Olaparib combined with abiraterone in metastatic castration-resistant prostate cancer: a randomised placebo-controlled phase 2 trial

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Research in Context

Evidence before this study

We searched PubMed and the databases of the American Society of Clinical Oncology and European Society for Medical Oncology to identify journal publications and meeting abstracts published between January 1, 2012 and March 1, 2018, that included the search terms “poly(ADP-ribose) polymerase” or “PARP” and “inhibitor” or “inhibition” and “prostate cancer”. No language restrictions were used in our search. Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that is approved in ovarian and breast cancer indications. Other PARP inhibitors in clinical development include niraparib, pamiparib, rucaparib, talazoparib, and veliparib. Abiraterone is an androgen synthesis inhibitor and standard of care treatment for castration-resistant metastatic prostate cancer. In a previous study, the efficacy of olaparib monotherapy in advanced prostate cancer patients was shown to be almost exclusively limited to patients with a homologous recombination repair mutation. A phase 2 trial of veliparib in combination with abiraterone reported no significant efficacy benefit for metastatic castration-resistant prostate cancer patients treated with the combination compared with abiraterone alone.

Added value of this study

We conducted a randomised double-blind placebo-controlled trial of olaparib plus abiraterone compared with abiraterone alone in metastatic castration-resistant prostate cancer patients who had previously received docetaxel. To our knowledge, our data are the first to show a significant improvement in radiologic progression-free survival (rPFS) for men treated with the combination of a PARP inhibitor and

androgen synthesis inhibitor. In addition, and in contrast to results seen previously with olaparib monotherapy in this indication, the rPFS benefit was observed for metastatic castration-resistant prostate cancer patients in the olaparib plus abiraterone arm, who were not required to have a homologous recombination repair mutation; an effect that has not previously been reported. In our study, more patients treated with olaparib and abiraterone experienced grade ≥3 or serious adverse events than those treated with abiraterone alone; however, the increased duration of exposure in the combination arm suggests that increased tolerability risk may be offset by the observed efficacy benefit. No detriment to health-related quality of life was observed in the combination arm compared with the comparator arm.

Implications of all the available evidence

The significant improvement in rPFS observed for metastatic castration-resistant prostate cancer patients treated with olaparib plus abiraterone compared with abiraterone alone suggests that these patients, who were not selected based on biomarker criteria, may benefit from the combination treatment irrespective of homologous recombination repair mutation status. This result, which opens up the possibility of clinical benefit for a broader patient population, is consistent with preclinical data that indicate a synergy between olaparib and agents inhibiting androgen synthesis or function, potentially caused by PARP inhibition of androgen-receptor-dependent transcription or creation of a '*BRCA*-like' phenotype that is susceptible to PARP inhibition. Larger studies are needed to confirm our observations; however, our data suggest that the combination of olaparib and abiraterone has the potential to provide additional and practice-changing therapeutic options to men with metastatic castration-resistant prostate cancer.

Summary

Background

Metastatic castration-resistant prostate cancer (mCRPC) patients with homologous recombination repair (HRR) mutations have shown greater response to the PARP inhibitor olaparib than patients without. Preclinical data suggest synergy between olaparib and androgen pathway inhibitors. We performed a phase 2 randomised double-blind study evaluating olaparib plus abiraterone in mCRPC patients, regardless of HRR mutation status.

Methods

Eligible mCRPC patients had previously received docetaxel (but no second generation antihormonal agents, e.g. abiraterone or enzalutamide), and were candidates for abiraterone treatment. There was no requirement for patients in our trial to have a HRR mutation. Patients were randomised 1:1 to oral olaparib 300 mg bid (tablets; combination) or placebo (comparator); all patients received oral abiraterone 1000 mg od alongside prednisone/prednisolone 5 mg bid. Randomisation was carried out using a computer-generated randomisation scheme and interactive voice/web response system and patients and investigators were blinded to assigned treatment by use of individual treatment Kit ID numbers. No stratification factors were used. The primary endpoint was investigator-assessed radiologic progression-free survival (rPFS; RECIST v1·1, PCWG-2). Efficacy endpoints were assessed on an intention-to-treat basis, and safety and tolerability were assessed in patients who received at least one dose of olaparib or placebo. The trial is ongoing, but no longer recruiting. ClinicalTrials.gov: NCT01972217.

Findings

142 patients were randomised (71 per arm), received treatment and were included in efficacy and safety analyses. A significant rPFS improvement was observed for combination- versus comparator-arm patients (median 13·8 vs 8·2 months; HR 0·65, 95% CI 0·44–0·97, p=0·034). More combination-arm patients experienced grade ≥3 adverse events (38/71 patients [54%] vs 20/71 [28%], including anaemia [n=15 vs 0], pneumonia [n=4 vs 3] and myocardial infarction [n=4 vs 0]) and serious adverse events (SAE; 24/71 [34%] vs 13/71 [18%], respectively), including cardiovascular events (7 SAEs vs 1). One fatal adverse event, pneumonitis, in the combination arm was thought to be causally related to study treatment. Median time to deterioration in quality of life (FACT-P) was 5·7 versus 6·0 months, respectively (HR 0·97 [0·68–1·40], p=0·89).

Interpretation

Olaparib in combination with abiraterone provided clinical efficacy benefit for mCRPC patients compared with abiraterone alone. More SAEs were observed with the combination, but no QoL detriment was seen and together our data suggest that the combination of olaparib and abiraterone may have the potential to provide an additional clinical benefit to a broad population of mCRPC patients.

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Introduction

Prostate cancer is the fifth largest cause of cancer-related deaths for men worldwide.[1] The standard of care for metastatic castration-resistant prostate cancer (mCRPC) includes taxane chemotherapy, such as docetaxel or cabazitaxel, second-generation antihormonal agents, such as abiraterone or enzalutamide, which target the androgen-receptor pathway or radium-223. However, response is often short-lived because patients develop tumour resistance, and improved therapeutic options are needed for men with mCRPC.[2]

In a preliminary phase 2 study (NCT01682772, TOPARP-A), patients with mCRPC who were pretreated with chemotherapy (almost all also having previously received a second-generation antihormonal agent such as abiraterone or enzalutamide) were treated with the poly(ADP-ribose) polymerase (PARP) inhibitor, olaparib. Patients whose tumours carried a homologous recombination repair (HRR) mutation (based on a 113-gene panel test) showed a markedly higher response rate than patients whose tumours lacked a HRR mutation.[3] These clinical data are supported by preclinical studies that demonstrate the mechanism of action for olaparib, which traps PARP at sites of DNA damage, causing an accumulation of DNA double-strand breaks.[4] Synthetic lethality is seen when PARP is trapped in HRR-deficient cells, which depend on low-fidelity pathways for repairing DNA double-strand breaks.[5,6]

Preclinical data have suggested synergy between olaparib and agents affecting the androgen receptor pathway, regardless of HRR mutation status.[7,8] Therefore, we performed a phase 2 randomised trial (ClinicalTrials.gov: NCT01972217) to assess the efficacy and tolerability of olaparib in combination with abiraterone compared

with placebo plus abiraterone in patients with mCRPC, irrespective of their HRR mutation status.

