Clinical Study Report Addendum 2 Synopsis	
Drug Substance	Olaparib (AZD2281, KU 0059436)
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A Randomised, Double-blind, Placebo-controlled, Multicentre Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men with Metastatic Castration-resistant Prostate Cancer

Final OS Analysis

Study dates:
First subject enrolled: 31 October 2018
Last subject enrolled: 11 March 2020
The analyses presented in this report are based on a clinical data cut-off date of 12 October 2022

Phase of development:
Therapeutic confirmatory (III)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

This addendum reports the results based on the third data cut-off (DCO3, 12 October 2022).

Study Centres

Patients were randomised at 126 centres in 17 countries ([redacted]): 195 (24.5%) patients in Asia, 350 (44.0%) in Europe, and 251 (31.5%) in North and South America.

Publications

Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evid. 2022;1(9);EVIDoa2200043. DOI: 10.1056/EVIDoa2200043.

Saad F, Armstrong AJ, Thiery-Vuillemin A, Oya M, Loredo E, Procopio G, et al. PROpel: Phase III trial of olaparib (ola) and abiraterone (abi) versus placebo (pbo) and abi as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) [abstract]. J Clin Oncol. 2022;40 Suppl 6:11-11.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints Reported in this CSR Addendum

Objectives [a]	Endpoints
Primary	
• To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of rPFS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• rPFS, defined as the time from randomisation to 1) radiological progression, assessed by investigator per RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), or 2) death from any cause, whichever occurs first.
Key Secondary	
• To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of OS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• OS, defined as the time from randomisation to death from any cause.
Other Secondary	
• To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone as assessed by time to start of first subsequent anticancer therapy or death (TFST) in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• TFST, ie, the time from randomisation to: 1) the start of the first subsequent anticancer therapy or 2) death from any cause. [b]
• To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone as assessed by time to pain progression (TTPP) in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• TTPP is defined as the time from randomisation to pain progression based on the BPI-SF Item 3 ‘worst pain in 24 hours’ and opiate analgesic use (AQA score). [c]

Table S1 Objectives and Endpoints Reported in this CSR Addendum

Objectives [a]	Endpoints
• To further evaluate the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of time to opiate use, time to an SSRE, and PFS2 in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• Time to opiate use: The time from randomisation to the first opiate use for cancer-related pain. • Time to an SSRE: the time from randomisation to the first SSRE. An SSRE is defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention. • PFS2: The time from randomisation to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression, or death.
• To assess the effect of the combination of olaparib and abiraterone vs placebo and abiraterone on disease related symptoms and HRQoL using BPI-SF and Functional Assessment of Cancer Therapy (FACT) - Prostate Cancer (FACT-P) questionnaires in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• BPI-SF: progression in pain severity domain, change in pain interference domain. • Change in FACT-P total score, FACT-G total score, TOI, FWB, PWB, PCS, and FAPSI-6.
Safety	
• To evaluate the safety and tolerability of the combination of olaparib and abiraterone vs placebo and abiraterone in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• AEs and SAEs, physical examination findings, vital signs (including BP and pulse rate), ECG findings and laboratory test results (including clinical chemistry and haematology parameters).

[a] Other secondary endpoints and several exploratory objectives were defined in the protocol, but the results are not reported in this synopsis.

[b] Subsequent systemic anticancer therapies (excluding radiotherapy) were reviewed prior to data unblinding to assess which represented clinically important treatments intended to control prostate cancer. TFST was defined as the time from randomisation to the earlier of 1) the first subsequent anticancer therapy start date following study treatment discontinuation or 2) death from any cause. Any patient not known to have died at the time of the analysis and not known to have had a further anticancer therapy was to be censored at the last known time to have not received subsequent therapy, ie, the last follow-up visit where this was confirmed.

[c] Pain progression defined as: 1) for patients who were asymptomatic at baseline, a ≥ 2 point change from baseline in the average (4-7 days) BPI-SF Item 3 score observed at 2 consecutive evaluations (with ≥ 2 weeks between the end of the initial visit and start of the subsequent visit) OR initiation of opioid use for pain; 2) for patients who are symptomatic at baseline (average BPI-SF Item 3 score > 0 and/or currently taking opioids), a ≥ 2 point change from baseline in the average BPI-SF Item 3 score observed at 2 consecutive visits and average worst pain score ≥ 4, and no decrease in average opioid use (≥ 1-point decrease in AQA score from starting value of 2 or higher) OR any increase in opioid use (eg, 1-point change in AQA score) at 2 consecutive follow-up visits (with ≥ 2 weeks between the end of initial visit and start of subsequent visit). Any patient who had > 2 consecutive visits that were not evaluable for pain progression was to be censored at the last evaluable assessment.

