Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial

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Summary

Background PROpel met its primary endpoint showing statistically significant improvement in radiographic progression-free survival with olaparib plus abiraterone versus placebo plus abiraterone in patients with first-line metastatic castration-resistant prostate cancer (mCRPC) unselected by homologous recombination repair mutation (HRRm) status, with benefit observed in all prespecified subgroups. Here we report the final prespecified overall survival analysis.

Methods This was a randomised, double-blind, phase 3 trial done at 126 centres in 17 countries worldwide. Patients with mCRPC aged at least 18 years, Eastern Cooperative Oncology Group performance status 0–1, a life expectancy of at least 6 months, with no previous systemic treatment for mCRPC and unselected by HRRm status were randomly assigned (1:1) centrally by means of an interactive voice response system–interactive web response system to abiraterone acetate (orally, 1000 mg once daily) plus prednisone or prednisolone with either olaparib (orally, 300 mg twice daily) or placebo. The patients, the investigator, and study centre staff were masked to drug allocation. Stratification factors were site of metastases and previous docetaxel at metastatic hormone-sensitive cancer stage. Radiographic progression-free survival was the primary endpoint and overall survival was a key secondary endpoint with alpha-control (alpha-threshold at prespecified final analysis: 0·0377 [two-sided]), evaluated in the intention-to-treat population. Safety was evaluated in all patients who received at least one dose of a study drug. This study is registered with ClinicalTrials.gov, NCT03732820, and is completed and no longer recruiting.

Findings Between Oct 31, 2018 and March 11, 2020, 1103 patients were screened, of whom 399 were randomly assigned to olaparib plus abiraterone and 397 to placebo plus abiraterone. Median follow-up for overall survival in patients with censored data was 36·6 months (IQR 34·1–40·3) for olaparib plus abiraterone and 36·5 months (33·8–40·3) for placebo plus abiraterone. Median overall survival was 42·1 months (95% CI 38·4–not reached) with olaparib plus abiraterone and 34·7 months (31·0–39·3) with placebo plus abiraterone (hazard ratio 0·81, 95% CI 0·67–1·00; p=0·054). The most common grade 3–4 adverse event was anaemia reported in 64 (16%) of 398 patients in the olaparib plus abiraterone and 13 (3%) of 396 patients in the placebo plus abiraterone group. Serious adverse events were reported in 161 (40%) in the olaparib plus abiraterone group and 126 (32%) in the placebo plus abiraterone group. One death in the placebo plus abiraterone group, from interstitial lung disease, was considered treatment related.

Interpretation Overall survival was not significantly different between treatment groups at this final prespecified analysis.

Funding AstraZeneca and Merck Sharp & Dohme.

Introduction

Patients in first-line metastatic castration-resistant prostate cancer (mCRPC) clinical trials have a median overall survival of approximately 3 years and 5-year overall survival of approximately 30%.[1–3] In real-world clinical practice, median overall survival is less than 2 years.[4] Approximately 50% of patients receive only one line of life-prolonging systemic therapy, highlighting the importance of optimising outcomes in first-line mCRPC. Since the early 2010s, next-generation hormonal agents (NHAs) abiraterone and enzalutamide, and taxane-based chemotherapy have been key first-line treatment options in mCRPC, but no new treatments have emerged as a standard-of-care for a broad first-line mCRPC population.

Inhibition of poly (ADP-ribose) polymerase (PARP) by olaparib results in unrepaired DNA single-strand breaks and the induction of DNA double-strand breaks.[5] Preclinical evidence suggests that the androgen receptor

Research in context

Evidence before this study

PubMed, Embase, MEDLINE, and oncology congress websites were searched from Jan 1, 2012 to Oct 31, 2018 for clinical trials of poly (ADP-ribose) polymerase (PARP) inhibitors and next-generation hormonal agents used to treat metastatic castration-resistant prostate cancer (mCRPC). The search terms used were "castration-resistant prostate cancer", "poly(ADP-ribose) polymerase inhibitor", "next-generation hormonal agent", "new hormonal agent", "abiraterone", and "enzalutamide". No language preferences were specified. When the trial was initiated, there were no published results from phase 3 trials of PARP inhibitors in combination with next-generation hormonal agents. The results of a phase 2 trial of olaparib plus abiraterone versus placebo plus abiraterone have been reported. Results from the primary analysis of PROpel have been reported along with results from secondary analyses.

Added value of this study

PROpel was the first positive phase 3 trial of a PARP inhibitor in combination with a next-generation hormonal agent in patients in an homologous recombination repair mutation (HRRm)–unselected first-line mCRPC population, showing a statistically significant and clinically meaningful improvement in radiographic progression-free survival with olaparib plus abiraterone versus placebo plus abiraterone. This analysis presents data from the key secondary endpoint of overall survival, which, although not signficantly different between arms, provides further insight on the clinical benefit of olaparib plus abiraterone as a first-line mCRPC treatment.

Implications of all the available evidence

In current practice, approximately 50% of patients with mCRPC receive only one life-prolonging therapy. The current standard-of-care first-line mCRPC treatment is a next-generation hormonal agent (abiraterone or enzalutamide) or taxane-based chemotherapy. Preclinical studies and results from a phase 2 trial of olaparib plus abiraterone versus placebo plus abiraterone have indicated that there is a combined treatment effect with olaparib plus abiraterone that is irrespective of HRRm status. The phase 3 PROpel trial efficacy and safety results show clinical benefits and a manageable safety profile of olaparib plus abiraterone versus a life-prolonging standard-of-care, abiraterone, in first-line mCRPC, with the greatest benefit observed in patients with BRCA mutations. Combined olaparib plus abiraterone provides an important new treatment option for patients.

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is required for the repair of DNA double-strand breaks in prostate cancer cells beyond those repaired by the homologous recombination repair (HRR) pathway.[5,6] Since androgen receptor-dependent DNA repair can be prevented by the reduction of nuclear androgen receptor concentrations from treatment by an NHA, this provides a mechanistic rationale for the combination effects seen in preclinical models.[5,6] The phase 2 Study 8 trial (NCT01972217) confirmed preclinical findings, and showed that treatment with olaparib plus abiraterone in patients with mCRPC who had previously received docetaxel and were unselected by HRR mutation (HRRm) status, resulted in statistically significantly longer radiographic progression-free survival versus placebo plus abiraterone (hazard ratio [HR] 0·65, 95% CI 0·44–0·97; p<0·034).[7] Prespecified and post-hoc analyses were consistent with a treatment effect independent of HRRm status.[7,8]

Given that Study 8 met its primary endpoint, the phase 3, randomised, double-blind PROpel study (NCT03732820) was done in patients who had newly developed mCRPC and had not received previous treatment for this condition. PROpel met its primary endpoint at the primary analysis (data cutoff 1: July 30, 2021) showing a statistically significant and clinically meaningful radiographic progression-free survival benefit in first-line patients with mCRPC treated with standard doses of olaparib plus abiraterone versus placebo plus abiraterone: median radiographic progression-free survival was 24·8 months (95% CI 20·5–27·6) versus 16·6 months (13·9–19·2) at primary analysis (investigator-assessed; HR 0·66, 95% CI 0·54–0·81; p<0·001), with benefit observed in all prespecified subgroups.[9] Sensitivity analysis by blinded independent central review was consistent with the primary endpoint (27·6 months, 19·6–not reached [NR] *vs* 16·4 months, 13·8–19·1; HR 0·61, 0·49–0·74; p<0·001).[9]

On the basis of PROpel, European approval (European Commission decision: Dec 21, 2022) was granted for olaparib in combination with abiraterone and prednisone or prednisolone in patients with mCRPC for whom chemotherapy is not clinically indicated.[10] US Food and Drug Administration approval (May 31, 2023) was granted for the combination in patients with deleterious or suspected deleterious BRCA-mutated mCRPC.[11]

The hazard ratio for overall survival was 0·86 (28·6% maturity; 95% CI 0·66–1·12) at primary analysis and 0·83 (40·1% maturity; 0·66–1·03; data cutoff 2: March 14, 2022) at subsequent interim overall survival analysis.[9] We report here the results from the final prespecified overall survival analysis (data cutoff 3: Oct 12, 2022).

Methods

Study design and participants

PROpel study design, eligibility criteria, and methods have been published previously.[9] In brief, this randomised, double-blind, phase 3 trial recruited patients from 126 centres in 17 countries in North America, Europe, Asia, and South America (appendix p 2).

See Online for appendix

Eligible patients were aged at least 18 years (or aged at least 19 years in South Korea); had histologically or cytologically confirmed prostate adenocarcinoma with at least one documented metastatic lesion on either a bone scan, CT, or MRI; had Eastern Cooperative Oncology Group (ECOG) performance status 0–1; and had a life expectancy of at least 6 months. With the exception of androgen depletion therapy, and first-generation anti-androgen agents with a 4-week washout period, previous systemic treatment in the first-line mCRPC setting was not allowed. Docetaxel during neoadjuvant or adjuvant treatment for localised prostate cancer and the metastatic hormone-sensitive prostate cancer (mHSPC) stage of disease was permitted as long as there was no sign of progression during or immediately following docetaxel treatment. Patients were allowed previous NHA exposure (except for exposure to abiraterone) provided that patients had not had prostate-specific antigen progression, or clinical or radiographic progression during the treatment and that the treatment was stopped at least 12 months before random assignment. See appendix (p 3) for medical conditions excluded from the trial.

