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Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial

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Summary

Background Metastatic castration-resistant prostate cancers are enriched for DNA repair gene defects (DRDs) that can be susceptible to synthetic lethality through inhibition of PARP proteins. We evaluated the anti-tumour activity and safety of the PARP inhibitor niraparib in patients with metastatic castration-resistant prostate cancers and DRDs who progressed on previous treatment with an androgen signalling inhibitor and a taxane.

Methods In this multicentre, open-label, single-arm, phase 2 study, patients aged at least 18 years with histologically confirmed metastatic castration-resistant prostate cancer (mixed histology accepted, with the exception of the small cell pure phenotype) and DRDs (assessed in blood, tumour tissue, or saliva), with progression on a previous next-generation androgen signalling inhibitor and a taxane per Response Evaluation Criteria in Solid Tumors 1.1 or Prostate Cancer Working Group 3 criteria and an Eastern Cooperative Oncology Group performance status of 0–2, were eligible. Enrolled patients received niraparib 300 mg orally once daily until treatment discontinuation, death, or study termination. For the final study analysis, all patients who received at least one dose of study drug were included in the safety analysis population; patients with germline pathogenic or somatic biallelic pathogenic alterations in *BRCA1* or *BRCA2* (*BRCA* cohort) or biallelic alterations in other prespecified DRDs (non-*BRCA* cohort) were included in the efficacy analysis population. The primary endpoint was objective response rate in patients with *BRCA* alterations and measurable disease (measurable *BRCA* cohort). This study is registered with ClinicalTrials.gov, NCT02854436.

Findings Between Sept 28, 2016, and June 26, 2020, 289 patients were enrolled, of whom 182 (63%) had received three or more systemic therapies for prostate cancer. 223 (77%) of 289 patients were included in the overall efficacy analysis population, which included *BRCA* (n=142) and non-*BRCA* (n=81) cohorts. At final analysis, with a median follow-up of 10·0 months (IQR 6·6–13·3), the objective response rate in the measurable *BRCA* cohort (n=76) was 34·2% (95% CI 23·7–46·0). In the safety analysis population, the most common treatment-emergent adverse events of any grade were nausea (169 [58%] of 289), anaemia (156 [54%]), and vomiting (111 [38%]); the most common grade 3 or worse events were haematological (anaemia in 95 [33%] of 289; thrombocytopenia in 47 [16%]; and neutropenia in 28 [10%]). Of 134 (46%) of 289 patients with at least one serious treatment-emergent adverse event, the most common were also haematological (thrombocytopenia in 17 [6%] and anaemia in 13 [4%]). Two adverse events with fatal outcome (one patient with urosepsis in the *BRCA* cohort and one patient with sepsis in the non-*BRCA* cohort) were deemed possibly related to niraparib treatment.

Interpretation Niraparib is tolerable and shows anti-tumour activity in heavily pretreated patients with metastatic castration-resistant prostate cancer and DRDs, particularly in those with *BRCA* alterations.

Funding Janssen Research & Development.

Introduction

Patients with metastatic castration-resistant prostate cancer who have progressed on a next-generation androgen signalling inhibitor and taxane chemotherapy (docetaxel, cabazitaxel, or both) have few treatment options.[1,2] DNA repair gene defects (DRDs), seen in approximately 12–23% of tumours in patients with metastatic prostate cancer when considering both germline and somatic alterations,[3–5] are associated with cancer development, aggressiveness, and progression.[6] These DRD-altered tumours are not only frequent in metastatic disease, but are also associated with poor prognosis and potential resistance to systemic therapies.[7] Developing more effective treatments to improve survival for these patients is therefore a critical unmet need.

Cancers with DRDs, particularly those with defects in homologous recombination repair, are highly sensitive to the blockade of DNA single-strand break repair via inhibition of the PARP family of nuclear proteins, which

Research in context

Evidence before this study

At the time that the GALAHAD study was designed, docetaxel and the androgen signalling inhibitors abiraterone acetate and enzalutamide were the only established treatment options for patients with metastatic castration-resistant prostate cancer, but there remained a subset of patients who either did not initially respond or became refractory to these agents and for whom no approved therapeutic options were available. Given that genomic instability is a hallmark of cancer that has been documented in this patient population, we evaluated the medical literature by searching PubMed from database inception up to Aug 31, 2016, with (castration) AND (resistant) AND ("prostatic neoplasm" OR "prostate cancer") AND ("genomic instability" OR "DNA repair" OR "DNA repair defect") as search terms of interest with no additional restrictions (eg, to English language publications only). The search yielded 33 results. Only two of these were clinical trial publications, which presented results from an early phase 1 study of veliparib and the phase 2 TOPARP study of olaparib—both PARP inhibitors—in this disease setting. Veliparib was reported to have low efficacy, but the high response rate observed among patients with specified DNA repair gene defects (DRDs) in the TOPARP study provided a compelling rationale for assessing the clinical activity and safety of other such agents in a genetically selected patient population. Coauthors of the current study also contributed appropriate citations of importance that were not detected by the original search strategy or that were found in subsequent literature, with an emphasis on randomised clinical trials, systematic reviews, meta-analyses, and prospective observational studies. Taken together, the findings indicated that PARP inhibitors show notable activity in cancers with DRDs. In articles published since the GALAHAD study was initiated, further clinical activity has since been reported in metastatic castration-resistant prostate cancers with selected DRDs for the PARP inhibitors olaparib, rucaparib, and talazoparib (for which key primary publications are cited in the present work), but not yet for niraparib, which is also a potent and highly selective PARP inhibitor with established efficacy and tolerability in other cancers.