AE, adverse event; AQA, analgesic quantification algorithm; BP, blood pressure; BPI-SF, Brief Pain Inventory-Short Form; CSR, Clinical Study Report; ECG, electrocardiogram; FACT, Functional Assessment of Cancer Therapy; FACT-G, FACT – General; FACT-P, FACT – Prostate Cancer; FAPSI-6, FACT Advanced Prostate Symptom Index 6; FWB, FACT-P Functional Well-Being Subscale; HRQoL, health-related quality of life; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; OS, overall survival; PCS, FACT-P Prostate Cancer Subscale; PCWG-3, Prostate Cancer Working Group 3; PFS2, time from randomisation to second progression or death; rPFS, radiological progression-free survival; PSA, prostate specific antigen; PWB, FACT-P Physical Well-Being Subscale; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SAE, serious adverse event; SSRE, symptomatic skeletal-related event; TFST, time to start of first subsequent anticancer therapy or death; TOI, FACT-P Trial Outcome Index; TTPP, time to pain progression.

Study Design

This randomised, double-blind, placebo-controlled, multicentre, international Phase III study was designed to evaluate olaparib in combination with abiraterone versus placebo in combination with abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) who had not received prior chemotherapy or new hormonal agent (NHA) at the mCRPC stage (first-line setting). The study was ongoing at the time of writing this addendum, which reports the results based on the third data cut-off (DCO3, 12 October 2022) for the final overall survival (OS) analysis.

Eligible patients were randomised (1:1 ratio) to receive either olaparib in combination with abiraterone, or placebo in combination with abiraterone. Patients were centrally assigned to randomised study treatment using a Randomisation and Trial Supply Management System (Interactive Response Technology). The patient, the investigator, and study centre staff were blinded to study drug allocation.

At DCO3, radiological progression free survival (rPFS) was assessed by investigators using the Response Evaluation Criteria in Solid Tumours v1.1 (RECIST 1.1; soft tissue) and Prostate Cancer Working Group 3 (PCWG-3) (bone) criteria for all randomised patients. Survival status was assessed every 12 weeks following objective disease progression or treatment discontinuation. Homologous recombination repair (HRR) gene mutation status was determined by testing of circulating tumour DNA (ctDNA), tumour tissue, and germline blood samples. The Brief Pain Inventory-Short Form (BPI-SF), Functional Assessment of Cancer Therapy-Prostate Cancer (FACT-P) and the EuroQol 5-dimension, 5-level health state utility index (EQ-5D-5L) questionnaires were electronically administered. Safety assessments included reporting of adverse events (AEs) and serious adverse events (SAEs), physical examinations, vital signs (including blood pressure and pulse rate), electrocardiograms (ECGs), and laboratory tests (including clinical chemistry and haematology).

Target Population and Sample Size

Eligible patients were biomarker unselected (‘all-comers’) with confirmed prostate adenocarcinoma and metastatic disease who had not received prior chemotherapy or NHAs for mCRPC (first-line setting). Prior to mCRPC stage, treatment with second-generation antiandrogen agents (except abiraterone) without prostate-specific antigen (PSA)

progression/clinical progression/radiological progression during treatment was allowed, provided it was stopped ≥ 12 months before randomisation. Treatment with first-generation antiandrogen agents before randomisation was allowed if there was a 4-week washout period. Docetaxel was allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at metastatic hormone-sensitive prostate cancer (mHSPC) stage, provided there were no signs of failure or disease progression during or immediately after such treatment. Patients had to be candidates for abiraterone therapy with documented evidence of progressive disease defined by PSA progression and/or radiological progression. Both symptomatic and asymptomatic/mildly symptomatic patients were eligible as well as patients with visceral metastases (except brain metastases) as long as they were considered candidates for abiraterone by the investigator. An archival formalin-fixed, paraffin-embedded tumour tissue sample, or a new biopsy taken during the screening window, was required before randomisation.

Approximately 720 patients were planned to be randomised across ~200 study sites in ~20 countries worldwide. As a result of faster than anticipated enrolment, 796 patients were randomised in total. [redacted] In the global cohort, formal interim analysis of the primary endpoint, rPFS, at DCO1 (30 July 2021) was planned. A hazard ratio (HR) of 0.68 was assumed for the true treatment effect, corresponding to an assumed increase in median rPFS from 16.5 months (placebo+abiraterone) to 24.3 months (olaparib+abiraterone). Estimated overall dropout rate was 18%. The first DCO was planned to occur when approximately 379 progression or death events had accrued in 796 patients (47.6% of patients had an event [maturity], information fraction 83.7%) and would provide 94.1% power to show a statistically significant difference in rPFS. DCO1 was anticipated to occur ~31 months after the first patient was randomised.