Both tumour tissue (mostly archival) and blood samples at baseline were collected from more than 98% of randomly assigned patients and preplanned assessment of HRRm status by tumour tissue (FoundationOne CDx; Foundation Medicine, Cambridge, MA, USA) and circulating tumour DNA (ctDNA)-based test (FoundationOne Liquid CDx; Foundation Medicine) was established after randomisation but before primary analysis (appendix pp 4–6). Germline blood testing (Myriad myRisk; Myriad Genetics, Salt Lake City, UT, USA) was done to establish germline versus somatic HRRm status. Race or ethnicity were defined by self-report and medical records. 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 done in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca and Merck policies on bioethics.

For the **study protocol** see https://classic.clinicaltrials.gov/ct2/show/study/NCT03732820

Randomisation and masking

Eligible patients were randomly assigned (1:1) to treatment with abiraterone acetate with prednisone or prednisolone (referred to as abiraterone throughout this manuscript) in combination with either olaparib or placebo. Patients were centrally assigned to randomised study treatment by means of an interactive voice response system–interactive web response system. Before the study was initiated, the telephone number and call-in directions for the interactive voice response system–interactive web response system or the login information and directions for the interactive voice response system–interactive web response system were provided to each site. The actual treatment given to individual patients was established by a randomisation scheme that was loaded into the interactive voice response system–interactive web response system database, which incorporates a standard procedure for generating random numbers. Block randomisation was generated and all centres used the same list in order to minimise any imbalance in the number of patients assigned to each treatment group. The study was done in a double-blind manner. Patients, the investigator, and study centre staff were masked to study drug allocation and study medications were identical and presented in the same packaging to ensure masking.

Patients were stratified by known prognostic factors: distant metastasis type (bone-only, visceral, or other) at baseline and by docetaxel treatment at the mHSPC stage of disease (yes or no) by means of a mixed allocation from a block randomisation schedule. Bone-only disease was defined as the presence of metastasis in the bone and no other distant site. Visceral disease was defined as distant soft tissue metastasis in an organ (such as liver or lung) even if the patient had lesions in other metastatic sites. "Other" included all other patients with distant metastatic disease (eg, patients with disease present only in distant lymph nodes).

Procedures

Patients received oral treatment with olaparib 300 mg twice daily taken approximately 12 h apart plus abiraterone once daily 1000 mg taken on an empty stomach, or placebo twice daily plus abiraterone once daily taken on an empty stomach. Both treatment groups received prednisone or prednisolone 5 mg twice daily as it is indicated in combination with abiraterone. Study treatment continued until objective radiographic progressive disease assessed by investigator (by means of Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST 1.1] for soft tissue lesions and Prostate Cancer Working Group 3 [PCWG3] criteria for bone lesions), unacceptable toxicity, or withdrawal of consent. Study assessment visits were done every 2 weeks for the first 12 weeks, then every 4 weeks. CT or MRI and bone tumour assessments were done every 8 weeks for the first 24 weeks and then every 12 weeks until treatment discontinuation. After radiographic progression, patients were assessed every 12 weeks for second progression or death. An independent review of all scans used in the assessment of tumours was done. Baseline pain score was based on the Brief Pain Inventory-Short Form questionnaire item 3 (worst pain) during the 7-day baseline period. The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire was used to assess health-related quality of life; patients were asked to complete the questionnaire every 4 weeks from day 1 until week 52, then every 8 weeks until treatment discontinuation (including at the treatment discontinuation visit) or until 12 weeks after progressive disease.

Following objective disease progression, further treatment options were at the discretion of the

investigator. Patients could continue study treatment if the investigator believed, and the AstraZeneca Study Physician agreed, that the patient could continue to receive clinical benefit, was not having serious toxicity, and there was no better alternative treatment available. Crossover from placebo to receive olaparib in combination with abiraterone was not allowed as per protocol. However, patients were unmasked to HRRm status at progression on request for consideration of subsequent therapy. Risk mitigation factors for COVID-19 were implemented related to study conduct and patient management as described in the trial protocol. Patients withdrawing from the study could continue to be followed-up if they provided consent.

Safety was assessed by reporting of adverse events and serious adverse events (according to Common Terminology Criteria for Adverse Events version 4.03) on the basis of physical examination findings, vital signs, electrocardiogram findings, and laboratory test results. Adverse event management and dose modification strategies are detailed in the appendix (p 7). Protocol deviations are detailed in the appendix (p 8).

Outcomes

The primary endpoint was investigator-assessed radiographic progression-free survival (previously published)[9] defined as the time from randomisation to radiographic progression, assessed by investigator per RECIST 1.1 (soft tissue) and PCWG3 criteria (bone), or death from any cause, whichever occurs first. Sensitivity analysis by masked independent central review was also done (previously published).[9]

A key secondary endpoint was overall survival, defined as the time from randomisation to death from any cause. Assessment of 2-year and 3-year overall survival was post-hoc. Other secondary endpoints were time to first subsequent therapy or death (time from randomisation to the start of the first subsequent anticancer therapy or death from any cause [whichever was earlier]), time to second progression or death (time from randomisation to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, prostate-specific antigen progression, or death), time to progression in pain (to be reported separately), time to opiate use (to be reported separately), time to symptomatic skeletal-related event (to be reported separately), disease-related symptoms and health-related quality of life assessed by the Brief Pain Inventory–Short Form (to be reported separately) and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) cancer questionnaire (least-square mean change from baseline in total score across all visits; additional analyses to be reported separately), and steady-state exposure to abiraterone and olaparib (to be reported separately). Prostate-specific antigen progression was defined as an increase in prostate-specific antigen (after week 12) of at least 25% greater than the nadir and an absolute increase of at least 2 ng/mL above nadir, confirmed by a second increased or equivalent prostate-specific antigen measurement taken at least 3 weeks later (PCWG3 criteria). The study included preplanned analysis of overall HRRm status and outcomes in HRRm subgroups were a secondary endpoint of the study. The genes assessed by tumour tissue and ctDNA-based testing were *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. These genes were selected on the basis of genes validated in the PROfound trial.[12] Single-gene analysis was not a prespecified endpoint. The genes assessed by germline blood testing were *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CHEK2*, *PALB2*, *RAD51C*, and *RAD51D*.

Time to prostate-specific antigen progression (time from randomisation to prostate-specific antigen progression per PCWG3 criteria) and circulating tumour cell conversion rate (proportion of patients who achieve a decline in the number of circulating tumour cells from ≥5 cells per 7·5 mL at baseline to <5 cells per 7·5 mL at any time post-baseline in whole blood) were exploratory endpoints.

Duration of exposure to the study treatments (time from first dose, up to and including the last day that the dose was greater than 0 mg) was a prespecified safety endpoint.

Statistical analysis

Efficacy was analysed for the intention-to-treat population comprising all patients randomly assigned into the study, and safety was analysed for all patients who received any amount of abiraterone, olaparib, or placebo. Patients who received at least one dose of olaparib were included in the olaparib plus abiraterone group for the safety analysis.

With a sample size of 796 patients, the first interim analysis was planned to occur when there had been approximately 379 progression or death events (47·6% maturity), to provide 94·1% power at a one-sided alpha of 0·014 to show a statistically significant difference in radiographic progression-free survival between the trial groups, assuming an HR for progression or death of 0·68. Overall survival was formally tested at all points, including a third data cutoff for final overall survival. This final prespecified overall survival analysis was planned to take place approximately 48 months after the first patient was randomly assigned.

A multiple testing procedure controlled the overall one-sided type 1 error rate of 2·5%. If the primary endpoint of radiographic progression-free survival was significant, then overall survival would be tested in a hierarchical fashion (appendix p 8).

Interim analysis of radiographic progression-free survival at data cutoff 1 (primary analysis) and data cutoff 2, and overall survival at data cutoff 1, data cutoff 2,

and data cutoff 3 (final prespecified analysis) were planned according to a group-sequential design, with O'Brien and Fleming spending function calculations for each endpoint. The alpha-threshold for this final prespecified analysis of overall survival was 0·0377 (two-sided).