Added value of this study

To our knowledge, the GALAHAD study is the first to show the anti-tumour activity of niraparib in patients with metastatic castration-resistant prostate cancer and DRDs who previously progressed on both androgen signalling inhibitors and taxanes, with notable activity particularly in the cohort of patients with defects in *BRCA1* or *BRCA2*.

Implications of all the available evidence

This final analysis of the GALAHAD study suggests that in patients with heavily pretreated metastatic castration-resistant disease, niraparib could offer promising clinical activity with a manageable safety profile. These findings motivate the further assessment of niraparib alone or in combination with other agents to improve treatment options and underscore the importance of biological disease profiling in informing treatment decisions.

are involved in single-strand DNA break repair.[8] PARP inhibitors, such as olaparib, rucaparib, and talazoparib, have been studied in patients with metastatic castration-resistant prostate cancer and DRDs in previous phase 2 and 3 studies.[9–13] Olaparib is approved in the EU for *BRCA1*-mutated or *BRCA2*-mutated metastatic castration-resistant prostate cancer[14] and by the US Food and Drug Administration (FDA) for patients with metastatic castration-resistant prostate cancer and DRDs progressing after treatment with enzalutamide, abiraterone, or both,[15] whereas rucaparib is approved for patients with *BRCA1*-mutated or *BRCA2*-mutated metastatic castration-resistant prostate cancer who have been treated with an androgen signalling inhibitor therapy and a taxane.[16]

Niraparib, a potent and highly selective inhibitor of PARP-1 and PARP-2, is approved by the FDA for the maintenance treatment of select patient populations with ovarian, fallopian tube, and primary peritoneal cancers.[17,18] Here, we report the final anti-tumour activity and safety results of a multicentre, open-label, phase 2 study of niraparib in patients with metastatic castration-resistant prostate cancer and tumour DRDs, whose disease had progressed on androgen signalling inhibitor therapy and taxane chemotherapy (docetaxel, cabazitaxel, or both).

Methods

Study design and participants

GALAHAD is an open-label, phase 2 study at 115 hospitals or health-care centres in 15 countries (appendix pp 8–9), which consisted of the following phases: prescreening, screening, treatment, follow-up, and long-term extension.

Male patients aged at least 18 years with histologically confirmed metastatic castration-resistant prostate cancer (mixed histology was acceptable, with the exception of the small cell pure phenotype, which was excluded) were eligible if they had a predefined DRD and disease progression on an androgen signalling inhibitor and taxane chemotherapy (docetaxel, cabazitaxel, or both). Disease progression was defined as progression of metastatic prostate cancer in the setting of castrate levels of testosterone of up to 50 ng/dL on a gonadotropin-releasing hormone analogue or with history of bilateral orchiectomy at study entry, with progression specifically defined as prostate-specific antigen (PSA) progression or radiographic progression of soft tissue by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or bone disease by Prostate Cancer Working Group 3 (PCWG3) criteria.[19,20] Patients were also required to have an Eastern Cooperative Oncology Group (ECOG)

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See **Online** for appendix

performance status of 2 or less. Patients with measurable and non-measurable disease were enrolled. Exclusion criteria included previous treatment with a PARP inhibitor or platinum-based chemotherapy regimen, and a known history or current diagnosis of myelodysplastic syndrome or acute myeloid leukaemia. The full eligibility criteria are available in the protocol (appendix).

All patients provided written informed consent. Independent ethics committees or institutional review boards of each participating institution approved this study. The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol is available in the appendix.

Procedures

Patients were prescreened using a blood sample (Resolution Bioscience, Kirkland, WA, USA) or tumour tissue sample (Foundation Medicine, Cambridge, MA, USA[21]) for evaluation of DRD alterations. The Resolution Bioscience assay, Resolution HRD, is a targeted hybrid capture, next-generation sequencing assay that detects single-nucleotide variants, indels, and copy number variation (including homozygous deletions) in genes involved in homologous recombination repair using cell-free DNA from plasma. The specific genes of interest for DRD consisted of eight candidates: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*. In addition, three genes that are commonly mutated in metastatic castration-resistant prostate tumours were evaluated: *AR*, *CDKN2A*, and *TP53*. This Resolution Bioscience assay can also identify patients with monoallelic and biallelic pathogenic alterations in the genes of interest. Patients were eligible to enter the screening phase if a deleterious germline or somatic alteration was found in at least one of the following genes: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*. Patients were considered DRD-positive if they had an alteration with known pathogenic consequences including homozygous deletions; rearrangements; and nonsense, missense, frame-shift, and splice-site mutations. After the assay was developed to distinguish between biallelic and monoallelic DRD, patients who had been enrolled with monoallelic or non-pathogenic DRD were excluded from the final analysis according to an approved protocol amendment (amendment 3; October, 2017). As such, only patients with germline pathogenic or biallelic pathogenic alterations in *BRCA1* or *BRCA2* (*BRCA* cohort) or other prespecified non-*BRCA* genes (non-*BRCA* cohort) were included in the final analysis. Additional details on testing methods are available in the appendix (p 4).