The Clinical Study Report (CSR) for the DCO1 (30 July 2021) presents the results from the primary analysis of rPFS. At the time of DCO1, 394 rPFS events in 796 patients (49.5% maturity) were observed and the study met its primary endpoint of rPFS, demonstrating a statistically significant and clinically meaningful 34% reduction in the risk of disease progression or death in the olaparib+abiraterone arm compared with the placebo+abiraterone arm (HR 0.66; 95% CI 0.54, 0.81; $p < 0.0001$ below the controlled alpha spending allocation at that interim analysis (0.0324 [2-sided]).

At the time of the second DCO (DCO2: 14 March 2022), 457 rPFS events (57.4% maturity) and 319 OS events (40.1% maturity) in 796 patients had occurred, and the results of this analysis are described in the first addendum to the main CSR. The results at DCO2 were highly consistent with DCO1 (DCO1: 30 July 2021), and there continued to be a clinically meaningful 33% reduction in the risk of radiological disease progression or death in the

olaparib+abiraterone arm compared with the placebo+abiraterone arm (HR 0.67; 95% CI 0.56, 0.81; nominal $p < 0.0001$).

At the time of the third DCO (DCO3: 12 October 2022), 496 rPFS events (62.3% maturity) and 381 OS events (47.9% maturity) in 796 patients had occurred. This second addendum to the main CSR describes the results of the analysis of this DCO.

Investigational Product and Comparator(s): Dosage, Mode of Administration, and Batch Numbers

Olaparib (AZD2281, KU 0059436) film-coated tablets (150 mg and 100 mg) were manufactured by AbbVie and AstraZeneca AB, and matching placebo was manufactured by PCI Pharmaceuticals. Patients took olaparib or placebo orally at a dose of 300 mg twice daily (bd) as 2×150 mg tablets. Each dose was to be taken at the same time each day, approximately 12 hours apart with a glass of water, with or without food (except on pharmacokinetic [PK] sampling days when the dosing was fasted). The tablets were swallowed whole and not chewed, crushed, dissolved, or divided. The 100 mg and 150 mg tablets were used to manage dose reductions. Batch numbers of olaparib 100 mg, 150 mg, and matching placebo were:

Commercially available abiraterone with supportive prednisone or prednisolone was background treatment. Patients were administered abiraterone 1000 mg once daily (qd) in combination with prednisone or prednisolone 5 mg orally twice daily (bd). In accordance with local prescribing information, abiraterone was taken on an empty stomach; tablets were swallowed whole with water and not crushed or chewed.

Duration of Treatment

Patients started study treatment as soon as possible after randomisation (ideally, within 24 hours post randomisation), and treatment was to continue until objective radiological disease progression as assessed by the investigator (using RECIST 1.1 for soft tissue lesions and PCWG-3 criteria for bone lesions), occurrence of unacceptable toxicity, severe non-compliance with the protocol, or the patient withdrew consent. Following objective disease progression, further treatment options were at the discretion of the investigator. Crossover from placebo+abiraterone to olaparib+abiraterone was not allowed.

Statistical Methods

The full analysis set (all-comers) was the primary population for reporting efficacy, and comprised all randomised patients, analysed according to randomised treatment (intention to-treat principle). The PK analysis set included all patients who received ≥ 1 dose of

randomised study drug and provided ≥ 1 post-dose analysable plasma sample for PK analysis. The safety analysis set consisted of all randomised patients who received any amount of olaparib, placebo, or abiraterone, and was used for summaries of safety data, according to the treatment received.

Three DCOs were planned for this study. The 1-sided alpha of 0.025 was allocated to the rPFS assessment. If the result for rPFS was statistically significant, the OS hypothesis was to be tested in a hierarchical fashion. A multiplicity testing procedure based on the graphical approach in group sequential trials of Maurer and Bretz, analogous to a simple sequential gatekeeping method, strongly controlled the overall familywise 1-sided error rate of 2.5%.

The rPFS endpoint was planned to be tested at DCO1 and DCO2. The OS endpoint was planned to be tested at DCO1, DCO2, and DCO3. For each endpoint with an interim analysis, the O'Brien and Fleming spending function calculated based upon actual observed events, was to be used to strongly control the overall type 1 error, with the restriction that alpha spend for the OS interim analysis at DCO1 would not exceed 0.0005.