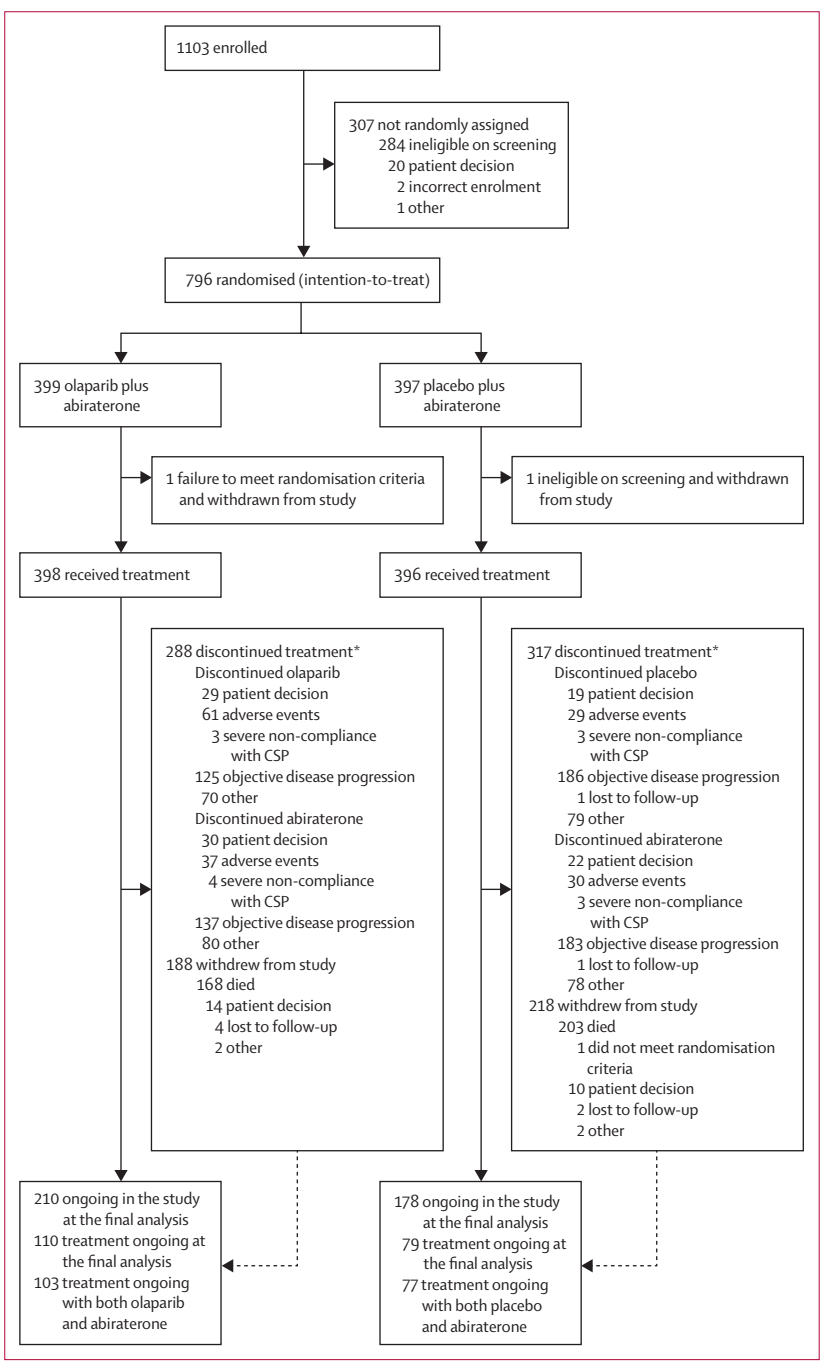


Figure 1: **Trial profile**
Data cutoff—Oct 12, 2022. CSP=clinical study protocol. *Discontinued treatment means discontinued both olaparib and abiraterone or discontinued both placebo and abiraterone; reasons for discontinuing each study treatment were collected separately and are thus reported separately.

For time-to-event endpoints, a stratified log-rank test was used to calculate two-sided p values. HRs and 95% CIs were calculated by means of the Cox proportional hazards model including the two stratification variables at randomisation as covariates. The Kaplan–Meier method was used to calculate medians. Change from baseline in Functional Assessment of Cancer Therapy-Prostate (FACT-P) Total Score across all visits was analysed using a mixed model for repeated measures (MMRM) analysis of all the post-baseline FACT-P scores for each visit. Missing data was handled as per the functional assessment of chronic illness (FACIT) scoring guidelines.

Post-hoc analysis of aggregate tumour tissue and ctDNA data was done to maximise the proportion of patients with assigned HRRm status and minimise potential false negatives. Patients were classified into three groups: HRRm, non-HRRm, and HRRm unknown. The HRRm group included patients with at least one HRR gene mutation detected by either tumour tissue or ctDNA-based test. The non-HRRm group comprised patients with no HRR gene mutation detected by either tumour tissue or ctDNA-based test with at least one obtaining a result. The unknown HRRm group comprised patients for whom mutation testing was not done or where there was no valid result from either tumour tissue or ctDNA-based test. BRCA-mutated subgroups (patients with *BRCA1*-mutated and/or *BRCA2*-mutated) were defined and classified in the same way as HRRm status subgroups.

Prespecified subgroup analyses for radiographic progression-free survival and overall survival were done to assess consistency of treatment effect across prespecified prognostic factors of potential importance (appendix p 9). Post-hoc exploratory radiographic progression-free survival, overall survival, time to first subsequent therapy or death, time to second progression or death, and time to prostate-specific antigen progression subgroup analysis by aggregate HRRm status and BRCA-mutated (*BRCA1* or *BRCA2*) status were done (radiographic progression-free survival previously published for the HRRm and non-HRRm populations[9]). Prespecified and post-hoc exploratory subgroup analyses estimated the HRs for radiographic progression-free survival and overall survival (olaparib plus abiraterone *vs* placebo plus abiraterone) and associated CIs by means of a Cox proportional hazards model with the Efron method being used for handling ties that contain the treatment term, factor, and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison with their CIs were obtained for each level of the subgroup from this single model. No adjustment to the significance level for testing of subgroups was made since all of these subgroup analyses were considered exploratory.

The proportional hazards assumption was assessed for the final overall survival data by examining plots of complementary log–log (event times) versus log (time), Schoenfeld residuals, and by fitting a time-dependent

	Olaparib plus abiraterone (n=399)	Placebo plus abiraterone (n=397)
Age at randomisation, years	69·0 (63–74)	70·0 (65–76)
Gleason score		
≥8	265 (66%)	258 (65%)
Missing	13 (3%)	5 (1%)
Eastern Cooperative Oncology Group performance status		
(0) normal activity	286 (72%)	272 (69%)
(1) restricted activity	112 (28%)	124 (31%)
Missing	1 (<1%)	1 (<1%)
Symptomatic (Brief Pain Inventory-Short Form #3 ≥4* or opiate use)	103 (26%)	80 (20%)
Previous docetaxel treatment before mCRPC		
Yes	97 (24%)	98 (25%)
mHSPC	90 (23%)	89 (22%)
Previous treatment with next-generation hormonal agent		
Yes	1 (<1%)	0
Site of disease†		
Bone	349 (87%)	339 (85%)
Distant lymph nodes	133 (33%)	119 (30%)
Locoregional lymph nodes	82 (21%)	89 (22%)
Prostate and adjacent structures	47 (12%)	46 (12%)
Respiratory (including lung)	40 (10%)	42 (11%)
Liver	15 (4%)	18 (5%)
HRRm status (aggregate)‡		
HRRm	111 (28%)	115 (29%)
Non-HRRm	279 (70%)	273 (69%)
HRRm unknown	9 (2%)	9 (2%)
HRRm status (ctDNA testing)		
HRRm	98 (25%)	100 (25%)
Non-HRRm	269 (67%)	267 (67%)
HRRm unknown	32 (8%)	30 (8%)
HRRm status (tumour tissue testing)		
HRRm	62 (16%)	56 (14%)
Non-HRRm	207 (52%)	210 (53%)
HRRm unknown	130 (33%)	131 (33%)
(Table 1 continues in next column)		
(Continued from previous column)		
BRCAm status (aggregate)		
BRCAm	47 (12%)	38 (10%)
Non-BRCAm	343 (86%)	350 (88%)
Baseline serum prostate specific antigen, µg/L	17·90 (6·09–67·00)	16·81 (6·26–53·30)
Race		
White	282 (71%)	275 (69%)
Black or African American	14 (4%)	11 (3%)
Asian	66 (17%)	72 (18%)
Native Hawaiian or other Pacific Islander	2 (1%)	0
American Indian or Alaska Native	1 (<1%)	0
Other	12 (3%)	9 (2%)
Missing	22 (6%)	30 (8%)
Ethnicity		
Hispanic or Latinx	68 (17%)	63 (16%)
Not Hispanic or Latinx	310 (78%)	305 (77%)
Missing	21 (5%)	29 (7%)

Data are median (IQR) or n (%). Data derived from electronic case report forms. mCRPC=metastatic castration-resistant prostate cancer. HRRm=homologous recombination repair gene mutatation; any deleterious or suspected deleterious HRR gene mutation detected by either test. Non-HRRm=no deleterious or suspected deleterious HRR gene mutation detected by either test. HRRm unknown=patients for whom mutation testing was not done or where there was no valid result from either test owing to insufficient sample quantity or quality or technical failure at sequencing or post-sequencing analysis steps. BRCAm=BRCA mutation. ctDNA=circulating tumour DNA. mCRPC=metastatic castration-resistant prostate cancer. mHSPC=metastatic hormone-sensitive prostate cancer. *Baseline pain score was based on a patient completing the Brief Pain Inventory-Short Form questionnaire item 3 (worst pain) at least once during the 7-day baseline period and was determined as an average. †Investigators could enter more than one site of disease. Entries for "Other locally advanced sites", "Other distant sites" and "Other" have been excluded. ‡Post hoc analysis of aggregate tumour tissue and ctDNA data.