Methods

Study design and participants

This two-part phase 2 trial was conducted at 41 sites in 11 European and North American countries, and comprised an open-label safety run-in (described in the Supplementary Appendix, page 2), followed by a randomised, double-blind phase. Eligible patients were at least 18 years of age and had documented evidence of mCRPC. Castration-resistant prostate cancer was defined as rising prostate-specific antigen (PSA) levels or other signs of disease progression, despite androgen-deprivation therapy and castrate levels of testosterone (≤50 ng/dL). Metastatic disease was defined as at least one metastatic lesion on bone scan, computed tomography, or magnetic resonance imaging. There was no requirement for patients in our trial to have a HRR mutation. Patients had no more than two prior lines of chemotherapy, no previous exposure to second-generation antihormonal agents and all were candidates for abiraterone treatment. In addition, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a life expectancy ≥12 weeks. For the randomised phase, patients were required to have received prior treatment with docetaxel in the mCRPC setting, but response to this treatment was not necessary. Patients had normal organ, bone marrow and cardiac function at baseline and were excluded on this basis if they met any of the criteria listed in the Supplementary Appendix (page 3). Patients were excluded from the trial if they had had other malignancies within 5 years prior to trial entry; any evidence of severe or uncontrolled systemic diseases including hypertension or infection, or spinal cord compression or brain metastases (unless asymptomatic and stable). 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 performed according to the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on bioethics.[9] The trial is ongoing, but is no longer recruiting patients. No further analyses of the primary outcome measure are planned. The study protocol is available in the Supplementary Appendix (page 10).

Randomisation and masking

Patients were enrolled by investigators and assigned 1:1 to a randomised treatment arm by an interactive voice/web response system using random numbers generated by the AstraZeneca Global Randomisation System. Stratification factors were not used during randomisation. Investigators contacted the centralised interactive voice/web response system by telephone or online for allocation of the randomised treatment Kit ID number, which were assigned sequentially to each patient as they became eligible. Assigned treatment was masked for patients, those giving the interventions, data collectors and data analysers. Those involved in data analysis remained blinded until the time of the primary analysis and all investigators and patients remained blinded until verification and closure of the study database, except for medical emergencies where appropriate patient management required knowledge of randomised treatment.

Procedures

In the combination arm, patients received oral olaparib (300 mg tablets; Lynparza, AstraZeneca, Cambridge, UK, Merck & Co., Inc., Kenilworth, NJ, USA) twice daily with doses taken approximately 12 hours apart, plus oral abiraterone (1000 mg;

Zytiga, Janssen, Raritan, NJ, USA) taken once daily in the morning, or matching placebo plus abiraterone. The olaparib dose was based on the safety run-in results. In both arms, prednisone/prednisolone (5 mg) was administered orally twice daily alongside abiraterone, as indicated, with doses taken approximately 12 hours apart.[10] Treatment was continued until disease progression or lack of clinical benefit (investigator-assessed). Olaparib or placebo dose interruptions of up to 14 days were permitted to manage any toxicities at the investigator's discretion, and were required for treatment related adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grades 3 or 4. Treatment was reinitiated once adverse events resolved to grade 1 or less. Patients were considered for dose reduction, first to 250 mg bid and then 200 mg bid if the toxicity recurred. Interruptions or reductions of abiraterone or prednisone/prednisolone dose were not permitted. Patients could withdraw from the study voluntarily or be withdrawn due to severe protocol non-compliance; patients who could not be reached following ≥3 unsuccessful contact attempts were considered lost to follow-up.

Soft-tissue (CT or MRI) and bone scans were performed every 12 weeks until week 72, then every 24 weeks until disease progression, death, or withdrawal of consent. Blood samples for assessment of circulating tumour cells were taken at baseline, week 4, week 12, and upon discontinuation of study treatment. Blood samples for assessment of PSA levels were taken every 4 weeks until week 12 and every 12 weeks thereafter. Adverse events were monitored throughout the study treatment, and follow-up periods using the National Cancer Institute's CTCAE version 4·0 and included measurements of clinical chemistry and haematology (at baseline, every 4 weeks until week 52 and every 12 weeks from week 60), vital signs (at baseline,

every 4 weeks until week 12 and every 12 weeks thereafter) and recording of adverse events and serious adverse events (SAEs) (at baseline, every 4 weeks until week 24 and every 12 weeks thereafter). Health-related quality of life (HRQoL) was assessed every 4 weeks until week 12, then every 12 weeks using the Functional Assessment of Cancer Therapy – Prostate Cancer (FACT-P) questionnaire. A higher FACT-P score represented better HRQoL (range: 0–156).

Plasma (mandatory), whole-blood (germline; optional), and archival tumour tissue (optional), samples were tested for deleterious or suspected deleterious (loss-of-function) mutations in 15 HRR genes according to pre-specified American College of Medical Genetics and Genomics criteria.[11] Tumour and whole-blood samples were tested first, and subsequently patients with no data (no material provided or technical test failure) were prioritised for plasma analyses (excluding the five patients with novel HRR mutations already identified by germline testing; Supplementary Appendix, page 4).

Loss-of-function mutations were assessed in *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* by commercially available Clinical Laboratory Improvement Amendments (CLIA) FoundationOne tumour assay at Foundation Medicine (Cambridge, MA, USA); *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *PALB2*, *RAD51C,* and *RAD51D* by commercially available germline CLIA assay at Color Genomics (Burlingame, CA, USA); and *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* by research use only plasma assay at AstraZeneca. The plasma assay (circulating tumour DNA [ctDNA] next-generation sequencing analysis) was done on

an Illumina NexSeq using 2x150 high throughput runs, at the AstraZeneca Genomics Laboratory in Cambridge, UK, which operates in accordance with Good Laboratory Practice principles. The assay is a 112 gene panel using IDT xGen capture probes that covers the full coding sequence of the HRR genes listed above. The targeted panel and unique molecular indices enrichment method were validated using commercial plasma samples harbouring somatic alterations at known allele frequencies. For the ctDNA analyses in this study, the average circulating free DNA input was 29 ng, the detection limit was 0.5% allele frequency, and the average depth after deduplication was 2900x.

Outcomes

The primary endpoint of the randomised phase was radiologic progression-free survival (rPFS) defined as time from randomisation to radiologic progression (investigator-assessed according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1·1 for soft-tissue disease or Prostate Cancer Working Group 2 [PCWG-2] criteria for bone disease), or death. Exploratory rPFS subgroup analyses by HRR mutation status were predefined. Key secondary endpoints included safety and tolerability, time to second progression (PFS2; defined as time from randomisation to the investigator-assessed progression event [using RECIST version 1·1 or PCWG-2 criteria] following that used for the primary rPFS analysis, or death) and overall survival (OS; defined as time from randomisation to death, by any cause). Other secondary endpoints included radiologic objective response (ORR; RECIST v1·1, PCWG-2), soft-tissue response (RECIST v1·1), time to first and

second subsequent anticancer therapy (TFST; TSST; defined as time from randomisation to the first or second subsequent therapy for prostate cancer following discontinuation of olaparib/placebo, or death), confirmed prostate-specific antigen (PSA) response (reduction of ≥50% from baseline, confirmed at the next assessment ≥4 weeks later), circulating tumour cell (CTC) conversion (change from ≥5 cells/7·5 mL at baseline to <5 cells/7·5 mL post-baseline), and HRQoL (a deterioration event was defined as a decrease of ≥6 points in baseline FACT-P score).