The rPFS primary endpoint was analysed using a log rank test stratified by the following factors if applicable: Metastases (bone only versus visceral versus other); Docetaxel treatment at mHSPC stage (yes versus no). The HR and corresponding 95% confidence interval (CI) were estimated using a Cox proportional hazards model (with ties = Efron and the stratification variables as covariates) and the 2-sided CI calculated using a profile likelihood approach (a HR < 1 favours olaparib+abiraterone combination therapy).

A sensitivity analysis was conducted using rPFS as assessed for all patients by BICR per RECIST 1.1 and PCWG-3 criteria, at DCO1 and DCO2. Further pre-defined sensitivity analyses of rPFS were also performed including analysis using unequivocal clinical progression in addition to radiological progression. Subgroup analyses were conducted to assess the consistency of the rPFS treatment effect based on the stratification factors, clinical characteristics (Eastern Cooperative Oncology Group [ECOG] performance status, age at randomisation, region, race, and baseline PSA) and HRR gene mutation status.

The key secondary endpoint, OS, was analysed using the same methodology as for rPFS. Analyses of the other secondary endpoints were not part of the multiplicity strategy, but further describe the efficacy and health-related quality of life (HRQoL) benefits of olaparib+abiraterone compared to placebo+abiraterone.

Safety and tolerability data were summarised using appropriate descriptive measures.

Study Population

This study enrolled 1103 patients, of which 796 were randomised at 126 centres: 399 patients were randomised to olaparib+abiraterone and 397 were randomised to placebo+abiraterone. In

total, 794 patients received study treatment; one patient from each treatment group did not receive study treatment. At the time of this addendum, reporting the results at DCO3, 388 patients (48.7%) were ongoing in the study and 180 patients (22.7%) were still ongoing with combination treatment: 103 patients (25.9%) in the olaparib+abiraterone arm and 77 (19.4%) in the placebo+abiraterone arm.

For demographic and disease characteristics, refer to the synopses for the CSR (DCO1: 30 July 2021) and CSR addendum 1 (DCO2: 14 March 2022).

Summary of Efficacy Results

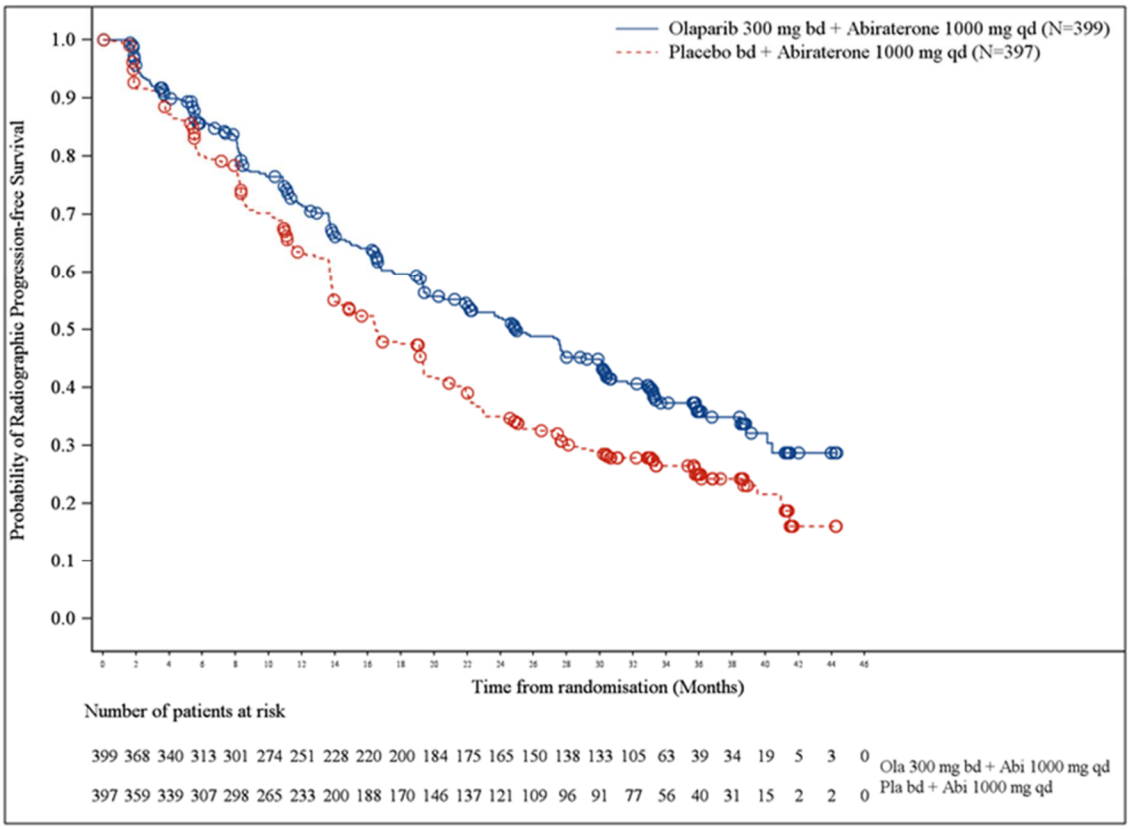
Primary endpoint (exploratory analysis), rPFS based on investigator assessment