Table 1: **Characteristics of patients at baseline (data cutoff July 30, 2021)**

covariate. There was some evidence of a violation of the proportional hazards assumption for the final pre-specified overall survival data. In the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. All statistical analyses were done by means of SAS version 9.4. There was an independent data monitoring committee for this study. This trial is registered with ClinicalTrials.gov, NCT03732820.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, and data interpretation. The report was written with medical writing assistance from the funder, with critical review and input by the authors. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Results

This multicentre trial spanning 17 countries screened 1103 patients between Oct 31, 2018, and March 11, 2020. 796 patients met eligibility criteria and were randomly assigned to study treatment and included in the analyses (399 olaparib plus abiraterone, 397 placebo plus abiraterone; figure 1).

At final analysis, 210 patients in the olaparib plus abiraterone group and 178 in the placebo plus abiraterone group remained in the trial; 110 patients in the olaparib plus abiraterone group and 79 in the placebo plus abiraterone group, remained on study treatment. Median follow-up for overall survival in

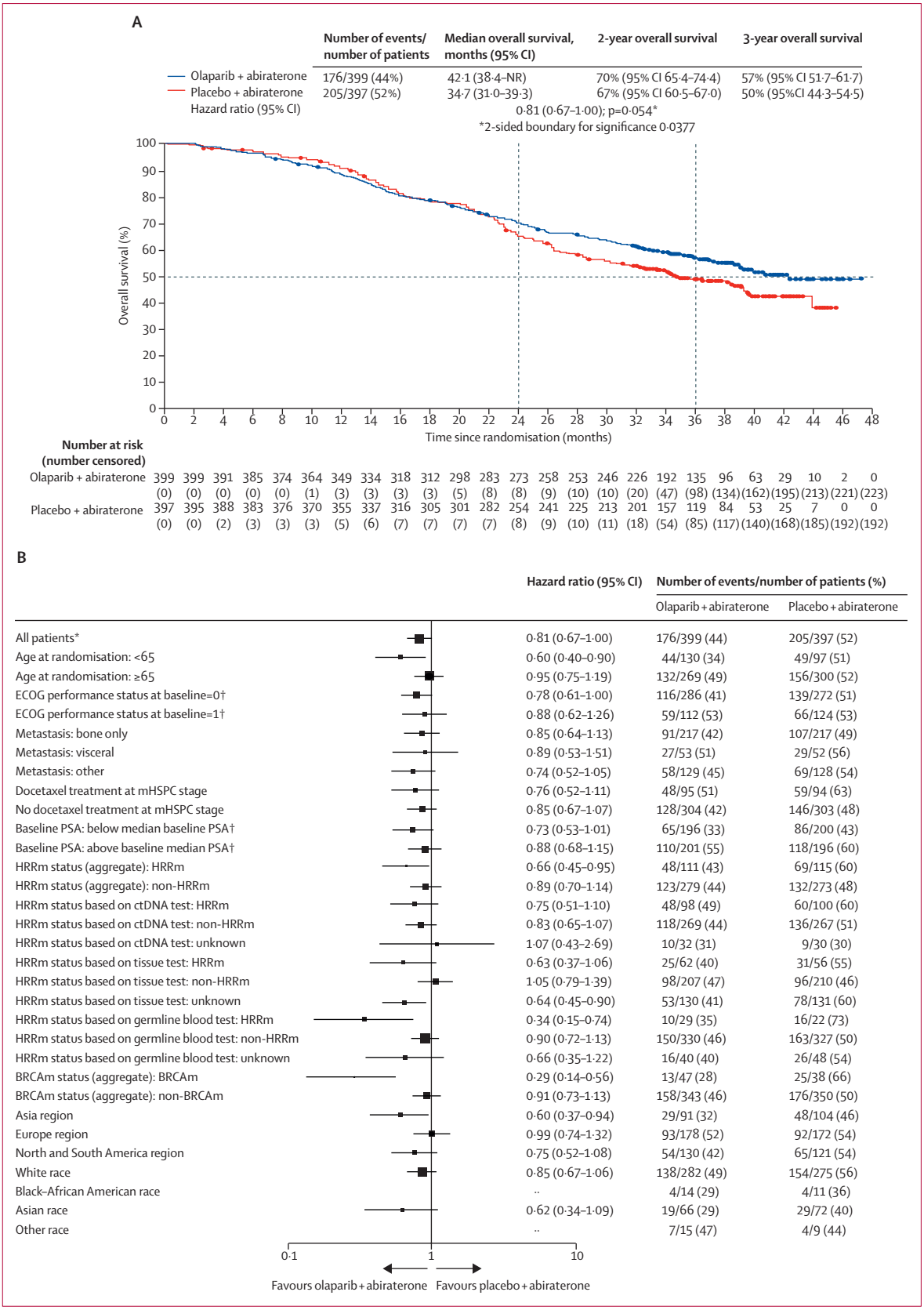


Figure 2: **Overall survival**
(A) Kaplan–Meier estimate of overall survival in the intention-to-treat population. Data cutoff—Oct 12, 2022. Median follow-up for overall survival in patients with censored data was 36·6 months (IQR 34·1–40·3) for olaparib plus abiraterone and 36·5 months (33·8–40·3) for placebo plus abiraterone. Any patient not known to have died at the time of analysis will be censored on the basis of the last recorded date on which the patient was known to be alive. A circle indicates a censored observation. (B) Forest plot of subgroup analysis of overall survival. Data cutoff—Oct 12, 2022. Data derived from interactive voice response system–web response system stratification variables. Each subgroup analysis was done by means of a Cox proportional hazards model that contains a term for treatment, factor, and treatment by factor interaction. A hazard ratio <1 implies a lower risk of death on olaparib. The size of a square is proportional to the number of events. Subgroup categories with fewer than five events in either treatment group are not reported. BRCAm=BRCA-mutated. ctDNA=circulating tumour DNA. ECOG=Eastern Cooperative Oncology Group. HRRm=homologous recombination repair gene mutation. mHSPC=metastatic hormone-sensitive prostate cancer. NR=not reached. PSA=prostate-specific antigen. *Analysis included the stratification factors selected in the primary pooling strategy as covariates. †Excludes patients with no baseline assessment.

patients with censored data was 36·6 months (IQR 34·1–40·3) for olaparib plus abiraterone and 36·5 months (33·8–40·3) for placebo plus abiraterone. Demographic and clinical characteristics at baseline were similar between treatment groups (table 1).

Radiographic progression-free survival analysis at this final prespecified analysis was descriptive, as radiographic progression-free survival at the primary analysis was statistically significant. Radiographic progression-free survival results at this final prespecified analysis were consistent with the primary analysis (appendix p 10). Post-hoc exploratory assessment of radiographic progression-free survival at the primary analysis in aggregate HRRm, non-HRRm, BRCA-mutated, and non-BRCA-mutated subgroups favoured olaparib plus abiraterone. The assessment in aggregate BRCA-mutated and non-BRCA-mutated subgroups is shown in the appendix (pp 11–12), and