Statistical analyses

The study was designed to include approximately 140 patients in the randomised phase to give 80% power to detect a statistically significant difference between treatment arms at the one-sided 10% level after 100 progression events, assuming a true hazard ratio (HR) of 0·65. A hierarchical multiple-testing strategy was prespecified for the primary analysis of rPFS and the key secondary endpoints PFS2 and OS. If statistical significance was shown for rPFS, PFS2 was then compared between arms. If the null hypothesis of no difference between arms was rejected for PFS2, OS was tested as part of the multiple-testing procedure; however, all planned analyses were performed irrespective of the outcome of the multiple testing strategy. Efficacy data were analysed on an intention-to-treat basis, and safety and tolerability were assessed in patients who received at least one dose of olaparib or placebo. ORR and soft-tissue response rate were assessed in patients with measurable disease at baseline, and CTC-conversion rate and PSA response rate were

assessed in patients with baseline CTC ≥5 and with a baseline PSA result, respectively. For the primary endpoint, rPFS, patients whose disease had not progressed or had progressed after two or more missed visits were censored at their last evaluable tumour assessment. HRs and confidence intervals (CI) were derived using a log-rank test with ties handled using the Breslow method; a HR less than one favoured olaparib. Time-to-event endpoints were measured from randomisation and medians were calculated using the Kaplan-Meier technique, with all analyses performed using SAS version 9·4. Reported p values are two-sided, and analyses with an observed two-sided p value less than 0·05 met the threshold for a statistically significant difference in clinical benefit between arms. Any p values determined outside the multiple testing strategy should be considered nominal.

Predefined exploratory subgroup analyses were performed for patients with a HRR mutation, wild-type HRR, and partially characterised HRR status. Patients with a qualifying loss of function mutation in any sample (tumour, plasma or whole-blood) were classified as having a HRR mutation; patients for whom all test results were negative were classified as HRR wild-type, as long as their results included a valid tumour test; all other patients were classified as HRR partially characterised, including those whose plasma and whole-blood samples both tested negative for HRR mutations, but for whom no valid tumour test result was available. Sensitivity analyses of rPFS, performed for attrition and evaluation-time bias, were prespecified and are described in the Supplementary Appendix (page 3). A logistic regression model including treatment as a factor variable was used to analyse ORR; no other variables were included in this model.

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

Role of funding source

The study was designed in collaboration between the first author and sponsor, AstraZeneca. AstraZeneca was responsible for overseeing data collection, analysis and interpretation. Merck & Co., Inc., who are developing olaparib in collaboration with AstraZeneca, provided input into data interpretation. All authors had access to the raw data and vouch for the completeness and accuracy of the data and analyses and the fidelity of the study to the protocol. The manuscript was written with medical writing support, funded by AstraZeneca and Merck & Co., Inc., with critical review and input from the authors. The decision to submit the manuscript for publication was made by all authors and the sponsor. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Patients

The safety run-in is described in the Supplementary Appendix (page 3). Patients were enrolled in the randomised phase between November 25, 2014 and July 14, 2015. One hundred and forty-two patients were randomised; all 71 patients, assigned to the combination arm, were treated with olaparib plus abiraterone and all 71, assigned to the comparator arm, received placebo plus abiraterone (Figure 1). All 71 patients in each arm were included in the efficacy and safety analysis sets. It was prespecified that the primary data cut-off (September 22, 2017) would take place after 100 rPFS events had occurred. At this point, seven (10%) of 71 patients were still receiving olaparib plus abiraterone, and eight (11%) of 71 were still receiving placebo plus abiraterone. Forty-three (61%) of 71 patients in the combination had died, 33 (46%) due to mCRPC, four (6%) due to adverse events, five (7%) for reasons unrelated to adverse events or the disease under investigation and one (1%) due to other reasons. Forty-five (63%) of 71 patients in the combination had died, 37 (52%) due to mCRPC, one (1%) due to an adverse event and seven (10%) for reasons unrelated to adverse events or the disease under investigation.

For the randomised phase, baseline characteristics are reported in Table 1. Combination-arm patients had higher median PSA concentration (86 μg/L [IQR 23–194] vs 47 [21–199] μg/L). Sixty-eight (48%) of 142 patients provided prostate tumour samples, 38 (56%) of which provided a valid HRR mutation test result. A breakdown of tumour, germline and plasma test results is shown in the

Supplementary Appendix (page 5). Overall, 21 (15%) of 142 patients had confirmed or suspected deleterious HRR mutations (combination arm: 3 *ATM*, 2 *BRCA2*, 2 *CDK12*, 2 *CHEK2*, 1 *BRIP1* and 1 *CHEK1*; comparator arm: 4 *ATM*, 4 *BRCA2*, 1 *CDK12* and 1 *PALB2;* Supplementary Appendix, page 6), and 35 (25%) were classified as HRR wild-type based on all their HRR mutation test results, including a tumour test, being negative. The remaining 86 (61%) patients had partially characterised HRR status; of these, 58 patients (67%) were HRR wild-type by plasma and germline testing, 17 patients (20%) were HRR wild-type by plasma testing only, five patients (6%) were HRR wild-type by germline testing only and 6 patients (7%) had no valid tumour, plasma or germline test result.

Of the 21 patients with a HRR mutation, 10 (48%) were identified who had results from only one sample type; one (5%), five (24%) and four (19%) by tumour, germline and plasma testing, respectively. In the 25 patients with both tumour and germline data there were two cases of HRR mutations (8%); both were germline variants that were detected by both assays. In the 69 patients with both germline and plasma results there were nine HRR mutation cases (13%); all were likely somatic, and two (22% of 9) were from genes not covered by Color Genomics' germline test (*CDK12* and *CHEK1*). There were no HRR mutation cases detected by plasma or tumour in the three cases (2% of 142) where a valid result was available for both sample types. It should be noted that plasma testing was prioritised for patients who did not provide a tumour sample, or who had no valid tumour test result due to technical failure (excluding the five patients with novel HRR mutations already identified by germline testing; Supplementary Appendix, page 4). Hence, concordance comparisons with

plasma testing results are intrinsically biased; however, we plan to address this in a future publication.

Efficacy

At the primary analysis, median follow up for rPFS was 15·9 months (IQR 8·1–25·5) in the combination arm compared with 24·5 months (8·1–27·6) in the comparator arm. Forty-six of 71 combination-arm patients (65%) and 54 of 71 comparator-arm patients (76%) had had a rPFS event (100 [70%] of 142 overall). In the combination arm, 24 (52%) of these 46 patients had soft-tissue progression only, 8 (17%) bone progression only, 1 (2%) both soft-tissue and bone progression, and 13 (28%) died ahead of progression (comparator arm: 28 [52%] of 54 patients, 14 [26%], 2 [4%] and 10 [19%], respectively). There was a statistically significant improvement in rPFS in the combination versus comparator arm (median 13·8 months [95% CI 10·8–20·4] vs 8·2 months [5·5–9·7]; HR 0·65, 95% CI 0·44–0·97, p=0·034; Figure 2a). Sensitivity analyses for attrition and evaluation-time bias were consistent with the primary analysis (reported in the Supplementary Appendix, page 6).