The study met its primary objective at DCO1 and the results at DCO2 and DCO3 were entirely consistent. At the time of the final OS analysis, the rPFS data were 62.3% mature (496 events/796 patients). There continued to be a clinically meaningful reduction in the risk of radiological disease progression or death (32%). An improvement in median rPFS of 8.5 months was observed in the olaparib+abiraterone arm (25.0 months) compared with the placebo+abiraterone arm (16.5 months), with HR 0.68 (95% CI: 0.57, 0.81); nominal $p < 0.0001$. Median duration of follow-up in all patients was 18.5 months in the olaparib+abiraterone arm and 14.3 months in the placebo+abiraterone arm. The median follow-up in censored patients was 32.5 months in the olaparib+abiraterone arm and 33.0 months in the placebo+abiraterone arm.

Based on Kaplan-Meier estimates, at 36 months, 35.88% of patients in the olaparib+abiraterone arm were alive and progression-free compared with 24.99% in the placebo+abiraterone arm. At 42 months, 28.74% of patients in the olaparib+abiraterone arm were alive and progression-free compared with 16.07% in the placebo+abiraterone arm. The Kaplan-Meier plot (Figure S1) shows a clear separation of the curves in favour of the olaparib+abiraterone arm, apparent from an early time point.

Clinical benefit in favour of olaparib+abiraterone was also seen consistently across the pre-defined rPFS exploratory subgroup analyses based on stratification factors and baseline demographic and disease characteristics, with the exception of the small group of patients with ‘Race: Other’ (n = 24). There was a clinically meaningful rPFS improvement with olaparib+abiraterone compared with placebo+abiraterone across the homologous recombination repair gene mutation (HRRm), non-HRRm, and HRRm unknown subgroups. Despite some numerical differences, all observed HR point estimates were associated with a clinically meaningful improvement of at least 5 months in favour of the olaparib+abiraterone arm, irrespective of HRRm status.

Figure S1 Radiological PFS Based on Investigator Assessment, Kaplan-Meier Plot (FAS)



A circle indicates a censored observation, RECIST 1.1 and PCWG-3.

Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to progression.

DCO3 date: 12 October 2022.

Abi, abiraterone; DCO, data cut-off; FAS, full analysis set; Ola, olaparib; PCWG-3, Prostate Cancer Working Group 3; Pla, placebo; qd, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; rPFS, radiological progression-free survival.

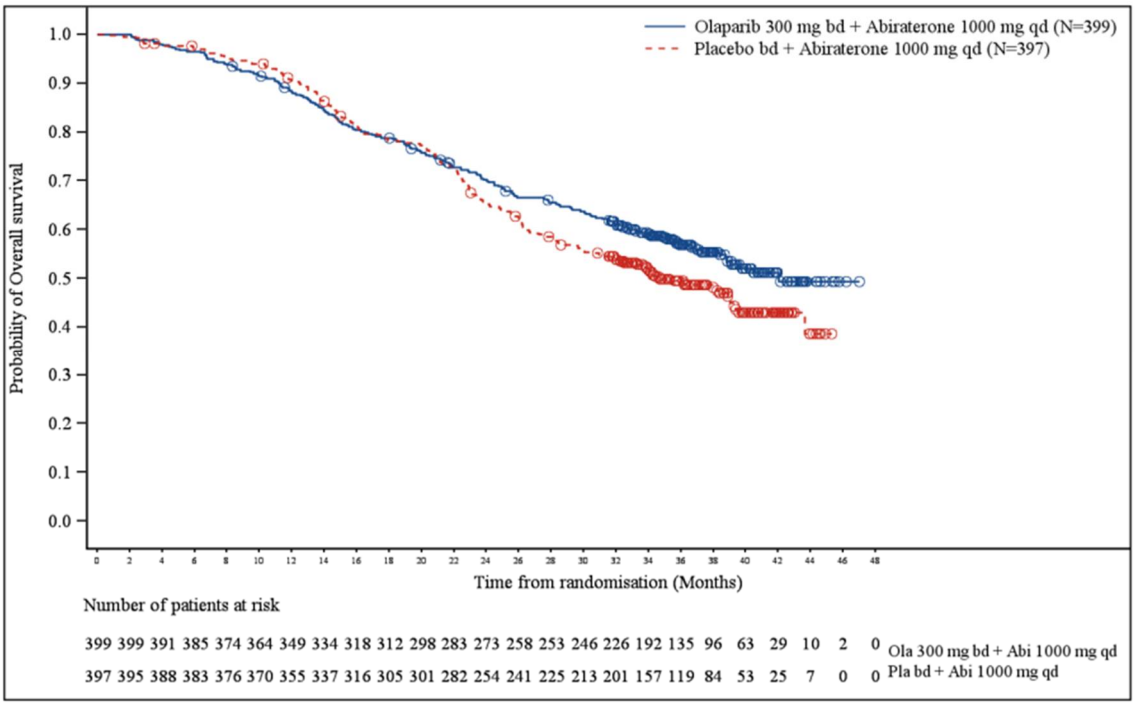
Source: Figure 14.2.1.2.1.