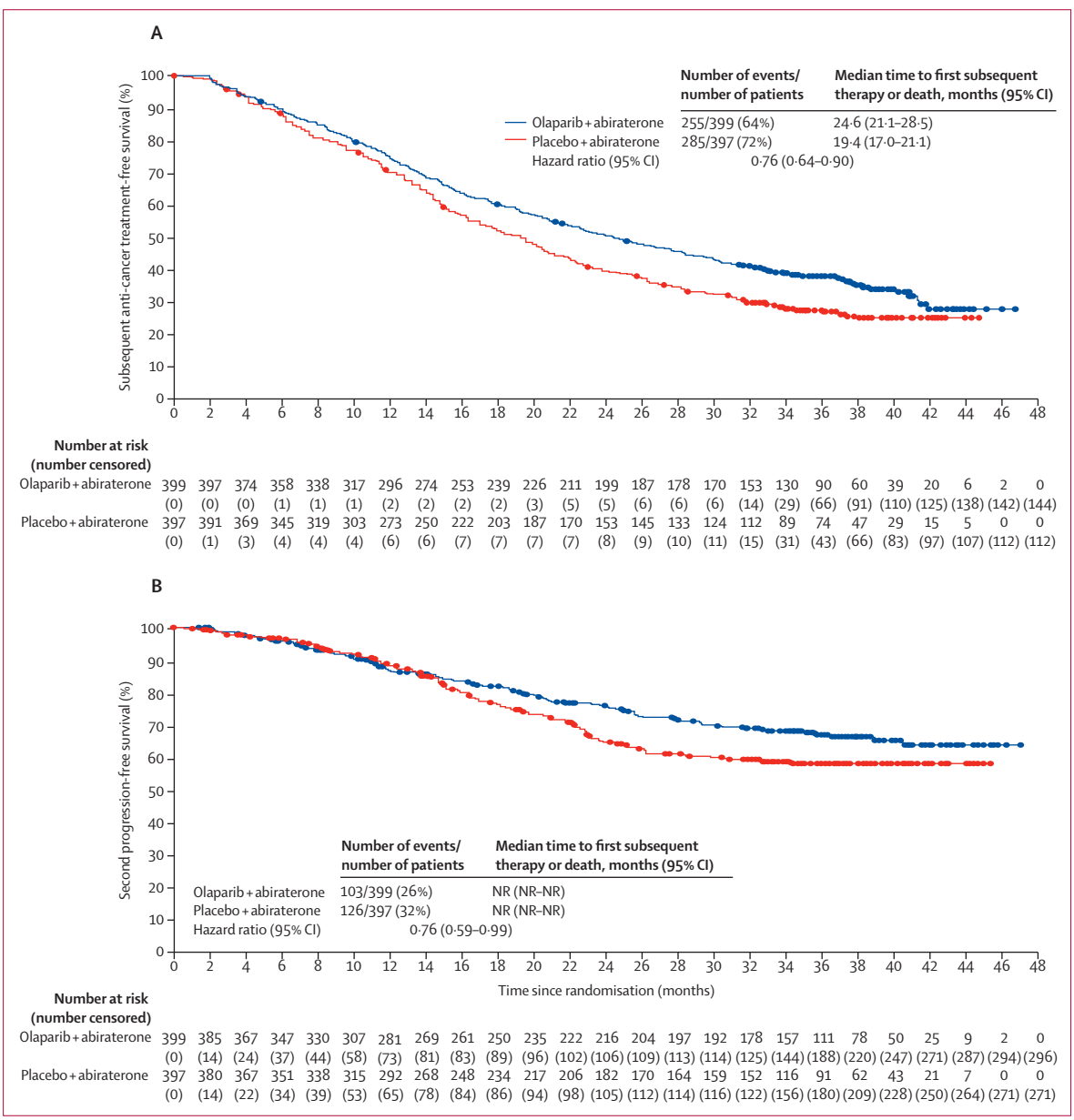
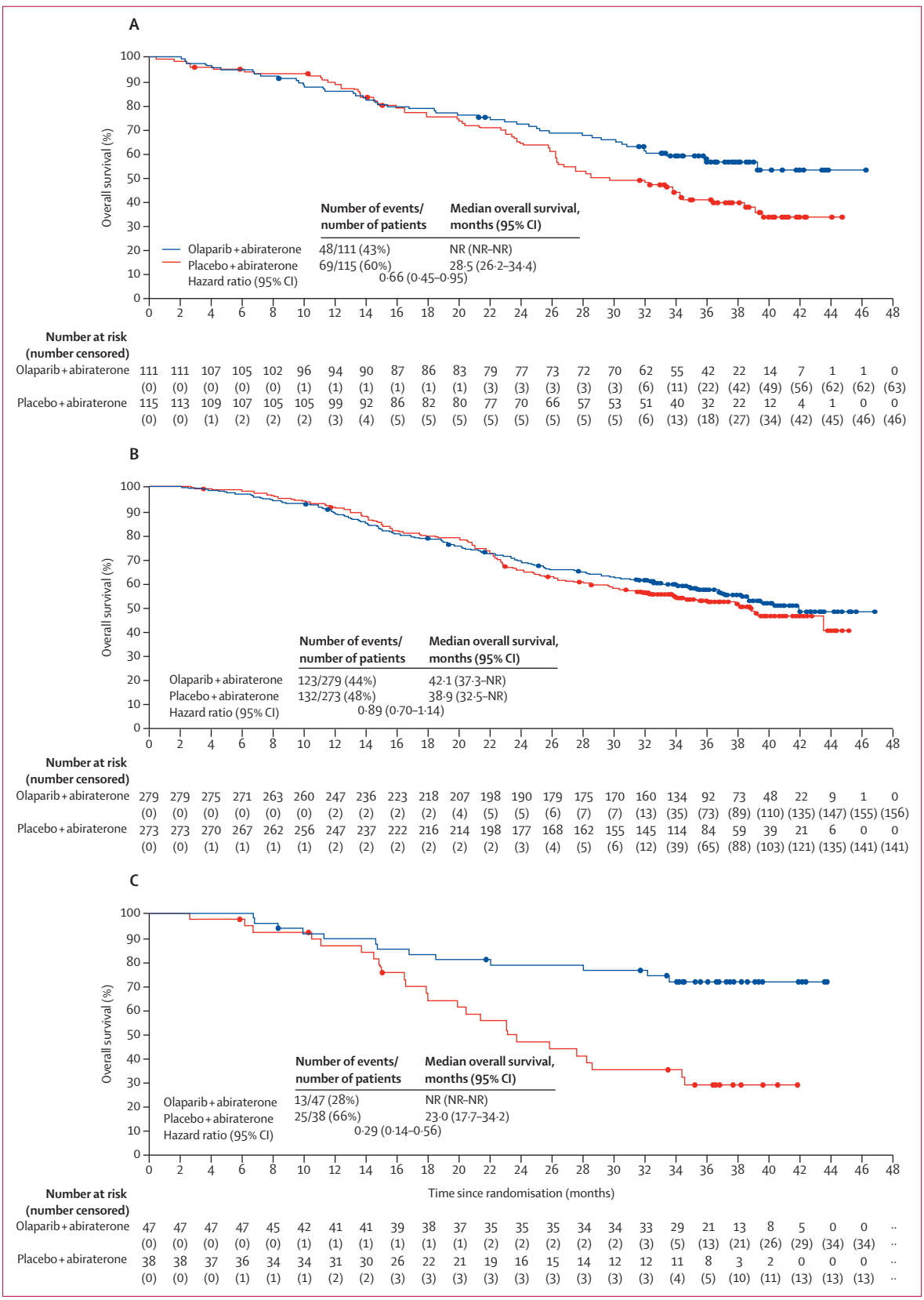


Figure 3: **Kaplan–Meier estimates of the secondary endpoints time to first subsequent therapy and time to second progression**
(A) Time to first subsequent therapy. Data cutoff—Oct 12, 2022. Any patient not known to have died at the time of the analysis and not known to have had a subsequent therapy was censored at the last known time to have not received first subsequent therapy. (B) Time to second progression (investigator-assessed) or death. Data cutoff—Oct 12, 2022. Patients who had not had a second disease progression event or died at the time of analysis, or who had second progression or died after two or more missed visits, were censored at the latest evaluable assessment when they were known to be alive and without a second disease progression. NR=not reached.



(Figure 4 continues on next page)

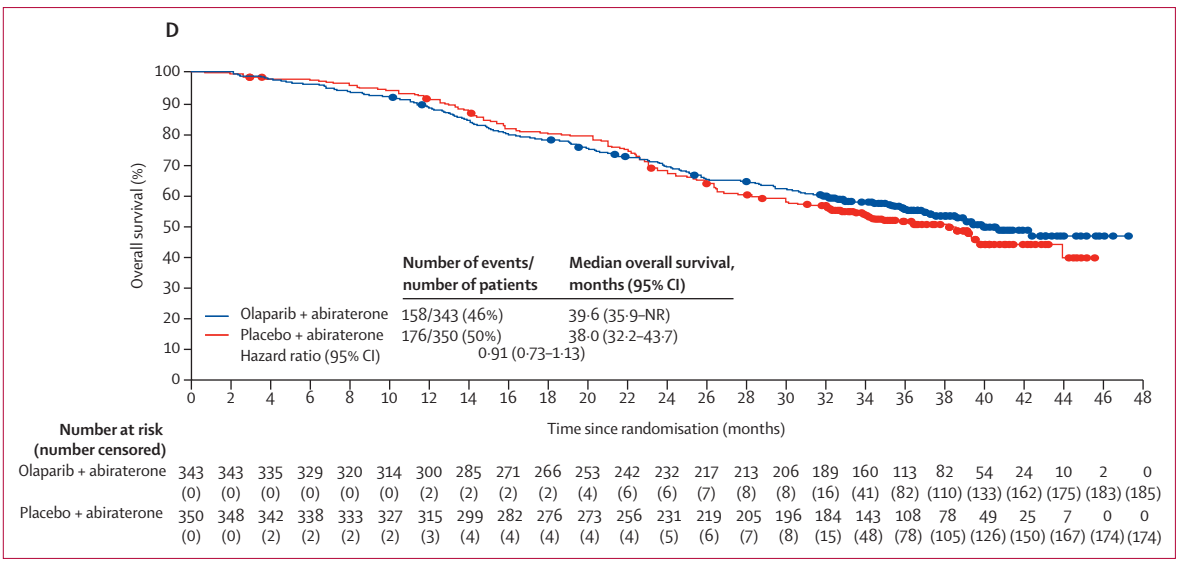


Figure 4: **Kaplan–Meier estimates of overall survival**

(A) Overall survival in the HRRm subgroup. (B) Overall survival in the non-HRRm subgroup. (C) Overall survival in the BRCA-mutated subgroup. (D) Overall survival in the non-BRCA-mutated subgroup. Data cutoff Oct 12, 2022. Any patient not known to have died at the time of analysis was censored on the basis of the last recorded date on which the patient was known to be alive. A circle indicates a censored observation. HRRm=homologous recombination repair gene mutation. NR=not reached.

was published previously for aggregate HRRm and non-HRRm subgroups.[9]

This final prespecified analysis was planned to take place approximately 48 months after the first patient was randomly assigned; at this time, 381 (48%) of 796 patients had died (data cutoff 3: Oct 12, 2022). Median overall survival was 42·1 months (95% CI 38·4–NR) with olaparib plus abiraterone versus 34·7 months (31·0–39·3) with placebo plus abiraterone (HR 0·81, 0·67–1·00; p=0·054 [two-sided alpha 0·0377]; figure 2A). Predefined exploratory subgroup analyses for olaparib plus abiraterone versus placebo plus abiraterone are shown in figure 2B.