A predefined exploratory subgroup analysis of rPFS by HRR mutation status was performed. For the 21 patients with HRR mutations, median rPFS was 17·8 months (95% CI 2·9–27·6) versus 6·5 months (2·7–non-calculable) in the combination versus comparator arm (Figure 2b). Eight (73%) of 11 combination arm patients had experienced a rPFS event compared with 7 (70%) of 10 comparator-arm patients. For the 35 patients with wild-type HRR, median rPFS was 15·0 months (95% CI 5·4–non-calculable) versus 9·7 months (2·9–17·5), respectively (Figure 2c). Eight (53%) of 15 combination arm patients had experienced a rPFS event compared with 17

(85%) of 20 comparator arm patients. For the 86 patients with partially characterised HRR status, median rPFS was 13·1 months (95% CI 8·1–22·4) versus 6·4 months (5·3–8·2), respectively (Figure 2d). Thirty (67%) of 45 combination arm patients had experienced a rPFS event compared with 30 (73%) of 41 comparator arm patients.

By the data cut-off, 82 patients (58% of 142) had experienced a second progression event or died; 37 (52%) of 71 patients in the combination arm compared with 45 (63%) of 71 patients in the comparator arm. Median PFS2 was 23·3 months (95% CI 17·4–non-calculable) in the combination arm, compared with 18·5 months (16·1–23·8) in the comparator arm, but statistical significance was not met (Figure 3a). Eighty-eight OS events (62% of 142 patients) had occurred by the data cut-off, with 43 (61%) and 45 (63%) of 71 patients having died in the combination and comparator arms, respectively. Median OS was 22·7 months (95% CI 17·4–29·4) for combination-arm patients, compared with 20·9 months (17·6–26·3) for comparator-arm patients, but there was no significant difference between arms (Figure 3b). During the study, post-progression anticancer therapy was received by fewer patients in the combination (20 [28%] of 71) than in the comparator arm (29 [41%] of 71); subsequent anticancer therapies received are reported in the Supplementary Appendix (page 7).

Thirty-three of 71 combination-arm patients (46%) and 38 of 71 comparator-arm patients (54%) had measurable disease at baseline. There was no significant difference in overall ORR between arms (27% [9 patients, combination] vs 32% [12 patients, comparator]; odds ratio 0·81, 95% CI 0·28–2·26, nominal p=0·62). There were no complete responses; more patients in the combination than comparator arm had stable disease as a best response (16 [48%] of 33 vs 8 [21%] of 38), and fewer

patients had progressive disease as a best response (7 [21%] of 33 vs 18 [47%] of 38). Median duration of response was 17·8 months in the combination arm (interquartile range [IQR] 8·3–non-calculable) and 12·1 months in the comparator arm (IQR 6·6–non-calculable). CTC-conversion rate was similar in the combination (15 [50%] of 30 patients with baseline CTC ≥5) and comparator arms (13 [46%] of 28), as was confirmed PSA response (34 [48%] of 71 patients with a baseline PSA result in the combination arm compared with 30 [42%] of 71 in the comparator arm). Soft-tissue responses and TFST and TSST analyses are reported in the Supplementary Appendix (pages 6–7).

Health-related quality of life

Sixty (85%) of 71 combination-arm patients experienced deterioration in HRQoL compared with 57 (80%) of 71 comparator-arm patients; median times to deterioration were 5·7 months (95% CI 2·8–11·2) and 6·0 months (1·9–11·2), respectively (HR 0·97, 95% CI 0·68–1·40, nominal p=0·89).

Safety and tolerability

Median treatment duration was longer in the combination arm compared with the comparator arm: 309 days (IQR 145–457) for olaparib compared with 253 days (113–421) for placebo, and for abiraterone 338 days (169–588) compared with 253 days (130–429), respectively. Most adverse events in the combination arm were grade 1 or 2 (Table 2). More patients experienced grade ≥3 adverse events in the combination versus the comparator arm (38 [54%] of 71 vs 20 [28%] of 71). Fifteen (21%) of the 71 combination-arm patients had grade ≥3 adverse events of anaemia, compared with none in the comparator arm. Grade ≥3 adverse events of

lymphopenia, thrombocytopenia and neutropenia were each experienced by one (1%) combination-arm patient, compared with none in the comparator arm.

SAEs were reported by 24 (34%) of 71 combination-arm patients and 13 (18%) of 71 comparator-arm patients. Seven (10%) of 71 patients in the combination arm had SAEs that were causally related to study treatment (anaemia, n=3; febrile neutropenia, n=1; pneumonitis, n=1; vomiting, n=1; general physical health deterioration, n=1), compared with 1 (1%) of 71 patients in the comparator arm (gastroenteritis, n=1). Seven combination-arm patients (10%), aged 66–88 years, had serious cardiovascular events (myocardial infarction, n=4; fatal cardiac failure, n=1; chronic cardiac failure, n=1; fatal ischaemic stroke, n=1), compared with one comparator-arm patient (1%; thrombotic stroke). The range of time to onset of serious cardiovascular events was 3–29 months in the combination arm. At baseline, 44 of 71 combination-arm patients (62%) and 40 of 71 comparator-arm patients (56%) had risk factors for cardiovascular events.

Pneumonitis/interstitial lung disease was reported by two (3%) of 71 combination-arm patients and one (1%) of 71 comparator-arm patients. Fatal adverse events were experienced by four (6%) of 71 combination-arm patients (pneumonitis, ischaemic stroke, cardiac failure, mediastinitis) and one (1%) comparator-arm patient (chronic pyelonephritis); of these, only pneumonitis was thought by the investigator to be causally related to study treatment (olaparib).

More patients in the combination than the comparator arm had dose interruptions and dose reductions caused by adverse events (24 [34%] vs 9 [13%] and 13 [18%] vs 0 of 71 patients in each arm, respectively; details are shown in the Supplementary

Appendix, page 8). Twenty-one of 71 combination-arm patients (30%) and seven of 71 comparator-arm patients (10%) experienced adverse events that led to treatment discontinuation. Adverse events that led to treatment discontinuation in more than one combination-arm patient were anaemia (4 [6%] of 71 vs 0 [comparator arm]), nausea (3 [4%] of 71 vs 0), muscular weakness (2 [3%] of 71 vs 0), and myocardial infarction (2 [3%] of 71 vs 0).

Pharmacokinetics

No obvious drug–drug interaction was detected between olaparib and abiraterone. However, the number of individuals in which pharmacokinetic data were determined was small. Full details are reported in the Supplementary Appendix (pages 8–9).

Discussion

In this randomised, placebo-controlled phase 2 trial of olaparib and abiraterone compared with abiraterone alone, a significant rPFS benefit was observed with the combination for mCRPC patients, who were not subject to any biomarker selection criteria. While more adverse events were experienced by patients in the combination arm, median treatment duration was longer for these patients and no detriment to HRQoL was observed. To our knowledge, this is the first study of a PARP inhibitor to show a clinical benefit when combined with abiraterone for patients with mCRPC who have previously received docetaxel. We observed a statistically significant improvement in rPFS for patients treated with the combination (HR 0·65; difference in median rPFS: 5·6 months), with a 35% decrease in the risk of disease progression or death compared to patients in the comparator arm. We note that median rPFS in our comparator arm (8.2 months) was longer than the 5.6 months observed in the active arm of a Phase III trial (COU-AA-301) that assessed abiraterone compared with placebo in a similar patient population.[2] One possible explanation for this difference in median rPFS in the abiraterone arm is the difference in tumour load; COU-AA-301 showed a higher baseline median PSA than that seen in our study. Another potential cause is the improvement in treatment methods and increased access to second and third line interventions for the patients in our study. Our primary endpoint was predicated on preclinical data, showing synergy between olaparib and agents affecting the androgen receptor pathway regardless of HRR mutation status; therefore, HRR mutation status was not used as a stratification factor at randomisation.[7,8] The study was not powered for subgroup analyses, and HRR mutation status was not known for all patients. However, with rPFS results