All patients received niraparib 300 mg orally in the form of 100 mg capsules (Quotient Sciences, Boothwyn, PA, USA) starting on day 1 of cycle 1 (once daily dosing, with a cycle defined as 28 days) until treatment discontinuation due to disease progression, unacceptable toxicity or adverse events, diagnosis of myelodysplastic syndrome or acute myeloid leukaemia, investigator decision in the best interest of the patient, patient withdrawal of consent, death, or study termination. Monitoring for the need of dose adjustments or interruptions (eg, with laboratory measurements) was at the discretion of the investigator, based on the severity of the adverse events experienced. Patients who were not surgically castrated continued regularly prescribed gonadotropin-releasing hormone analogue.

During the treatment phase, study visits occurred weekly for the first month, biweekly for the second month, and monthly thereafter. CT or MRI and ^{99m}technetium bone scans were performed during screening, every 8 weeks for 24 weeks, and then every 12 weeks thereafter. Circulating tumour cell (CTC) counts were assessed at every cycle until cycle 7 and then at the end-of-treatment visit. PSA assessments were done every 4 weeks until cycle 7 and then every three cycles thereafter.

The follow-up phase began after completion of the treatment phase. If a patient discontinued treatment without radiographic progression, imaging was done every 12 weeks (or within 2 weeks before or after this timepoint) until radiographic progression was documented. The long-term extension phase began after completion of the primary analysis, at which point patients could elect to discontinue treatment or continue niraparib until disease progression. Throughout the study, adverse events were evaluated and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03 or later). Safety evaluations included incidence, severity, and types of adverse events, as well as deaths. Adverse events were classified as treatment-emergent adverse events if they were reported on or after the date of first dose until 30 days (inclusive) after the last dose of study drug. Drug-related adverse events were determined by investigators if they were considered related to the study drug. Appropriate supportive measures to address adverse events could be administered at the discretion of investigators per institutional standards of care. A full schedule of study assessments and procedures is available in the protocol in the appendix.

Outcomes

The primary endpoint was investigator-assessed objective response rate (defined as the proportion of patients with a confirmed partial response or complete response as defined by RECIST version 1.1,[19] according to the sum of target tumour lesion diameters, with no evidence of bone progression on bone scan per PCWG3 criteria[20]) in patients with *BRCA* alterations and measurable disease (the measurable *BRCA* cohort). The primary endpoint was amended early on in this study (amendment 2; January, 2017) from a composite response endpoint to objective response rate to comply with feedback from health authorities, and hence the primary efficacy analysis included only these participants with measurable disease; additional details regarding this amendment are available in the study protocol in the appendix. Patients with non-measurable disease were still included in the

study to increase the size of the safety population and to assess the activity of niraparib in this population.

Secondary efficacy endpoints were objective response rate in patients with non-*BRCA* alterations (*ATM*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*) and measurable disease; CTC response (CTC0) defined as CTC=0 per 7·5 mL blood at 8 weeks post-baseline in patients with CTC count greater than 0 (1 or more) at baseline;[22,23] overall survival (time from enrolment to death from any cause); radiographic progression-free survival (time from enrolment to radiographic progression or death from any cause, whichever occurred first); time from enrolment to radiographic progression; time to PSA progression (defined as time from enrolment to first date of documented PSA progression based on PCWG3 criteria); time to symptomatic skeletal event (defined as time from enrolment to tumour-related spinal cord compression, radiotherapy to bone to relieve skeletal symptoms, surgery to bone or need for tumour-related orthopaedic surgical intervention, or symptomatic or pathological fracture); duration of objective response (defined as time from complete response or partial response to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurred first); and safety. With the exception of objective response rate in patients with non-*BRCA* alterations and measurable disease, all secondary endpoints were assessed in both the *BRCA* and non-*BRCA* populations.

Prespecified exploratory endpoints included the composite response rate, defined as either an objective response for patients with measurable disease, CTC conversion (defined as CTC count ≥5 per 7·5 mL blood at baseline and <5 per 7·5 mL blood post-therapy nadir), or at least a 50% decline in PSA (PSA_{50}). Both CTC conversion and PSA_{50} were also assessed separately as prespecified exploratory analyses.