At this final prespecified analysis, secondary endpoints were consistent with previous analyses, with median time to first subsequent therapy or death for patients in the olaparib plus abiraterone group 24·6 months (95% CI 21·1–28·5) compared with 19·4 months (17·0–21·1) for patients in the placebo plus abiraterone group (HR 0·76, 95% CI 0·64–0·90; figure 3A) and median time to second progression or death was not reached in the olaparib plus abiraterone group or the placebo plus abiraterone group (HR 0·76, 0·59–0·99; figure 3B).

Overall, 179 (45%) of 399 patients in the olaparib plus abiraterone group and 216 (54%) of 397 patients in the placebo plus abiraterone group received subsequent therapy, most commonly cytotoxic chemotherapy (290 [36%] of 796), which was received by 123 (31%) of 399 patients in the olaparib plus abiraterone group versus 167 (42%) of 397 patients in the placebo plus abiraterone group. NHAs were received by 67 (17%) of 399 patients in the olaparib plus abiraterone group and 75 (19%) of 397 patients in the placebo plus abiraterone group, and PARP inhibitors by two (1%) of 399 patients in the olaparib plus abiraterone group and five (1%) of 397 patients in the placebo plus abiraterone group (appendix p 13).

Median time to prostate-specific antigen progression was 24·2 months (95% CI 18·5–29·4) with olaparib plus abiraterone versus 12·0 months (11·0–13·8) with placebo plus abiraterone (HR 0·59, 95% CI 0·49–0·71). Circulating tumour cell conversion rate at the time of the primary analysis can be found in the appendix (p 13).

Consistent with previous analysis, least-square mean change from baseline in Functional Assessment of Cancer Therapy-Prostate (FACT-P) Total Score across all visits was –5·84 (95% CI –7·86 to –3·81) with olaparib plus abiraterone versus –5·30 (–7·38 to –3·22) with placebo plus abiraterone (difference –0·54; –3·00 to –1·92).

The post-hoc exploratory assessment of overall survival in the HRRm and non-HRRm subgroups and the BRCA-mutated and non-BRCA-mutated subgroups is shown in figure 4.

Consistent effects were seen across post-hoc exploratory assessment of time to first subsequent therapy or death, time to second progression or death, and time to prostate-specific antigen progression in BRCA-mutated and non-BRCA-mutated subgroups (appendix pp 14–19).

At this final prespecified analysis, median total duration of exposure was 18·5 months (IQR 7·4–33·8) for olaparib, 15·7 months (IQR 8·1–29·6) for placebo, 20·1 months (IQR 8·5–34·2) for abiraterone in the olaparib plus abiraterone group and 15·7 months (IQR 8·0–30·3) for abiraterone in the placebo plus

	Olaparib plus abiraterone group (n=398)					Placebo plus abiraterone group (n=396)				
	All grade	Grade 1–2	Grade 3	Grade 4	Grade 5	All grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	389 (98%)	167 (42%)	164 (41%)	32 (8%)	26 (7%)	380 (96%)	209 (53%)	135 (34%)	16 (4%)	20 (5%)
Anaemia†	198 (50%)	159 (40%)	61 (15%)	4 (1%)	0	70 (18%)	57 (14%)	13 (3%)	0	0
Fatigue or asthenia	154 (39%)	150 (38%)	10 (3%)	0	0	120 (30%)	117 (30%)	6 (2%)	0	0
Nausea	122 (31%)	121 (30%)	1 (<1%)	0	0	57 (14%)	56 (14%)	1 (<1%)	0	0
Back pain	86 (22%)	82 (21%)	4 (1%)	0	0	79 (20%)	73 (18%)	6 (2%)	0	0
Diarrhoea	82 (21%)	77 (19%)	5 (1%)	0	0	42 (11%)	41 (10%)	1 (<1%)	0	0
Constipation	74 (19%)	74 (19%)	0	0	0	59 (15%)	58 (15%)	1 (<1%)	0	0
Decreased appetite	66 (17%)	62 (16%)	4 (1%)	0	0	31 (8%)	31 (8%)	0	0	0
Vomiting	62 (16%)	56 (14%)	6 (2%)	0	0	37 (9%)	36 (9%)	1 (<1%)	0	0
Hypertension	61 (15%)	46 (12%)	15 (4%)	0	0	74 (19%)	56 (14%)	18 (5%)	0	0
Arthralgia	58 (15%)	58 (15%)	0	0	0	77 (19%)	75 (19%)	2 (1%)	0	0
COVID-19	51 (13%)	36 (9%)	7 (2%)	1 (<1%)	7 (2%)	35 (9%)	27 (7%)	4 (1%)	1 (<1%)	3 (1%)
Peripheral oedema	49 (12%)	49 (12%)	0	0	0	50 (13%)	49 (12%)	1 (<1%)	0	0
Dizziness	49 (12%)	49 (12%)	0	0	0	27 (7%)	27 (7%)	0	0	0
Urinary tract infection	46 (12%)	36 (9%)	10 (3%)	0	0	35 (9%)	31 (8%)	4 (1%)	0	0
Cough	47 (12%)	47 (12%)	0	0	0	29 (7%)	29 (7%)	0	0	0
Hot flush	35 (9%)	35 (9%)	0	0	0	51 (13%)	51 (13%)	0	0	0
Cardiac failure adverse events	7 (2%)	3 (1%)	5 (1%)	0	0	7 (2%)	6 (2%)	0	0	2 (1%)
Embolic and thrombotic arterial adverse events	10 (3%)	2 (1%)	8 (2%)	0	0	14 (4%)	4 (1%)	4 (1%)	5 (1%)	1 (<1%)
Embolic and thrombotic venous adverse events	34 (9%)	8 (2%)	28 (7%)	2 (1%)	1 (<1%)	16 (4%)	6 (2%)	8 (2%)	2 (1%)	0
Any serious adverse event	161 (40%)	NA	NA	NA	NA	126 (32%)	NA	NA	NA	NA
Interruption of olaparib/placebo because of an adverse event	195 (49%)	NA	NA	NA	NA	112 (28%)	NA	NA	NA	NA
Interruption of abiraterone because of an adverse event	145 (36%)	NA	NA	NA	NA	95 (24%)	NA	NA	NA	NA
Dose reduction of olaparib or placebo due to an adverse event	90 (23%)	NA	NA	NA	NA	24 (6%)	NA	NA	NA	NA
Dose reduction of abiraterone due to an adverse event	10 (3%)	NA	NA	NA	NA	17 (4%)	NA	NA	NA	NA
Discontinuation of olaparib or placebo due to an adverse event	69 (17%)	NA	NA	NA	NA	34 (9%)	NA	NA	NA	NA
Discontinuation of abiraterone due to an adverse event	45 (11%)	NA	NA	NA	NA	37 (9%)	NA	NA	NA	NA
Death due to an adverse event	26 (7%)	NA	NA	NA	NA	20 (5%)	NA	NA	NA	NA
Treatment-related deaths	0	NA	NA	NA	NA	1 (<1%)	NA	NA	NA	NA

Data are n (%). NA=not applicable. *Adverse events, regardless of the investigators' assessment of causality, are reported for those that occurred in at least 10% of patients in either treatment group. Patients were counted once for each type of adverse event. Adverse events with an onset date, or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment, are included. †Anaemia category includes anaemia, decreased haemoglobin level, decreased red-cell count, decreased haematocrit level, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia, and normocytic anaemia; one patient had two separate events of anaemia of grade 3 and grade 4 severity.

Table 2: **Treatment-emergent adverse events (safety analysis set)***

abiraterone group. No new safety signals were observed with longer follow-up.

All-grade adverse events are shown in table 2. Anaemia was the most common grade 3–4 adverse event, occurring in 64 (16%) of 398 patients in the olaparib plus abiraterone group and 13 (3%) of 396 patients in the placebo plus abiraterone group. 72 (18%) of 398 patients reporting anaemia received at least one blood transfusion in the olaparib plus abiraterone group, compared with 16 (4%) of 396 patients in the placebo plus abiraterone group. Serious adverse events were reported in 161 (40%) of 398 patients in the olaparib plus abiraterone group and 126 (32%) of 396 patients in the placebo plus abiraterone group. Anaemia was the most common serious adverse event reported in 23 (6%) of 398 patients in the olaparib plus abiraterone group versus three (1%) of 396 in the placebo plus abiraterone group.

69 (17%) of 398 patients discontinued olaparib and 34 (9%) of 396 patients discontinued placebo because of an adverse event. Discontinuations of abiraterone due to adverse events occurred in 45 (11%) of 398 patients in the olaparib plus abiraterone group and 37 (9%) of 396 patients in the placebo plus abiraterone group. Adverse events led to death in 26 (7%) of 398 and 20 (5%) of 396 patients, respectively (appendix p 20). One death in the placebo plus abiraterone group, from interstitial lung disease, was considered treatment related.

The rate of cardiovascular events (myocardial infarction, congestive heart failure, and ischaemic stroke) remained similar between groups (appendix p 20). Pulmonary embolism was reported in 29 (7%) of 398 patients with olaparib plus abiraterone and nine (2%) of 396 patients with placebo plus abiraterone. The majority of events were asymptomatic with incidental findings on planned imaging. Deep-vein thrombosis occurred in ten (3%) of 398 patients with olaparib plus abiraterone and three (1%) of 396 patients with placebo plus abiraterone.