Key Secondary Endpoint, OS

At DCO3, the final OS analysis, the OS data were 47.9% mature (381 events/796 patients), with approximately 36.5 months follow up in the full analysis set (FAS). The proportion of events was lower in the olaparib+abiraterone arm (44.1%) than in the placebo+abiraterone arm (51.6%). The OS HR point estimate numerically favoured the olaparib+abiraterone versus the placebo+abiraterone arm, suggesting a continued trend towards improved OS for olaparib+abiraterone-treated patients (HR 0.81; 95% CI: 0.67, 1.00; p = 0.0544). Continued separation of the Kaplan-Meier curves was observed with longer follow-up and reduced censoring overall. Clear separation between the arms was observed after approximately

22 months, and extensive censoring was observed only after 32 months (Figure S2). Patients continue to be followed up in this ongoing study. The median OS was 42.05 months in the olaparib+abiraterone arm and 34.69 months in the placebo+abiraterone and, and survival rates from 18 months were higher in the olaparib+abiraterone arm (at 24 months, 70.17% of patients in the olaparib+abiraterone arm were alive compared with 65.47% in the placebo+abiraterone arm; at 36 months, 56.85% of patients in the olaparib+abiraterone arm were alive compared with 49.51% in the placebo+abiraterone arm; and at 42 months, 51.11% of patients in the olaparib+abiraterone arm were alive compared with 42.99% in the placebo+abiraterone arm). Results of the exploratory subgroup analyses were generally consistent with the FAS and no evidence of detriment was observed in any pre-defined subgroup.

Figure S2 Overall Survival, Final OS Analysis, Kaplan-Meier Plot (FAS)



A circle indicates a censored observation.

DCO3 date: 12 October 2022.

Abi, abiraterone; bd, twice daily; DCO, data cut-off; FAS, full analysis set; Ola, olaparib; Pla, placebo; qd, once daily.

Source: Figure 14.2.4.2.1.

Other Secondary Endpoints

At DCO3, clinical benefit with olaparib+abiraterone was supported by a clinically meaningful improvement observed in the secondary endpoint of time to start of first subsequent anticancer therapy or death (TFST). The TFST data were 67.8% mature (540 events/796 patients). There was a clinically meaningful improvement in TFST (ie, a delay of 5.2 months) in the

olaparib+abiraterone arm versus the placebo+abiraterone arm (HR 0.76, 95% CI: 0.64, 0.90; nominal p = 0.0025; median 25.6 versus 19.4 months, respectively).

With the exception of TFST, the other secondary efficacy endpoints have low data maturity and should be interpreted with caution. Time from randomisation to second progression or death (PFS2) data were 28.8% mature (229 events/796 patients). There was a numerical improvement in PFS2 (ie, a delay) in the olaparib+abiraterone arm versus the placebo+abiraterone arm (HR 0.76, 95% CI: 0.59, 0.99; nominal p = 0.0534; the median was not calculable for either treatment arm. The time to pain progression (TTPP) data were 16.1% mature at DCO3 (128 events/796 patients). There was no difference in TTPP in the olaparib+abiraterone arm versus the placebo+abiraterone arm (HR 1.06, 95% CI: 0.75, 1.50; nominal p = 0.7456); median TTPP was not calculable for either treatment arm. With a maturity of 14.8% (103 events/697 patients) at DCO3, there was no clear evidence of a difference in the time to opiate use for cancer-related pain in the olaparib+abiraterone arm versus the placebo+abiraterone arm (HR 1.21, 95% CI: 0.82, 1.79; nominal p = 0.3099); the median time to opiate use for cancer pain was not calculable for either treatment arm. For time to first symptomatic skeletal-related event (SSRE), there was a total of 97 events in 796 patients (12.2%). There was a numerical improvement (ie, a delay) in time to first SSRE in the olaparib+abiraterone arm versus the placebo+abiraterone arm (HR 0.82, 95% CI: 0.55, 1.22; nominal p = 0.3212); the median time to first SSRE was not calculable for either treatment arm.