Statistical analysis

Statistical analysis followed Simon's two-stage design for phase 2, single-arm clinical trials.[24] Specifically for the non-*BRCA* cohort, a futility analysis for objective response rate based on this design was implemented, in which Simon's stage 1 was assessed after approximately 14 patients with measurable disease were evaluated for objective response rate with at least one post-treatment scan and a confirmatory scan; enrolment was to be terminated for this cohort if two or fewer responses were observed in the first stage. Otherwise, enrolment was specified to proceed to the second stage with a total of 45 patients enrolled for the two stages combined, and the null hypothesis was to be rejected if ten or more responses were observed. For the primary endpoint, the null hypothesis of an objective response rate of 15% or less was tested against the alternate hypothesis of an objective response rate of 32% or higher. With approximately 120 patients with biomarker-positive measurable disease (75 *BRCA* and 45 non-*BRCA*) planned for enrolment, the study had more than 90% power to show that the lower limit of the 95% CI for the primary endpoint of objective response rate exceeded 15% in the measurable *BRCA* cohort. Activity of niraparib was to be declared if the lower bound of the two-sided 95% exact CI for objective response rate was higher than 15% in this cohort. For the secondary endpoint of objective response rate in patients with non-*BRCA* alterations, the null hypothesis of an objective response rate of 15% or less was tested against the alternate hypothesis of an objective response rate of 32% or higher, with a one-sided α of 0·05 and power of 80%.

Objective response in soft tissue disease was evaluated in both *BRCA* and non-*BRCA* patients with measurable disease within the efficacy analysis population of patients who fulfilled the final biomarker assay criteria for this study; however, as prespecified, the primary endpoint was specifically evaluated in the cohort of *BRCA* patients with measurable disease, and the final primary endpoint analysis was planned for approximately 6 months after the last patient with measurable disease in the *BRCA* cohort was enrolled. For analysis of objective response rate, patients who discontinued treatment before any efficacy assessments were considered non-responders; patients with no imaging available for a particular study visit were considered not evaluable for that visit, and patients without valid baseline data were considered not evaluable. Anti-tumour activity, such as PSA response, CTC conversion or response, and composite response rate, was analysed separately for the *BRCA* and non-*BRCA* cohorts, with corresponding criteria for identification of non-responders and non-evaluable patients based on discontinuation or availability of laboratory measurements. Response rates were calculated along with exact two-sided 95% CIs. Time-to-event endpoints were summarised by Kaplan-Meier curves with median times and 95% CIs, as well as descriptive event-free rates analysed as prespecified. Analyses of additional study outcomes, such as the prespecified calculation of treatment compliance in the form of relative dose intensity, are described in further detail in the appendix (p 4).

Post-hoc analyses included objective response rate by baseline characteristics of interest (such as in subgroups of patients with visceral disease at baseline, patients who experienced stable disease for more than 6 months, or patients with three or more previous lines of therapy), specific evaluation of stable disease (defined as neither sufficient decrease in target lesions to qualify for partial response, nor sufficient increase to qualify for progressive disease, with respect to smallest sum of target lesion diameters while on study), and biomarker analyses for non-DRD alterations of interest (*AR* and *TP53* alteration) were also done using the available data. For the post-hoc analysis of patients with *AR* and *TP53* alterations, differences in objective response rates were assessed using Pearson's χ^2 test and p values were adjusted using false discovery rate correction for multiple testing (Benjamini-Hochberg procedure).