COVID-19-related adverse events were reported at a higher frequency in the olaparib plus abiraterone group versus the placebo plus abiraterone group (63 [16%] of 398 *vs* 39 [10%] of 396; appendix p 21).

There were two cases of myelodysplastic syndrome in the olaparib plus abiraterone group (appendix p 21). The incidence of new primary cancers (18 [5%] of 398 olaparib plus abiraterone *vs* 14 [4%] of 396 placebo plus abiraterone) and pneumonitis (grouping interstitial lung disease, pneumonitis, and radiation pneumonitis; five [1%] of 398 *vs* three [1%] of 396) were balanced between groups. Other adverse events are reported in the appendix (pp 22–27).

Discussion

To our knowledge, PROpel was the first positive phase 3 trial of a PARP inhibitor in combination with an NHA in a biomarker-unselected first-line mCRPC population. Olaparib plus abiraterone resulted in a statistically significant and clinically meaningful improvement in radiographic progression-free survival versus active standard-of-care abiraterone as first-line treatment for mCRPC.[9] We describe the final prespecified overall survival analysis from PROpel, in which olaparib plus abiraterone showed a median overall survival of 42·1 months (95% CI 38·4–NR) compared with 34·7 months (31·0–39·3) with life-prolonging standard-of-care, abiraterone, in patients with first-line mCRPC. Aggregate biomarker subgroup analyses generally favoured olaparib plus abiraterone, with HRRm and BRCA-mutated patients having greater benefit than those without these mutations. No new safety signals were identified with longer follow-up and no change in health-related quality of life as assessed by FACT-P Total Score was observed with the addition of olaparib to abiraterone.

At the primary analysis, radiographic progression-free survival benefits were observed across all prespecified subgroups including by age, sites of metastases, previous docetaxel at the mHSPC stage, ECOG status, region, race, baseline prostate-specific antigen, and HRRm status.[9] Radiographic progression-free survival is recognised by PCWG2/PCWG3 consensus guidelines and many studies showing a close association between intermediate endpoints and overall survival.[13–16] Optimising first-line treatment and delaying radiographic progression-free survival is particularly important as many patients with mCRPC only receive one line of therapy.[17] Delaying radiographic progression-free survival can also provide patient-centred benefits, including delaying deterioration of symptoms and quality of life associated with disease progression, and prolonging time until chemotherapy.[18]

This final prespecified alpha-controlled overall survival analysis (data cutoff 3: Oct 12, 2022) was a key secondary endpoint to support the primary radiographic progression-free survival analysis. Results were consistent with overall survival at the primary analysis (data cutoff 1: July 30, 2021),[9] although not statistically significant. Additional secondary endpoints of time to first subsequent therapy or death and time to second progression or death in the overall population were consistent with the primary analysis and support the clinical benefit of olaparib plus abiraterone. Furthermore, our results are consistent with the Study 8 and TALAPRO-2 trials, which show the benefit of PARP inhibitors in combination with NHAs for patients with mCRPC with or without HRRm.[7, 19]

NHAs and docetaxel are standard-of-care treatments for first-line mCRPC based on results from COU-AA-302, PREVAIL, and TAX-327. To our knowledge, the PROpel study marks the first positive phase 3 study for first-line mCRPC in nearly 10 years. The control group of PROpel did as expected on the basis of the COU-AA-302 study (median 34·7 months in both trials), in which abiraterone showed a 4·4-month improvement in median overall survival over placebo plus prednisone (HR 0·81; 95% CI 0·70–0·93).[1]

PROpel was designed to assess olaparib plus abiraterone in the overall population, and numbers of patients and events in some subgroups were small. Prespecified subgroup analyses of overall survival were generally consistent with the primary analysis in which a clinically meaningful improvement in radiographic progression-free survival was observed in all prespecified subgroups, including by previous docetaxel at the mHSPC stage, sites of metastases at baseline, and HRRm status.[9] It is noted that 261 (33%) of 796 patients did not have a valid test result with tissue testing and were not included in the HRRm or non-HRRm, by tissue test, subgroups. As such, the biomarker subgroup results by tissue test should be interpreted with caution. The aggregate approach (discussed below) provided the most complete dataset to enable more robust biomarker subgroup analyses.

A post-hoc exploratory assessment of overall survival was done in aggregate HRRm, non-HRRm, BRCA-mutated, and non-BRCA-mutated subgroups, with BRCA-mutated patients deriving greatest radiographic progression-free survival and overall survival benefits with olaparib plus abiraterone versus placebo plus abiraterone. These results are not unexpected given that several observational and clinical studies in the past

5–10 years have provided an increasing body of evidence highlighting that patients with BRCA-mutated mCRPC have a poorer prognosis and worse outcomes with first-line NHAs, and the known sensitivity of BRCA-mutated cancers to PARP inhibition.[12,20–23] Poor outcomes for patients with BRCA-mutated mCRPC on NHA monotherapy are shown in the comparator group of PROpel, in which patients in the BRCA-mutated or HRRm subgroups have shorter overall survival than patients in the non-BRCA-mutated and non-HRRm subgroups, reinforcing the continued importance of molecular testing to inform prognosis. Further research will help to expand our understanding of which patients in the non-BRCA-mutated and non-HRRm subgroups derive the greatest benefit.

The safety profile in this final analysis was consistent with the primary analysis,[9] with no new signals identified with longer follow-up. Incidence of grade 3 or higher anaemia was lower than observed in other trials of PARP inhibitors in combination with an NHA,[19,24] and the majority of anaemia events were managed with olaparib dose reductions or temporary interruptions. The proportion of patients in the olaparib plus abiraterone group receiving blood transfusions was consistent with the proportion reporting grade 3 or higher anaemia, for which blood transfusion is recommended by guidelines.[25] For those receiving olaparib, the median time to onset of adverse events was less than 4 months,[26] with a median time to recovery of less than 6 months from the time of study initiation.[26] There was a small but higher rate of pulmonary embolism events observed with olaparib plus abiraterone; however, the overall adverse event profile was consistent with known individual toxicity profiles and did not indicate increase in toxicity of either drug when used in combination or with longer follow-up.[20,27]

Adding olaparib to abiraterone had no clinically meaningful effect on overall health-related quality of life. FACT-P data were similar between treatment groups, indicating that addition of olaparib to abiraterone had no overall detriment on patients' health-related quality of life.[9]

Investigators had access to HRR mutational status on request at the time of progression. This might have influenced treatment selection for subsequent therapy in markets in which olaparib monotherapy was approved and available, which would have been primarily toward the end of the PROpel study enrolment period.

A limitation is that the study did not enrol patients who had progressed on a previous NHA pre-mCRPC. With the treatment landscape evolving, many patients now receive NHAs in the castration-sensitive setting. Notably, as enrolment in PROpel was not based on HRRm status or whether patients had asymptomatic, mildly symptomatic, or symptomatic disease, patients were representative of those eligible for abiraterone in the real-world setting. Importantly, the overall data from PROpel, including key clinical and biomarker subgroup analyses, quality of life, and tolerability analyses, can inform discussions with patients regarding the benefit–risk profile of olaparib plus abiraterone. As recommended by guidelines,[28–30] molecular testing for HRRm remains important even in the era of combination therapy to make an informed assessment regarding benefit–risk.

In conclusion, overall survival was not statistically significantly different between treatment groups at the final prespecified analysis, although the primary endpoint of radiographic progression-free survival was met and showed a statistically significant and clinically meaningful difference in favour of the olaparib plus abiraterone group. Further research will help to expand our understanding of the clinical benefit in patients with mCRPC with and without HRR mutations.

Contributors

FS, NWC, AJA, and MO contributed to conceptualisation, investigation, resources, supervision, validation, visualisation, writing, review, and editing. NS, GP, JDG, CA, NM, FP, EB, FS, JYJ, MS, and OS contributed to investigation, resources, writing, review and editing. Y-ZL, CP, LB, and PMdR contributed to conceptualisation, resources, original draft preparation, writing, review, and editing, and also accessed and verified data. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol.