indicative of similar benefit with the combination between HRR subgroups, our data suggest that the combination of olaparib and abiraterone may have resulted in rPFS benefit for patients regardless of HRR mutation status. Whilst 61% of patients were classified as having partially characterised HRR mutation status by our prespecified criteria, 69% of these patients tested negative for HRR mutations by both plasma and germline testing, although this could not be confirmed by tumour testing. Studies have shown the prevalence of HRR mutations in metastatic castration-resistant prostate cancer patients to be up to around 30%.[3,12,13] In our trial, the prevalence of detected HRR mutation was 15% (21/142; Supplementary Appendix, page 5). Within the cohort tested at Color Genomics, 93 out of 102 patients also had a tumour or plasma result, and seven out of the 16 detected mutations were germline, in line with recently published data.[3,12,13] All samples in our study were from prostate tumours, however a matched study of primary and metastatic tumour samples from mCRPC patients found only a limited number of additional HRR mutations in metastatic samples,[14] suggesting the type of sample used in our study is likely to have had little impact on the prevalence of detected HRR mutations. Additionally, *BRCA2* mutations have been associated with worse prognosis in mCRPC, which may explain the increased prevalence.[15,16] A limitation of our study is the number of patients with a HRR mutation that may remain in the group of 86 patients defined as HRR partially characterised. Based on the 30% prevalence from recent studies, one would project as many as 13 patients with a HRR mutation in the HRR partially characterised group, to give a total of 31 patients (30%) with a mutation in the group of 104 with no valid tumour test result. However, the actual number is likely to be much lower than this, given that 63 out of 86 HRR partially characterised patients did not have a germline HRR mutation by Color Genomics testing, and 75 out of 86

patients did not have a detectable mutation in their plasma (which would be expected, at a minimum, to detect all germline variants and point mutations in patients whose tumours shed sufficient ctDNA). Hence, we would expect that a maximum of 13 (15%) patients in the HRR partially characterised group have HRR mutations, but that the number is likely to be much lower and that this subgroup is unlikely to be driving the treatment effect observed in this HRR partially characterised subgroup or in the study as a whole. It has been suggested that abiraterone (irrespective of PARP inhibitor use) may be more efficacious in patients with a HRR mutation; however, in our study the number of patients with a known HRR mutation is similar between arms, meaning any impact of HRR mutation status on abiraterone efficacy is also likely to be well balanced.

In the TOPARP-A study, the efficacy of olaparib monotherapy in mCRPC patients appeared to be almost completely limited to those with HRR mutations, whereas our data suggest that synergy between olaparib and abiraterone may result in clinical benefit for patients unselected by HRR mutation status.[3] Preclinical studies suggest a dual mode of synergy. Firstly, PARP is involved in androgen-receptor-dependent transcription and PARP inhibition impairs this process.[8] Secondly, the androgen receptor regulates transcription of DNA repair genes; androgen depletion impairs HRR, which may create a '*BRCA*ness' phenotype that is susceptible to PARP inhibition.[17–19] Further work is required to elucidate the mechanism further. However, a broad patient population may derive benefit from PARP inhibitor treatment through combination with '*BRCA*ness'-inducing agents. In a similarly-sized phase 2 study (n=148) testing a different PARP inhibitor, veliparib, in combination with abiraterone compared with abiraterone alone, no significant efficacy benefit was observed for

mCRPC patients including those with DNA damage repair defects.[12] However, these results are consistent with preclinical data that show veliparib to have weaker PARP trapping activity than olaparib.[20]

Although no statistically significant difference in PFS2 or OS was seen between arms, the study was underpowered for these analyses. The OS analysis may also have been confounded by the higher proportion of comparator-arm patients who received post-progression anticancer therapies, as well as some notable differences between arms in baseline prognostic factors such as age, ECOG status and PSA level, which were more favourable in the comparator arm; because this was a relatively small phase 2 trial, no stratification factors were used during randomisation. Despite there being no significant difference between arms, the magnitude and direction of the PFS2 data were consistent with the primary rPFS analysis, and the difference in median OS between arms (1·8 months) is similar to that reported for available second-line therapies.[21] However, the number of patients in these analyses is too small to draw conclusions and further studies are needed to determine whether the observed rPFS benefit translates into improved OS. Overall response, confirmed PSA response and CTC-conversion rates were similar in both arms, which might be a result of the potency of abiraterone and its cytostatic mode of action.[2,22] The observed difference in rPFS between arms is therefore likely to be due to an increase in the proportion of patients with stable disease and an increased duration of response in the combination arm, rather than the result of an increased number of complete responders. This is consistent with the proposed mechanism of action for the combination, discussed above, in which a '*BRCA*ness' phenotype is only created in patients for whom abiraterone is efficacious.

The most frequent adverse events in combination-arm patients were nausea and anaemia. More grade ≥3 adverse events, SAEs, and other clinically significant adverse events, including cardiovascular events, were reported in the combination arm compared with the comparator arm. No difference in risk factors for cardiovascular events was seen between arms at baseline. Additionally, more combination-arm patients experienced dose modification or treatment discontinuation because of an adverse event; patients could discontinue olaparib or abiraterone only, resulting in a longer median duration of treatment for abiraterone than olaparib in this arm. However, the longer duration of treatment in the combination arm suggests any risk of decreased tolerability may be offset by the additional efficacy benefit received and the increase in rPFS with the combination was observed despite more treatment discontinuations due to adverse events. There was no detriment to HRQoL reported in the combination arm relative to the comparator arm. This lack of difference in HRQoL between arms is not unexpected due to the additional disease burden experienced by patients in the comparator arm and the natural history of the disease at this late stage.

Our study is limited by the number of patients enrolled, and larger trials are needed to confirm and extend our observations. It should also be noted that patients who have received docetaxel, but no second-generation antihormonal agents, might be increasingly rare, making recruitment and appropriate statistical power in this setting a challenge and increasing the importance of assessing this combination in other mCRPC settings. Assessing the impact of prior docetaxel treatment on the efficacy of olaparib and abiraterone will be an important area for future research and, as recent studies have shown significant increases in OS for hormone-therapy- or

chemotherapy-naïve patients treated with abiraterone, testing the combination of PARP inhibitor and abiraterone in pre-chemotherapy settings may be of particular interest.[23,24] An ongoing phase 2 study (NCT03012321) in the pre-chemotherapy mCRPC setting is evaluating olaparib versus abiraterone versus olaparib combined with abiraterone in patients with DNA repair defects.[25] Olaparib is also currently being studied as monotherapy in a phase III trial (NCT02987543) of mCRPC patients with a HRR mutation who have previously received treatment with an antihormonal agent.[26] Our results are encouraging for the future development of PARP inhibitor–antihormonal agent combinations and open up the possibility of larger trials being run in mCRPC patients, irrespective of HRR mutation status.

In conclusion, our data provide evidence of clinical benefit, worthy of further study, for men with mCRPC who received olaparib in combination with abiraterone compared with abiraterone alone, and indicate the potential of the combination to benefit patients unselected by HRR mutation status.

Contributors

NC was responsible for study design and writing of the manuscript. NC, PW, BA, NS, RJ, IK, VEC, JJ, AF, CR, and FS were responsible for patient accrual, trial conduct and obtaining the data. CG, JB, RK, DH and ML analysed the data. All authors interpreted the data and reviewed the draft and final versions of the manuscript.