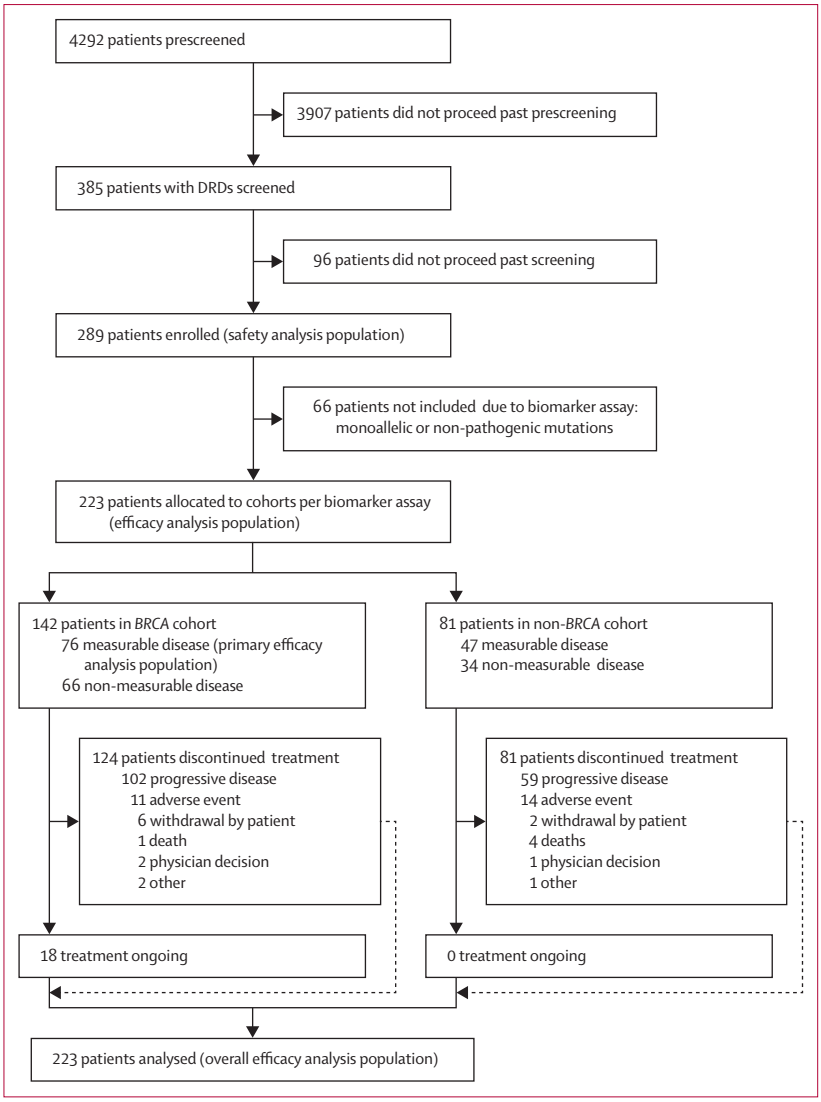

Figure 1: **Trial profile**
DRD=DNA repair gene defect.

Safety and treatment compliance were analysed in the safety analysis population (ie, all patients who received at least one dose of the study drug). Adverse events and serious adverse events were reported and summarised. Sensitivity analyses with censoring rules were done if warranted. Additional details from the statistical analysis plan are available in the appendix. Statistical analyses were performed using SAS (version 15.1).

This study is registered with ClinicalTrials.gov, NCT02854436, and with the European Clinical Trials database, EudraCT 2016-002057-38).

Role of the funding source

The sponsor and employees of the sponsor of this study participated in the study design, data collection, data analysis, and data interpretation, with writing and editorial assistance also funded by the sponsor. All authors participated in the writing process and provided critical input.

Results

385 patients were screened for this study; of these, 289 (75%) patients were enrolled between Sept 28, 2016, and June 26, 2020. All 289 patients were included in the safety analysis population, and 223 (77%) of 289 patients were included in the efficacy analysis population, based on DRD eligibility from the validated biomarker assay (142 with *BRCA* alterations [139 biallelic, three monoallelic germline pathogenic] and 81 with biallelic non-*BRCA* alterations; figure 1). 66 (23%) of 289 patients with monoallelic or non-pathogenic DRD from the safety analysis were not included in the final efficacy analysis. Additional information on the prescreening results is available in the appendix (p 5). For patients with measurable disease, 76 with *BRCA* alterations (primary efficacy population) and 47 with non-*BRCA* alterations were enrolled, which fulfilled the numbers required per study sample size estimation for evaluation of objective response rate. The types and frequencies of genotypes observed in the efficacy analysis are reported in the appendix (p 10).

Based on the Simon's two-stage design, enrolment proceeded through both stages to fulfill the estimated sample size requirements. At the clinical cutoff date of Jan 26, 2021, 271 (94%) of 289 patients had discontinued treatment, with reasons summarised in the appendix (p 11). Seven (9%) of 76 patients in the primary efficacy cohort (patients with *BRCA* alterations and measurable disease) discontinued therapy before their first study evaluation due to progressive disease (n=4), urosepsis leading to death (n=1), or withdrawal of consent (n=1 due to fear of COVID-19; n=1 received radium-223 due to bone disease burden). The median treatment duration was 6·5 months (IQR 3·3–9·4) in the *BRCA* cohort and 3·6 months (1·8–5·6) in the non-*BRCA* cohort. Dose adjustments and interruptions are summarised in the appendix (p 12), with most treatment dose reductions occurring due to an adverse event.

Patients were heavily pretreated and showed advanced disease in both the *BRCA* and non-*BRCA* populations (table 1). Nearly all patients had bone metastases and, in the primary efficacy population (the measurable *BRCA* cohort), a notable proportion of patients had visceral disease, including liver and lung metastases, as well as many patients having nodal disease.

At baseline, 182 (63%) of 289 patients in the safety analysis population had received at least three previous systemic therapies for metastatic prostate cancer; 94 (33%) had received two previous androgen signalling inhibitor therapies, and 107 (37%) had received two previous taxane-based chemotherapies. The demographics and baseline characteristics of the safety analysis population are presented in the appendix (p 13). The final activity results

for the overall *BRCA* cohort (with a median follow-up of 10·1 months [IQR 7·5–13·4]) are shown in tables 2 and 3 and the appendix (pp 6, 7, 14).

The primary endpoint, objective response rate per protocol in the measurable *BRCA* cohort, was met in 26 of 76 patients (34·2%, 95% CI 23·7–46·0; table 2) with a median follow-up of 10·0 months (IQR 6·6–13·3). Of the 76 patients in the measurable *BRCA* cohort, 35 (46%) had at least a 30% decrease of maximum change from baseline in the sum of longest target lesion diameters relative to baseline (appendix p 6). Median duration of objective response was 5·55 months (95% CI 3·91–7·20; table 3); eight (31%) of 26 responses were ongoing at the time of data cutoff.