Declaration of interests

FS received honoraria from AAA, AbbVie, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen Oncology, Knight Therapeutics, Merck, Myovant Sciences, Novartis, Pfizer, and Sanofi; acted in a consulting or advisory role for AAA, AbbVie, Astellas Pharma, AstraZeneca–MedImmune, Bayer, Janssen Oncology, Knight Therapeutics, Myovant Sciences, Novartis, Pfizer, and Sanofi; and received research funding (institutional) from Advanced Accelerator Applications, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen Oncology, Merck, Novartis, Pfizer, and Sanofi. NWC received honoraria from AstraZeneca, Bayer, Janssen, and Pfizer; acted in a consulting or advisory role for AstraZeneca; and received travel and accommodation expenses from AstraZeneca. MO received honoraria from Astellas, AstraZeneca, Bayer, MSD, Janssen, Takeda, and Nippon Kayaku; acted in a consulting or advisory role for Bayer; and received research funding from Bayer and AstraZeneca. NS acted in a consulting or advisory role for AbbVie, Accord, Alessa Therapeutics, Antev, Arquer, Asieris, Amgen, Astellas, AstraZeneca, Aura biosciences, Bayer, Bioprotect, Bristol Myers Squibb, Boston Scientific, CGOncology, Clarity, Dendreon, Exact Imaging, Ferring, Fize Medical, Genentech–Roche, Foundation Medicine, Genesis Care, Immunity Bio, Incyte, Invitae, Janssen, Lantheus, Lilly, mDxhealth, Merck, Minomic, Myovant, Myriad, Nonagen, Novartis, Nymox, Palette Life, Platform Q, Pacific Edge, Pfizer, Profound Medical, Promaxo, Protara, Photocure, Sanofi Genzyme, Specialty Networks, Telix, Tolmar, and Urogen; and acted in a leadership or fiduciary role for Photocure. GP acted in a consulting or advisory role for Astellas, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Janssen, Merck Sharp & Dohme, Novartis, and Pfizer. JDG received honoraria from Agenus, AstraZeneca–Merck, Daiichi-Sankyo, Merck, Pierre Fabre, and Pint Pharma; research funding from Agenus, Amgen, AstraZeneca, Bayer, Blau Farmacêutica, Boehringer-Ingelheim, Bristol Myers Squibb, BRAVA, Daiichi-Sankyo, Eurofarma, ARO-Einstein, Genetech, HUYABIO, Incyte, Lilly, MSD, Novartis, Pfizer, Polyphor, PTC Therapeutics, Roche, Sanofi, Seagen, Takeda, and Tigermed; and travel and accommodation expenses from Daiichi Sankyo and Gilead. NM received honoraria from Bureau Prevents, Medscape, and MedTalks; acted in a consulting or advisory role for Astellas Pharma, AstraZeneca, Bayer, Janssen-Cilag, and MSD Oncology (institutional); received research funding (institutional) from Astellas Pharma, AstraZeneca–Merck, Janssen-Cilag, Pfizer, Roche/Genentech, and Sanofi; received travel and accommodation expenses from Astellas Pharma, Bristol Myers Squibb, Janssen-Cilag, MSD Oncology, and Roche;

acted in a leadership–fiduciary role for Dutch Uro-Oncology study Group; and participated in a data safety monitoring–advisory board for the GLOW trial (glioblastoma). FP acted in a consulting or advisory role for Ipsen, Janssen Oncology, and Merck Serono. FS received honoraria from Advanced Accelerator Applications, AstraZeneca, Astellas, Bayer, Janssen, and Merck; acted in a consulting or advisory role for Advanced Accelerator Applications, AstraZeneca, Astellas, Bayer, Janssen, MSD/Merck, and Lilly; received travel and accommodations expenses from Advanced Accelerator Applications, AstraZeneca, Astellas, Bayer, and Janssen; and provided expert testimony for Advanced Accelerator Applications, AstraZeneca, Astellas, Bayer, Bristol Myers Squibb, Janssen, MSD/Merck, and Lilly. MS received honoraria from Astellas, AstraZeneca, Janssen Pharmaceuticals, and Takeda; research funding from Astellas, AstraZeneca, Bristol Myers Squibb, Janssen, MSD, and Pfizer; and travel and accommodation expenses from Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, and MSD. OS acted in a consulting or advisory role for AAA, Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Bavarian Nordic, Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis, Constellation, Dendreon, EMD Serono, Fusion, Isotopen Technologien Muenchen, Janssen, Myovant, Myriad, Noria Therapeutics, Novartis, Noxopharm, Progenics, POINT Biopharma, Pfizer, Sanofi, Tenebio, Telix, and Theragnostics; received research funding from AAA, Amgen, AstraZeneca, Bayer, Endocyte, Invitae, Janssen, Lantheus, Merck, Progenics, and Tenebio; provided expert testimony for Sanofi; received travel and accommodation expenses from Lantheus and North Start; participated in a data safety monitoring–advisory board for AstraZeneca and Pfizer; and holds stock options with Ratio, Convergent, Fusion, and Telix. Y-ZL, LB, and PMdR are AstraZeneca employees and shareholders. CP is an employee and shareholder of Merck. AJA has acted in a consulting or advisory role for Astellas Scientific and Medical Affairs, AstraZeneca, Bayer, Bristol Myers Squibb, Dendreon, Exelixis, FORMA Therapeutics, GoodRx, Janssen, Merck, Myovant Sciences, Novartis, and Pfizer; has received research funding (institutional) from Amgen, Astellas Pharma, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Constellation Pharmaceuticals, Dendreon, FORMA Therapeutics, Gilead Sciences, Janssen Oncology, Merck, Novartis, Pfizer, and Roche–Genentech; owns patents, receives royalties, or other intellectual property for circulating tumour cell novel capture technology (institutional); and has received travel and accommodation expenses from Astellas Scientific and Medical Affairs. CA, EB, and JYJ declare no competing interests.

Data sharing

Data underlying the findings described in this manuscript can be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at http://www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiriesabout-studies-not-listed-on-the-vivli-platform/.
The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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References

1 Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015; **16:** 152–60.
2 Armstrong AJ, Lin P, Tombal B, et al. Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer from the PREVAIL trial. *Eur Urol* 2020; **78:** 347–57.
3 Francini E, Gray KP, Shaw GK, et al. Impact of new systemic therapies on overall survival of patients with metastatic castration-resistant prostate cancer in a hospital-based registry. *Prostate Cancer Prostatic Dis* 2019; **22:** 420–27.
4 Shore ND, Laliberté F, Ionescu-Ittu R, et al. Real-world treatment patterns and overall survival of patients with metastatic castration-resistant prostate cancer in the US prior to PARP inhibitors. *Adv Ther* 2021; **38:** 4520–40.
5 Goodwin JF, Schiewer MJ, Dean JL, et al. A hormone-DNA repair circuit governs the response to genotoxic insult. *Cancer Discov* 2013; **3:** 1254–71.
6 Polkinghorn WR, Parker JS, Lee MX, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov* 2013; **3:** 1245–53.
7 Clarke N, Wiechno P, Alekseev B, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2018; **19:** 975–86.
8 Carr TH, Adelman C, Barnicle A, et al. Homologous recombination repair gene mutation characterization by liquid biopsy: a phase II trial of olaparib and abiraterone in metastatic castrate-resistant prostate cancer. *Cancers (Basel)* 2021; **13:** 5830.
9 Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid* 2022; **1**: EVIDoa2200043.
10 European Medicines Agency. Lynparza. 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/lynparza (accessed June 19, 2023).
11 US Food and Drug Administration. Lynparza (olaparib) prescribing information. 2023. https://www.fda.gov/medical-devices/recently-approved-devices/foundationoner-cdx-p170019s017 (accessed June 19 2023).
12 de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 2020; **382:** 2091–102.
13 Rathkopf DE, Beer TM, Loriot Y, et al. Radiographic progression-free survival as a clinically meaningful end point in metastatic castration-resistant prostate cancer: the PREVAIL randomized clinical trial. *JAMA Oncol* 2018; **4:** 694–701.
14 Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; **26:** 1148–59.
15 Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol* 2016; **34:** 1402–18.
16 Gharzai LA, Jiang R, Jaworski EM, et al. Meta-analysis of candidate surrogate end points in advanced prostate cancer. *NEJM Evid* 2023; **2**: EVIDoa2200195.
17 Marschner N, Zacharias S, Lordick F, Hegewisch-Becker S, Martens U, Welt A, et al. Association of disease progression with health-related quality of life among adults with breast, lung, pancreatic, and colorectal cancer. *JAMA Network Open* 2020; **3**: e200643.
18 Eliasson L, de Freitas HM, Dearden L, Calimlim B, Lloyd AJ. Patients' preferences for the treatment of metastatic castrate-resistant prostate cancer: a discrete choice experiment. *Clin Ther* 2017; **39:** 723–37.
19 Agarwal N, Azad A, Carles J, et al. TALAPRO-2: phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *Proc Am Soc Clin Oncol* 2023; **41** (suppl 6)**:** LBA17 (abstr).
20 Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med* 2020; **383:** 2345–57.
21 Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. *Clin Cancer Res* 2010; **16:** 2115–21.

22 Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013; **31:** 1748–57.

23 Leongamornlert D, Saunders E, Dadaev T, et al. Frequent germline deleterious mutations in DNA repair genes in familial prostate cancer cases are associated with advanced disease. *Br J Cancer* 2014; **110:** 1663–72.

24 Chi KN, Rathkopf DE, Smith MR, et al. Phase 3 MAGNITUDE study: first results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations. *Proc Am Soc Clin Oncol* 2022; **40** (suppl 6)**:** 12 (abstr).

25 Aapro M, Beguin Y, Bokemeyer C, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. *Ann Oncol* 2018; **29** (suppl 4)**:** iv96–110.

26 Thiery-Vuillemin A, Saad F, Armstrong AJ, et al. Tolerability of abiraterone (abi) combined with olaparib (ola) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): further results from the phase III PROpel trial. *Proc Am Soc Clin Oncol* 2022; **40** (suppl 16)**:** 5019 (abstr).

27 Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; **368:** 138–48.

28 National Comprehensive Cancer Network. NCCN Guidelines. Prostate cancer version 3. 2023. https://www.nccn.org/professionals/physician_gls/default.aspx (accessed Aug 31, 2023).

29 European Association of Urology. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. 2023. https://uroweb.org/guidelines/prostate-cancer (accessed April 21, 2023).

30 Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; **31:** 1119–34.