Declaration of interests

BA has received grants, personal fees and non-financial support from AstraZeneca, Janssen, Pfizer, Merck & Co., Inc., Roche and Sanofi. NS has received personal fees from Astellas Pharma, Bristol-Myers Squibb and Janssen and. VEC has received personal fees and non-financial support from Bristol-Myers Squibb, Janssen and Pfizer. JJ has received personal fees from AstraZeneca. AF has received honoraria and travel support from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb Janssen, Pfizer and Sanofi . CG, JB, DH and ML are employees of AstraZeneca and own stock. RK was employed by AstraZeneca during manuscript development. FS has received grants and personal fees from Astellas Pharma, AstraZeneca, Bayer, Janssen and Sanofi . All other authors declare no competing interests.

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Table 1. Baseline characteristics for patients in the randomised phase

Characteristic	**Olaparib plus abiraterone arm (n=71)**	**Placebo plus abiraterone arm (n=71)**
Median age, years (IQR)	70 (65–75)	67 (62–74)
Race, n (%)		
White	67 (94)	67 (94)
Black/African American	1 (1)	1 (1)
Asian	1 (1)	0
Other	2 (3)	3 (4)
ECOG performance status, n (%)		
0	34 (48)	38 (54)
1	36 (51)	30 (42)
2	1 (1)	1 (1)

Unknown	0	2 (3)
Median PSA concentration, µg/L (IQR)	86 (23–194)	47 (21–199)
Median time from initial diagnosis to first dose, months (IQR)	62 (38–93)	48 (32–76)
Extent of disease*, n (%)		
Bone disease only	33 (46)	33 (46)
Soft-tissue disease only	8 (11)	11 (15)
Bone and soft-tissue disease	30 (42)	27 (38)
Number of bone metastases, n (%)		
0	5 (7)	6 (8)
1	3 (4)	4 (6)
2–4	24 (34)	36 (51)
5–9	39 (55)	25 (35)

HRR mutation status, n (%)		
HRR mutation	11 (15)	10 (14)
Wild-type HRR	15 (21)	20 (28)
HRR partially characterised	45 (63)	41 (58)
Prior treatments†, n (%)		
Docetaxel	71 (100)	71 (100)
Cabazitaxel	10 (14)	9 (13)
Abiraterone	0	1 (1)

*Soft-tissue disease includes visceral organs (liver and lung). †In the comparator arm, one patient had received three prior lines of chemotherapy and another had received abiraterone; these protocol deviations were discovered post-randomisation, so both patients were included in the intention-to-treat analysis set. ECOG, Eastern Cooperative Oncology Group

Table 2. Adverse events

Adverse event, n (%)	Olaparib plus abiraterone arm (n=71)				Placebo plus abiraterone arm (n=71)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	28 (39)	29 (41)	5 (7)	4 (6)	37 (52)	19 (27)	0	1 (1)
Nausea	26 (37)	1 (1)	0	0	13 (18)	2 (3)	0	0
Constipation	18 (25)	0	0	0	8 (11)	0	0	0
Back pain	17 (24)	1 (1)	0	0	13 (18)	1 (1)	0	0
Fatigue	14 (20)	1 (1)	0	0	7 (10)	2 (3)	0	0
Asthenia	13 (18)	3 (4)	0	0	10 (14)	0	0	0
Vomiting	13(18)	2 (3)	0	0	8 (11)	1 (1)	0	0
Peripheral oedema	13 (18)	0	0	0	8 (11)	0	0	0
Decreased appetite	12 (17)	0	0	0	4 (6)	1 (1)	0	0
Diarrhoea	11 (15)	0	0	0	7 (10)	1 (1)	0	0
Dyspnoea	10 (14)	0	0	0	4 (6)	1 (1)	0	0

Pyrexia	10 (14)	0	0	0	1 (1)	0	0	0
Cough	9 (13)	2 (3)	0	0	2 (3)	0	0	0
Bone pain	9 (13)	1 (1)	0	0	7 (10)	1 (1)	0	0
Urinary tract infection	8 (11)	1 (1)	0	0	1 (1)	2 (3)		
Arthralgia	8 (11)	0	0	0	3 (4)	1 (1)	0	0
Viral upper respiratory tract infection	8 (11)	0	0	0	3 (4)	0	0	0
Abdominal pain	8 (11)	0	0	0	1 (1)	0	0	0
Anaemia	7 (10)	14 (20)	1 (1)	0	1 (1)	0	0	0
Neutropenia	7 (10)	1 (1)	0	0	0	0	0	0
Musculoskeletal pain	6 (8)	1 (1)	0	0	5 (7)	1 (1)	0	0
Pain in extremity	5 (7)	0	0	0	3 (4)	1 (1)	0	0
Hypokalaemia	4 (6)	2 (3)	0	0	4 (6)	0	0	0
Weight decreased	3 (4)	1 (1)	0	0	4 (6)	0	0	0
Non-cardiac chest pain	3 (4)	0	0	0	1 (1)	1 (1)	0	0
Pneumonia	2 (3)	2 (3)	2 (3)	0	0	3 (4)	0	0

Hypertension	2 (3)	1 (1)	0	0	4 (6)	0	0	0
Muscular weakness	2 (3)	1 (1)	0	0	3 (4)	0	0	0
Blood creatinine increased	2 (3)	1 (1)	0	0	0	1 (1)	0	0
Osteonecrosis of jaw	2 (3)	0	0	0	0	1 (1)	0	0
Bacteraemia	1 (1)	1 (1)	1 (1)	0	0	0	0	0
Platelet count decreased	1 (1)	1 (1)	0	0	1 (1)	0	0	0
Pulmonary embolism	1 (1)	1 (1)	0	0	1 (1)	0	0	0
Thrombocytopenia	1 (1)	1 (1)	0	0	1 (1)	0	0	0
Dehydration	1 (1)	1 (1)	0	0	0	0	0	0
General physical health deterioration	1 (1)	1 (1)	0	0	0	0	0	0
Musculoskeletal chest pain	1 (1)	0	0	0	3 (4)	2 (3)	0	0
Alanine aminotransferase increased	1 (1)	0	0	0	0	1 (1)	0	0
Candida infection	1 (1)	0	0	0	0	1 (1)	0	0
Pain	1 (1)	0	0	0	0	1 (1)	0	0

Myocardial infarction	0	4 (6)	0	0	0	0	0	0
Respiratory failure	0	1 (1)	1 (1)	0	0	0	0	0
Pneumonitis	0	1 (1)	0	1 (1)	0	0	0	0
Aspartate aminotransferase increased	0	1 (1)	0	0	1 (1)	0	0	0
Blood alkaline phosphatase increased	0	1 (1)	0	0	1 (1)	0	0	0
Sinusitis	0	1 (1)	0	0	1 (1)	0	0	0
Blood bilirubin increased	0	1 (1)	0	0	0	0	0	0
Blood lactate dehydrogenase increased	0	1 (1)	0	0	0	0	0	0
Blood urea increased	0	1 (1)	0	0	0	0	0	0
Chronic cardiac failure	0	1 (1)	0	0	0	0	0	0
Cognitive disorder	0	1 (1)	0	0	0	0	0	0
Hypophosphataemia	0	1 (1)	0	0	0	0	0	0
Internal haemorrhage	0	1 (1)	0	0	0	0	0	0