Figure 2 and table 3 present radiographic progression-free survival, with 87 (61%) events at the time of data cutoff, and overall survival, with 88 (62%) events in the overall *BRCA* cohort. 12-month event-free survival in the overall *BRCA* cohort was 56·4% (95% CI 47·2–64·6), and 24-month event-free survival was 15·2% (7·7–25·1). Approximately a quarter of patients reached CTC0 (table 3). 85 (60%) of 142 patients in the *BRCA* cohort and 42 (55%) of 76 patients in the measurable *BRCA* cohort experienced PSA progression, and 46 (32%) of 142 patients and 23 (30%) of 76 patients had a documented symptomatic skeletal event in these cohorts, respectively.

The exploratory endpoint of composite response rate in the overall *BRCA* cohort is also presented in table 3. More than 40% of patients in the overall *BRCA* cohort had PSA_{50} and CTC conversion (also exploratory), and approximately two thirds of evaluable patients experienced a decrease in PSA levels from baseline (table 3; appendix p 7). Similar outcomes in composite response rate were obtained in the *BRCA* cohort for patients with measurable and non-measurable disease (appendix p 14).

Of note, two patients (both with biallelic alterations) in the measurable *BRCA* cohort had a complete response. One patient with visceral (adrenal) and nodal disease at baseline maintained the complete response for 9·7 months, and a second patient with nodal disease at baseline experienced a complete response that persisted for 9·5 months based on imaging, despite having received only 2·1 months of treatment that was discontinued due to an adverse event of anaemia (grade 3). In a post-hoc analysis, of the 30 patients in the measurable *BRCA* cohort who had visceral disease at baseline, 11 (37%) had an objective response. Furthermore, a post-hoc analysis of the 20 patients who experienced stable disease for more than 6 months in this study showed that 14 (70%) were in the *BRCA* cohort. 16 (21%) of the 76 patients in the measurable *BRCA* cohort continued treatment after radiographic progression with no unequivocal clinical progression because they were considered to still be benefiting from therapy.

For the measurable non-*BRCA* cohort (n=47; median follow-up of 8·6 months [IQR 4·8–14·0]), objective response rate per protocol and median duration of response (none of which are ongoing) are shown in table 2. An objective response was recorded in five of 47 patients (10·6%; 95% CI 3·5–23·1) in this cohort.

The corresponding maximum changes in the sum of target tumour lesion diameters from baseline in the

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)	Measurable non-*BRCA* cohort (n=47)
Age, years	67·0 (63·0–73·0)	66·0 (62·0–73·0)	70·0 (66·0–75·0)	71·0 (59·0–86·0)
Bodyweight, kg	82·7 (15·5)	80·5 (13·4)	79·9 (16·1)	77·6 (13·0)
Race				
White	101 (71%)	57 (75%)	54 (67%)	33 (70%)
Asian	9 (6%)	6 (8%)	6 (7%)	3 (6%)
Black or African American	5 (4%)	3 (4%)	0	0
Other	3 (2%)	0	2 (2%)	0
Multiple	1 (1%)	0	2 (2%)	1 (2%)
Not reported	11 (8%)	5 (7%)	8 (10%)	4 (9%)
Unknown	12 (8%)	5 (7%)	9 (11%)	6 (13%)
PSA at baseline, ng/mL	141·5 (41·0–512·4)	197·0 (40·1–653·9)	161·7 (43·7–611·1)	196·0 (43·7–662·3)
Patients with alterations in a single gene*				
BRCA1	4 (3%)	3 (4%)	..	..
BRCA2	127 (89%)	69 (91%)	..	..
ATM	..	..	37 (46%)	21 (45%)
BRIP1	..	..	1 (1%)	1 (2%)
CHEK2	..	..	5 (6%)	2 (4%)
FANCA	..	..	18 (22%)	10 (21%)
HDAC2	..	..	8 (10%)	5 (11%)
PALB2	..	..	0	0
ECOG performance status score				
0	48 (34%)	25 (33%)	18 (22%)	9 (19%)
1	78 (55%)	44 (58%)	47 (58%)	27 (57%)
2	16 (11%)	7 (9%)	16 (20%)	11 (23%)
Extent of disease progression at study entry				
Bone	127 (89%)	61 (80%)	79 (98%)	45 (96%)
Visceral	33 (23%)	30 (39%)	20 (25%)	16 (34%)
Liver	24 (17%)	23 (30%)	13 (16%)	12 (26%)
Lung	15 (11%)	13 (17%)	10 (12%)	7 (15%)
Lymph node	79 (56%)	67 (88%)	39 (48%)	33 (70%)
Soft tissue	22 (15%)	21 (28%)	16 (20%)	15 (32%)
Disease status				
Measurable	76 (54%)	76 (100%)	47 (58%)	47 (100%)
Non-measurable	66 (46%)	0	34 (42%)	0
Gleason score at diagnosis				
<8	39/135 (29%)	20/73 (27%)	26/77 (34%)	15/43 (35%)
≥8	96/135 (71%)	53/73 (73%)	51/77 (66%)	28/43 (65%)
Previous therapies for prostate cancer†				
Two	59 (42%)	29 (38%)	22 (27%)	10 (21%)
Three	54 (38%)	31 (41%)	31 (38%)	18 (38%)
Four	21 (15%)	12 (16%)	19 (23%)	12 (26%)
Five	7 (5%)	3 (4%)	9 (11%)	7 (15%)
Six	1 (1%)	1 (1%)	0	0