HRQoL

The adjusted least squares mean change from baseline in the FACT-P Total and subscale/ index scores showed no overall detriment for the olaparib+abiraterone treatment arm compared with the placebo+abiraterone arm. For the FACT-P total and all subscale/index scores, there was no overall HRQoL detriment in the time to deterioration between the olaparib+abiraterone treatment arm and the placebo+abiraterone arm, with the exception of the Physical Well-Being subscale, which favoured the placebo+abiraterone arm.

The mean change from baseline in BPI-SF scores (worst pain, pain severity, and pain interference) showed no overall differences between the olaparib+abiraterone arm compared with the placebo+abiraterone arm over the treatment period.

Summary of Pharmacokinetic Results

Refer to Section 11.2 of the CSR for DCO1 (DCO1: 30 July 2021) for full details of the PK results.

Summary of Safety Results

At DCO3, the median duration of exposure to olaparib was the same as at DCO2 (and approximately 1 month longer compared with DCO1), and the median duration of exposure to

abiraterone was the same as at DCO2 (and approximately 2 months longer compared with DCO1) in the olaparib+abiraterone arm. The median total duration of exposure of placebo + abiraterone remains unchanged. The median total duration of exposure to olaparib up to DCO3 was approximately 1.2 times longer than to placebo (18.5 versus 15.7 months, respectively). Median total duration of exposure to abiraterone was approximately 1.3 times longer in the olaparib+abiraterone arm than the placebo+abiraterone arm (20.1 versus 15.7 months, respectively), suggesting that the combination with olaparib did not reduce the planned administration of abiraterone. A higher proportion of patients remained on treatment in the olaparib+abiraterone arm at 36 months (16.1% on olaparib, 17.8% on abiraterone) than in the placebo+abiraterone arm (14.6% on placebo, 14.9% on abiraterone).

The 3 most common AEs of anaemia, nausea, and fatigue in the olaparib+abiraterone arm are known adverse drug reactions (ADRs) for olaparib. Other common AEs were consistent with the known ADR profiles for olaparib and abiraterone, or considered attributable to the underlying disease.

Coronavirus disease 2019 (COVID-19)-related AEs were reported at a higher frequency in the olaparib+abiraterone arm versus placebo+abiraterone (15.8% versus 9.8%), and AEs of pulmonary embolism were reported at a higher frequency in the olaparib+abiraterone arm versus placebo+abiraterone (7.3% versus 1.8%).

AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 were reported for 55.8% of patients on olaparib+abiraterone versus 43.2% on placebo+abiraterone. The most common Grade ≥ 3 AEs in the olaparib+abiraterone arm were anaemia (16.1%) and pulmonary embolism (7.3%); the most common in the placebo+abiraterone arm were hypertension (4.5%) and anaemia (3.3%). Anaemia is a known ADR of olaparib, and hypertension is a known ADR of abiraterone.

AEs of special interest reported for olaparib were similar between the treatment arms. In total, there were 2 myelodysplastic syndrome (MDS) events in the olaparib+abiraterone arm; between DCO2 and DCO3, one event of MDS was reported in one patient in the olaparib+abiraterone arm; no additional events of MDS/acute myeloid leukaemia were reported in the placebo+abiraterone arm. Pneumonitis was reported in 5 (1.3%) patients in the olaparib+abiraterone arm and 3 (0.8%) patients in the placebo+abiraterone arm. No additional patients in the olaparib+abiraterone arm reported pneumonitis between DCO2 and DCO3. Adjudicated new primary malignancies were reported in 18 patients (4.5%) in the olaparib+abiraterone arm and 14 patients (3.5%) in the placebo+abiraterone arm. Between DCO2 and DCO3, additional adjudicated new primary malignancies of plasma cell myeloma, colon cancer, rectal cancer, and squamous cell carcinoma of the tongue were reported for one patient each in the olaparib+abiraterone arm. In the placebo+abiraterone arm, non-small cell lung cancer was reported for one patient and gastric cancer was reported for 2 patients.