Large intestinal haemorrhage	0	1 (1)	0	0	0	0	0	0
Lymphopenia	0	1 (1)	0	0	0	0	0	0
Nerve root compression	0	1 (1)	0	0	0	0	0	0
Neutrophil count decreased	0	1 (1)	0	0	0	0	0	0
Odynophagia	0	1 (1)	0	0	0	0	0	0
Paraparesis	0	1 (1)	0	0	0	0	0	0
Patella fracture	0	1 (1)	0	0	0	0	0	0
Proctitis	0	1 (1)	0	0	0	0	0	0
Febrile neutropenia	0	0	1 (1)	0	0	0	0	0
Septic shock	0	0	1 (1)	0	0	0	0	0
Subdural haematoma	0	0	1 (1)	0	0	0	0	0
Cardiac failure	0	0	0	1 (1)	1 (1)	0	0	0
Ischaemic stroke	0	0	0	1 (1)	0	0	0	0
Mediastinitis	0	0	0	1 (1)	0	0	0	0
Interstitial lung disease	0	0	0	0	0	1 (1)	0	0
Peripheral ischaemia	0	0	0	0	0	1 (1)	0	0

Sepsis	0	0	0	0	0	1 (1)	0	0
Spinal cord compression	0	0	0	0	0	1 (1)	0	0
Squamous cell carcinoma of the tongue	0	0	0	0	0	1 (1)	0	0
Thrombosis	0	0	0	0	0	1 (1)	0	0
Urinary tract stoma complication	0	0	0	0	0	1 (1)	0	0
Weight increased	0	0	0	0	0	1 (1)	0	0
Chronic pyelonephritis	0	0	0	0	0	0	0	1 (1)

Figure legends

Figure 1. Patient randomisation, treatment, and outcomes

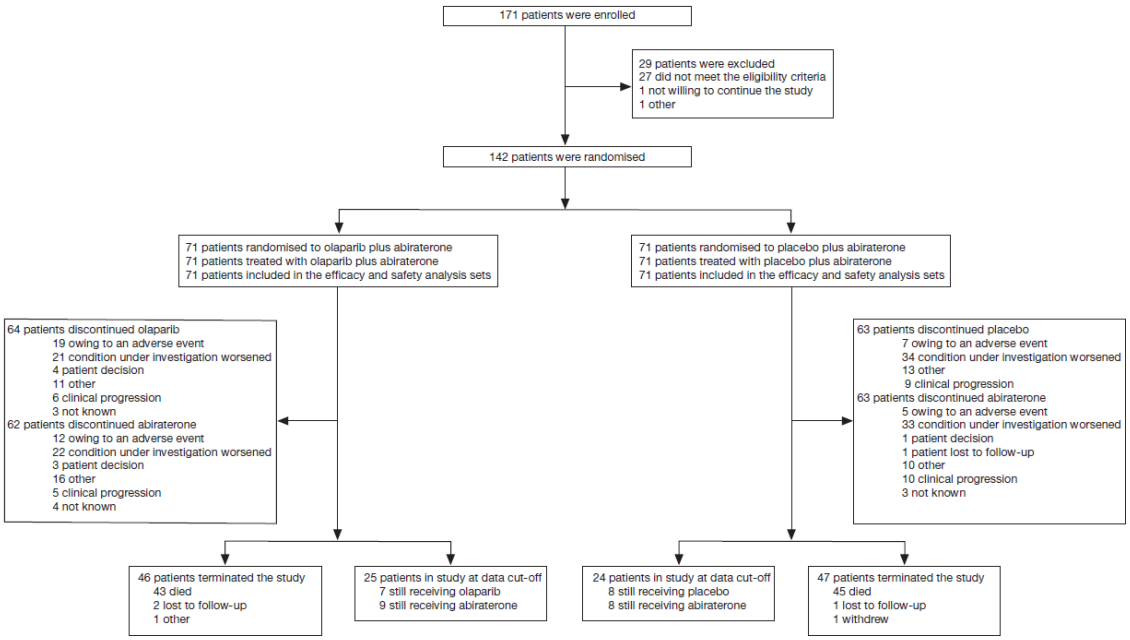
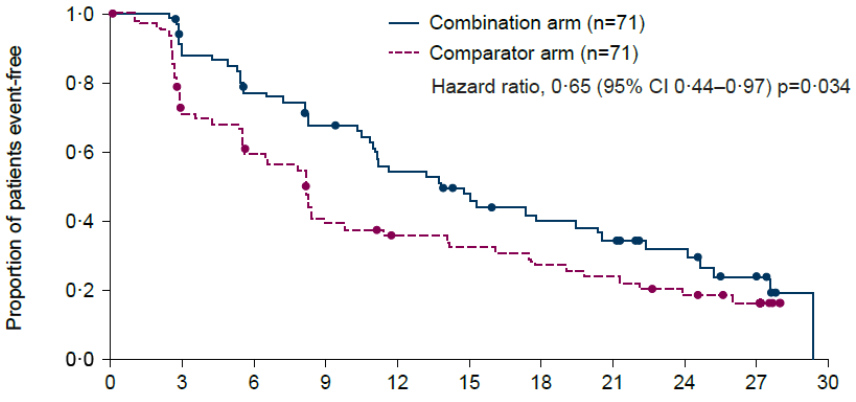


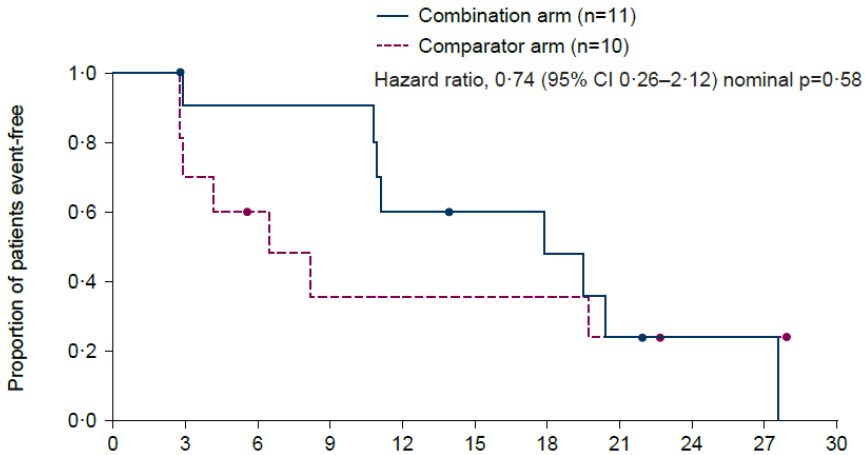
Figure 2. Kaplan–Meier estimates of rPFS in (a) all patients, (b) the subgroup with HRR mutations, (c) the subgroup with wild-type HRR, and (d) the subgroup with partially characterised HRR status