(Table 1 continues on next page)

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)	Measurable non-*BRCA* cohort (n=47)
(Continued from previous page)				
Previous androgen signalling inhibitor therapies				
One	97 (68%)	51 (67%)	45 (56%)	23 (49%)
Two	44 (31%)	25 (33%)	31 (38%)	21 (45%)
Three	1 (1%)	0	5 (6%)	3 (6%)
Previous taxane-based chemotherapies				
One	100 (70%)	51 (67%)	41 (51%)	21 (45%)
Two	42 (30%)	25 (33%)	40 (49%)	26 (55%)

Data are reported as median (IQR), mean (SD), n (%), or n/N (%). The measurable *BRCA* cohort (n=76) is the primary efficacy population and the *BRCA* and non-*BRCA* cohorts combined (n=223) is the overall efficacy analysis population. PSA=prostate-specific antigen. ECOG=Eastern Cooperative Oncology Group. *All patients with *PALB2* had co-occurring alterations and are thus not listed here; patient numbers and percentages might not add up to 100% because some patients had more than one gene alteration and are thus not listed here. †Number of androgen signalling inhibitors, taxane-based chemotherapies, cytotoxic chemotherapies, and other therapies received; specifically, previous therapies could include taxane-based chemotherapy for metastatic prostate cancer with evidence of disease progression, or next-generation androgen signalling inhibitor therapy for either metastatic prostate cancer with evidence of disease progression or non-metastatic castration-resistant prostate cancer with evidence of subsequent metastasis.

Table 1: **Baseline characteristics of patients in the overall efficacy analysis population**

	Measurable *BRCA* cohort* (n=76)	Measurable non-*BRCA* cohort† (n=47)
Objective response rate	26 (34·2%; 23·7–46·0)	5 (10·6%; 3·5–23·1)
Complete response	2 (3%)	0
Partial response	24 (32%)	5 (11%)

Data are n (%; 95% CI) or n (%). *Primary efficacy analysis cohort. †Objective response rate in measurable non-*BRCA* patients was a secondary efficacy endpoint.

Table 2: **Objective response rates**

overall non-*BRCA* cohort (n=81) are presented in the appendix (p 6).

Figure 2 and table 3 also present radiographic progression-free survival in the non-*BRCA* cohort, with 57 (70%) events at the time of data cutoff, and overall survival, with 65 (80%) events. 12-month event-free survival was 41·3% (95% CI 30·0–52·2), and 24-month event-free survival was 11·1% (4·4–21·2). Fewer than 10% of patients reached CTC0 in this cohort; 39 (48%) of 81 patients had PSA progression, and 19 (23%) of 81 patients had a documented symptomatic skeletal event.

The exploratory endpoint of composite response rate in the non-*BRCA* cohort is also presented in table 3, and the maximum change in PSA from baseline is presented in the appendix (p 7). Response by either PSA_{50} or CTC conversion (also exploratory) among non-*BRCA* patients with non-measurable disease is provided in the appendix (p 14).

In post-hoc analyses of the non-*BRCA* cohort, two (13%) of 16 patients with visceral disease and four (80%) of five patients who had received three or more lines of therapy experienced an objective response in the non-*BRCA* cohort; six patients in this cohort experienced stable disease for more than 6 months. 15 (32%) of 47 patients continued treatment after radiographic progression with no unequivocal clinical progression.

Of note, 11 (8%) of 142 patients in the *BRCA* cohort and seven (9%) of 81 patients in the non-*BRCA* cohort had co-expression of two or more eligible DRD biomarkers. Moreover, in addition to being DRD-positive, 162 (74%) of 220 patients with available plasma DNA results had alterations in the *AR* gene and 49 (22%) of 220 had alterations in *TP53*, of whom 42 (19%) had both *TP53* and *AR* alterations. These additional alterations in plasma DNA were similarly distributed between the *BRCA* and non-*BRCA* cohorts, and no substantial difference in objective response rate was observed in subgroups of patients with or without co-occurring alterations (appendix pp 15–16).