SAEs were reported for 40.5% of patients on olaparib+abiraterone and 31.8% on placebo+abiraterone. The most commonly reported SAE on olaparib+abiraterone was anaemia (5.8%). Most of the deaths were reported as due to the disease under investigation only (72.2% versus 79.0%, for the olaparib+abiraterone and placebo+abiraterone arms, respectively). AEs with fatal outcome were reported for a similar proportion of patients in the olaparib+abiraterone arm (6.5%) and the placebo+abiraterone arm (5.1%).

AEs leading to discontinuation of olaparib were more frequent than AEs leading to discontinuation of placebo (17.3% versus 8.6%, respectively). AEs leading to olaparib dose reduction were more frequent than AEs leading to placebo dose reduction (22.6% versus 6.1%), and AEs leading to olaparib dose interruption were more frequent than those leading to placebo dose interruption (49.0% versus 28.3%). Anaemia was the most common AE leading to discontinuation, dose reduction, or dose interruption of olaparib.

Except for haemoglobin, changes in haematology parameters were generally mild or moderate and transient. No hepatobiliary or renal safety concerns were identified from review of the laboratory and AE data. No new safety concerns were identified in the safety laboratory data. There were no additional cases of Hy's Law between DCO2 and DCO3. No clinically meaningful changes were noted in vital signs in patients in either treatment arm during the study. No significant difference between the treatment arms was seen in the ECG data: Similar proportions of patients had abnormal (clinically significant or non-significant) ECG findings between the 2 treatment groups.

No new safety concerns were identified since DCO2.

Conclusions

The results of the PROpel study based on DCO3 for the final OS analysis continue to demonstrate a favourable benefit-risk profile for the combination of olaparib with abiraterone, as detailed below:

- The final OS data were 47.9% mature (381 events); the OS HR point estimate numerically favoured the olaparib+abiraterone versus the placebo+abiraterone arm suggesting a continued trend towards improved OS with the addition of olaparib to abiraterone (HR 0.81; 95% CI 0.67, 1.00; p = 0.0544). Continued separation of the Kaplan-Meier curves was observed with longer follow-up and reduced censoring overall. Clear separation between the arms was observed after approximately 22 months, and extensive censoring was observed only after 32 months. Median OS was 42.05 months in the olaparib+abiraterone arm and 34.69 months in the placebo+abiraterone arm, and survival rates from 18 months were higher in the olaparib+abiraterone arm.
- The exploratory analysis rPFS results were highly consistent with the previous 2 DCOs; there was a 32% reduction in risk of disease progression or death, with HR 0.68 (95% CI: 0.57, 0.81); nominal p < 0.0001.

- The improvement in clinical benefit was also supported by a clinically meaningful improvement in the secondary endpoint of TFST (HR 0.76; 95% CI: 0.64, 0.90; nominal p = 0.0025) and numerical improvement in PFS2 (HR 0.76; 95% CI: 0.59, 0.99; nominal p = 0.0534). The patient-reported outcome data indicate that the combination of olaparib+abiraterone had no overall negative impact on the patients' HRQoL. Change from baseline in the FACT-P Total and subscale/index scores showed no overall detriment for the olaparib+abiraterone arm compared with the placebo+abiraterone arm. Change from baseline in BPI-SF scores (worst pain, pain severity, and pain interference) showed no overall differences between the 2 arms.
- Clinical benefit was also generally consistent with the result for the FAS across the OS and rPFS subgroups.
- The safety results show a manageable safety profile for olaparib and abiraterone given in combination, suitable for the treatment of patients with mCRPC:
  - Up to DCO3, the median total duration of exposure to olaparib was 1.2 times longer than to placebo (18.5 versus 15.7 months, respectively). Median total duration of exposure to abiraterone was 1.3 times longer in the olaparib+abiraterone arm than the placebo+abiraterone arm (20.1 versus 15.7 months, respectively).
  - The safety and tolerability of the combination of olaparib+abiraterone appeared to be consistent with the known safety profiles of the olaparib and abiraterone monotherapies in the context of this patient population. Imbalances were noted in COVID-19-related events and COVID-19-related events with a fatal outcome, which were both more frequently reported with the olaparib+abiraterone combination.
  - There continued to be an imbalance in venous thromboembolism events from DCO2 to DCO3. Since DCO2 (14 March 2022), events were reported for 2 additional patients in the olaparib+abiraterone arm and 3 additional patients in the placebo+abiraterone arm.
- No new safety concerns were identified since DCO2.