the placebo plus abiraterone arm had improvement in HRQOL (increase in FACT-P score of  $\geq 6$  points from baseline) and the time to improvement was 8.4 (95% CI 2.9–not calculable ) months in the olaparib plus abiraterone arm and 11.3 (95% CI 2.8–not calculable) months in the placebo plus abiraterone arm (HR 1.01, 95% CI 0.62–1.65; 1-sided  $p=0.455$ ).

Additional analyses of the FACT-P questionnaire responses showed that a best FACT-P Total Score response of 'improved' was reported by 22/71 patients (31.0%, 95% CI 20.5–43.1) in the olaparib plus abiraterone arm and 18/71 patients (25.4%, 95% CI 15.8–37.1) in the placebo plus abiraterone arm. Similar findings were observed for the TOI, FWB and PWB FACT-P subscales (figure 5A) and the symptom-related subscales FASPI-6, FASPI-8 and PCS. The proportion of patients who reported a FACT-P Total Score response of 'worsened' was 15/71 patients (21.1%, 95% CI 12.3–32.4) in the olaparib plus abiraterone arm and 22/71 patients (31.0%, 95% CI 20.5–43.1) in the placebo plus abiraterone arm (figure 5B). Furthermore, although the number of patients was small, and decreased over time, the proportion of patients in the olaparib plus abiraterone arm reporting an improvement in FACT-P Total Score increased over time, while the proportion of patients in the placebo plus abiraterone arm decreased (figure 6).

Improvement rates in the pain and discomfort domain of the EQ-5D-5L were similar in both the olaparib plus abiraterone and placebo plus abiraterone arms from baseline to week 48, beyond which a higher proportion of patients in the olaparib plus abiraterone arm reported an improvement compared to the placebo plus abiraterone arm (figure 7).

## Discussion

Recent data from the PROfound trial have shown that HRQoL was better preserved with olaparib monotherapy than with physician's choice of abiraterone or enzalutamide.<sup>25</sup> Therefore, the impact of adding olaparib in combination with abiraterone treatment on HRQoL remains an important question

This phase 2 trial previously showed that addition of olaparib to abiraterone for patients with metastatic castration-resistant prostate cancer significantly increased the rPFS benefit compared with placebo plus abiraterone (median rPFS 13.8 [95% CI 10.8–20.4] vs 8.2 months [5.5–9.7], respectively; HR 0.65, 95% CI 0.44–0.97,  $p=0.034$ ).<sup>16</sup>

Disease symptoms and HRQOL assessed using PRO questionnaires are of critical importance to patients and clinicians when considering treatment options and evaluating PRO in the metastatic castration-resistant prostate cancer setting is of particular importance in identifying new treatments that extend rPFS, are tolerable, and do not diminish patient's HRQOL. In general, it is expected that the HRQOL of patients with metastatic castration-resistant prostate cancer will be affected by both their disease and also the side effects of anti-cancer treatments.<sup>26</sup> Therefore, we assessed symptoms and HRQOL using validated scales to determine whether adding olaparib to abiraterone had an impact on these aspects for patients with metastatic castration-resistant prostate cancer by comparing data to that of patients receiving a placebo plus abiraterone.

We found that questionnaire compliance was generally high up to week 84, although there was a decline at week 96. This is not unexpected as a reduction in questionnaire compliance over time has been observed in other oncology trials.<sup>27,28</sup>

At baseline, HRQOL (measured by FACT-P Total Score and subscales) was low and many patients were experiencing back pain (18.3% in the olaparib plus abiraterone arm vs 9.9% in the placebo plus abiraterone arm). The low baseline HRQOL scores reflect the fact that patients with advanced prostate cancer often experience symptoms such as pain, and as a consequence generally have a poor HRQOL.<sup>29</sup> Hypertension (42.3%) and diabetes (14.8%) were the most common comorbidities but these were generally well balanced between the two treatment arms.

We evaluated pain and other cancer-related symptoms using multiple measures, and our findings show that there was no negative effect of combining olaparib with abiraterone treatment on pain (based on BPI-SF worst pain and worst bone pain scores) and overall HRQOL (based on FACT-P Total Score and subscales). In addition, combination therapy with olaparib and abiraterone did not impact TTD in pain or HRQOL, or time to improvement in pain or HRQOL.

We used FACT-P Total Score as a measure of overall HRQOL and although the difference was not statistically significant, a higher proportion of patients treated with olaparib plus abiraterone reported improved HRQOL with fewer reporting worsened HRQOL, compared with placebo plus abiraterone. These results suggest that adding olaparib to abiraterone does not cause a detriment to pain or HRQOL.

The findings for pain (assessed using BPI-SF worst pain and worst bone pain) and HRQOL (assessed by FACT-P Total Score and subscales) are supported by the EQ-5D-5L pain and discomfort domain analysis where there was no detrimental effect on pain and discomfort in the olaparib plus abiraterone arm compared with placebo plus abiraterone arm. A similar pattern of response was observed with the EQ-5D-5L pain

and discomfort domain and the FACT-P Total score where beyond week 48, there was a slight divergence between treatment groups with an improvement observed in the olaparib plus abiraterone arm compared to placebo plus abiraterone.

A limitation of the study is that all PRO analyses were exploratory, and the improvement analyses were post-hoc. In addition, patient numbers were low, with some imbalances in patient characteristics between the study arms, which may limit the generalisability of our findings.

However, this is the first reported analysis of HRQOL and disease-related symptoms for patients receiving treatment with a PARP inhibitor in combination with an NHA. An important observation of this phase 2 study is that patients with metastatic castration-resistant prostate cancer did not experience a detriment to HRQOL or pain when olaparib was combined with abiraterone as there are several randomised controlled trials currently investigating PARP inhibitors in combination with NHA. In particular, the phase 3 study (PROpel; NCT03732820) has been initiated to validate the efficacy and safety of olaparib plus abiraterone in the first-line setting, and these results will add to the understanding of patients' HRQOL for this combination.

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## **Data sharing**



Data underlying the findings described in this Article can be obtained in accordance with AstraZeneca's data sharing policy described online.

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## **Figure legends**

***Figure 1:*** Least-squares mean change from baseline in BPI-SF worst pain (A) and worst bone pain (B)

***Figure 2:*** TTD in BPI-SF worst pain (A) and worst bone pain (B)

***Figure 3:*** LS mean change in FACT-P Total Score from baseline per visit

***Figure 4:*** TTD in FACT-P Total Score

***Figure 5:*** Best response of 'improved' (A) or 'worsened' (B) for FACT-P Total and subscale scores

***Figure 6:*** Proportion of patients with improvement in FACT-P Total Score per visit

***Figure 7:*** Proportion of patients reporting improvement in pain and discomfort on EQ-5D-5L