(a) All patients



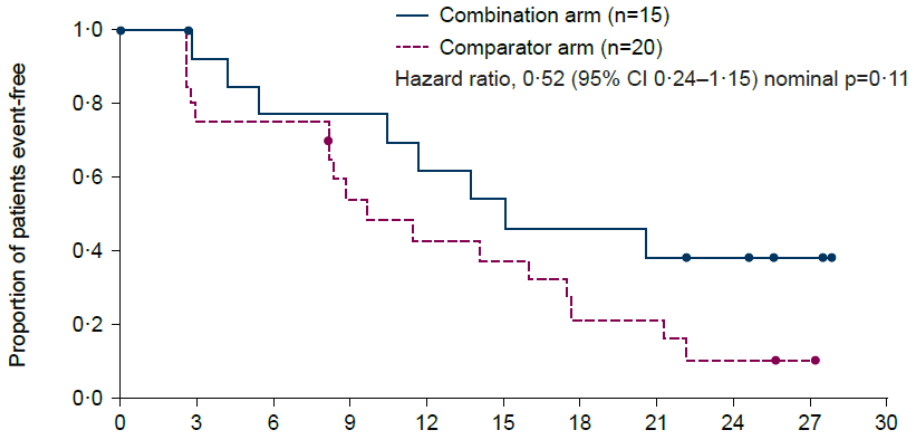
Number of patients at risk (censored)											
Combination arm	71(0)	58(5)	50(6)	42(8)	33(9)	26(12)	21(13)	18(13)	13(17)	8(19)	0(25)
Comparator arm	71(0)	48(3)	39(4)	25(5)	21(7)	19(7)	16(7)	14(7)	10(8)	7(10)	0(17)

(b) Subgroup with HRR mutations



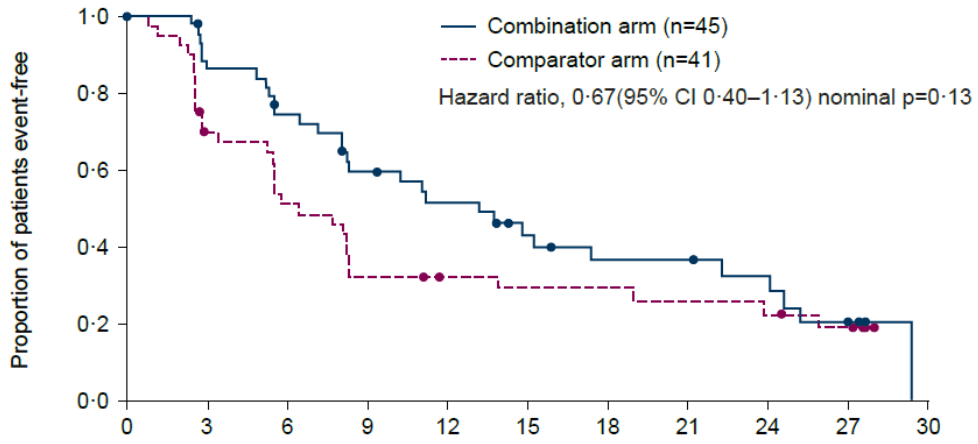
Number of patients at risk (censored)											
Combination arm	11(0)	9(1)	9(1)	9(1)	6(1)	5(2)	4(2)	2(2)	1(3)	1(3)	0(3)
Comparator arm	10(0)	7(0)	5(1)	3(1)	3(1)	3(1)	3(1)	2(1)	1(2)	1(2)	0(3)

(c) Subgroup with wild-type HRR



Number of patients at risk (censored)											
Combination arm	15(0)	12(2)	10(2)	10(2)	8(2)	7(2)	6(2)	5(2)	4(3)	2(5)	0(7)
Comparator arm	20(0)	15(0)	15(0)	10(1)	8(1)	7(1)	4(1)	4(1)	2(1)	1(2)	0(3)

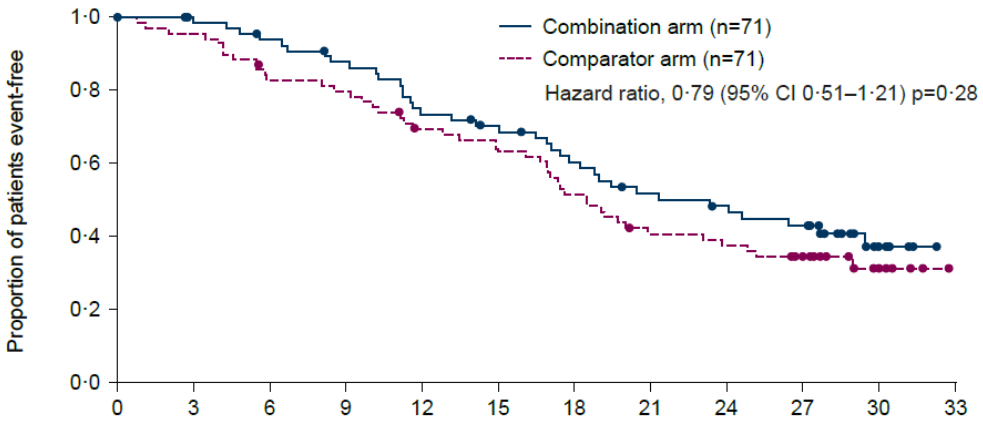
(d) Subgroup with HRR partially characterised



Number of patients at risk (censored)											
Combination arm	45(0)	37(2)	31(3)	23(5)	19(6)	14(8)	11(9)	11(9)	8(11)	5(11)	0(15)
Comparator arm	41(0)	26(3)	19(3)	12(3)	10(5)	9(5)	9(5)	8(5)	7(5)	5(6)	0(11)

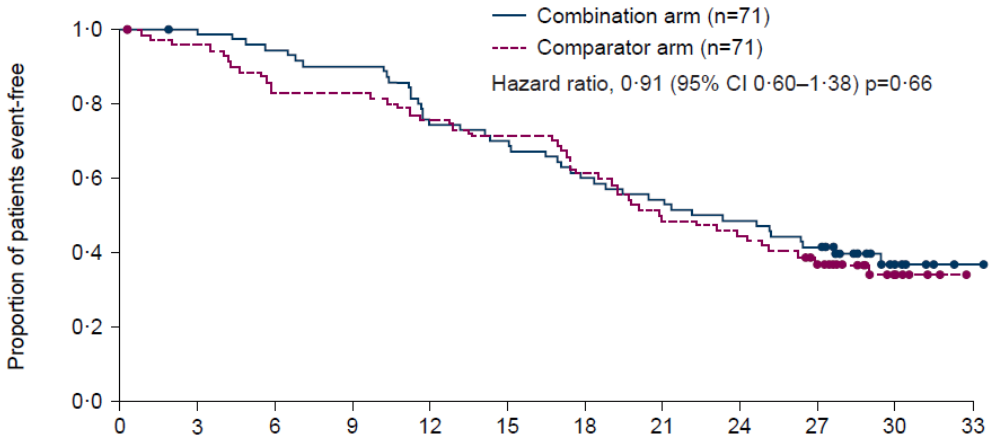
Figure 3. Kaplan–Meier estimates in all patients of (a) PFS2 and (b) OS

(a) PFS2



Number of patients at risk (censored)												
Combination arm	71(0)	65(5)	61(6)	56(7)	47(7)	43(9)	36(10)	30(11)	27(12)	24(12)	6(28)	0(34)
Comparator arm	71(0)	67(1)	57(2)	55(2)	46(4)	42(4)	34(4)	26(5)	24(5)	19(8)	6(20)	0(26)

(b) OS



Number of patients at risk (censored)												
Combination arm	71(0)	69(1)	66(1)	63(1)	52(1)	49(1)	42(1)	38(1)	34(1)	29(1)	9(19)	1(27)
Comparator arm	71(0)	67(1)	58(1)	58(1)	53(1)	50(1)	43(1)	34(1)	31(1)	22(5)	6(20)	0(26)