Safety results are summarised in table 4 and the appendix (pp 17–25, 28–30). Almost all patients in the safety population experienced at least one treatment-emergent adverse event. The most common adverse events (of any grade) were nausea (169 [58%] of 289), anaemia (156 [54%]), and vomiting (111 [38%]). Of the grade 3 or worse treatment-emergent adverse events reported in 217 (75%) of 289 patients, most were haematological, with both the most common grade 3 or worse adverse events overall and grade 3 or worse adverse events of special interest being anaemia (95 [33%] of 289), thrombocytopenia (47 [16%]), and neutropenia (28 [10%]). These events were manageable with one or more of: treatment interruptions, dose reductions, or supportive measures such as blood transfusions. One patient experienced neutropenic sepsis. The most common non-haematological grade 3–4 treatment-emergent adverse events were fatigue and nausea. 134 (46%) of 289 patients had at least one serious treatment-emergent adverse event, with haematological events being the most common (17 [6%] of 289 with thrombocytopenia and 13 [4%] of 289 with anaemia; appendix pp 21–23). Similarly, of 43 (15%) of 289 patients with drug-related serious treatment-emergent adverse events, the most common were thrombocytopenia (four [3%] of 142 in the *BRCA* cohort and seven [9%] of 81 in the non-*BRCA* cohort) and anaemia (three [2%] of 142 in the *BRCA* cohort and three [4%] of 81 in the non-*BRCA* cohort; appendix p 24). The most common adverse events overall by *BRCA* and non-*BRCA* cohorts are also summarised in the appendix (p 20).

Estimated relative dose intensities are presented in the appendix (pp 26–27), including a breakdown of relative dose intensities in responders versus non-responders in the primary efficacy analysis population (appendix p 26). In the safety population, 128 (44%) of 289 patients had an adverse event leading to a dose reduction; consistent with the aforementioned findings, 87 (68%) of 128 patients had haematological events

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)
CTC response*, n/N (%)	31/131 (24%)	18/71 (25%)	6/71 (8%)
Overall survival, months	13·01 (11·04–14·29)	10·87 (9·49–13·77)	9·63 (8·05–13·44)
Radiographic progression-free survival, months	8·08 (5·55–8·38)	5·52 (5·29–7·59)	3·71 (1·97–5·49)
Time to radiographic progression, months	8·08 (5·75–8·97)	5·55 (5·36–8·08)	3·78 (2·00–5·55)
Time to PSA progression, months	5·13 (4·60–5·59)	5·55 (4·60–8·31)	3·65 (2·83–3·71)
Time to symptomatic skeletal event, months	13·80 (10·41–NE)	13·80 (9·07–NE)	10·35 (8·18–NE)
Duration of objective response, months	6·28 (3·65–9·23)	5·55 (3·91–7·20)	5·16 (2·14–NE)
Composite response rate†, n/N (%; 95% CI)	82/142 (58%; 49·2–66·0)	46/76 (61%; 48·7–71·6)	12/81 (15%; 7·9–24·5)
CTC conversion‡, n/N (%; 95% CI)	55/117 (47%; 37·7–56·5)	28/64 (44%; 31·4–56·7)	9/60 (15%; 7·1–26·6)
PSA_{50}, n/N (%; 95% CI)	61/142 (43%; 34·7–51·5)	31/76 (41%; 29·7–52·7)	4/81 (5%; 1·4–12·2)

Data are median (95% CI) unless otherwise indicated. CTC=circulating tumour cell. PSA=prostate-specific antigen. NE=not estimable. PSA_{50}=at least 50% decline in prostate-specific antigen. *Defined per protocol and statistical analysis plan as CTC=0 per 7·5 mL blood at 8 weeks post-baseline in patients with baseline CTC count >0. †Defined as an objective response for patients with measurable disease, CTC conversion (defined as CTC count ≥5 per 7·5 mL blood at baseline and <5 per 7·5 mL blood post-therapy nadir), or PSA_{50}. ‡Among patients with baseline CTC count ≥5.

Table 3: **Secondary and exploratory efficacy endpoints**

(appendix p 28), which were manageable with one or more of the following: dose reductions, interruptions, or appropriate supportive measures (administered at the discretion of investigators per institutional standards of care). Among patients evaluated for anti-tumour activity, 70 (95%) of 74 patients with dose reductions in the *BRCA* cohort and 37 (93%) of 40 patients with dose reductions in the non-*BRCA* cohort had dose reductions due to adverse events versus other reasons; 103 (46%) of 223 patients received at least one transfusion (platelets or packed red blood cells), and the incidence of transfusions was similar between the *BRCA* and non-*BRCA* cohorts (data not shown). Other supportive measures included colony-stimulating factors, which were administered to 12 (4%) of 289 patients, and erythropoietin, which was administered to 15 (5%) of 289 patients. 37 (13%) of 289 patients were deemed to have discontinued treatment due to drug-related toxicities (treatment-emergent adverse events deemed related to study drug). The most common drug-related toxicities leading to discontinuation were thrombocytopenia (in seven patients with *BRCA* alterations and three patients with non-*BRCA* alterations) and anaemia (in six patients with *BRCA* alterations and one patient with non-*BRCA* alteration; appendix p 25).

Adverse events leading to death are summarised in the appendix (p 29). Of the 16 deaths related to adverse events, two events (one patient with urosepsis in the *BRCA* cohort and one patient with sepsis in the non-*BRCA* cohort) were deemed possibly related to niraparib treatment. 208 (72%) of 289 patients died during the study; reasons for deaths are summarised in the appendix (p 30). The only sensitivity analysis warranted was for COVID-19, but there was only one patient with a COVID-19-related adverse event (non-serious) and one death due to COVID-19 in this study (appendix p 30).

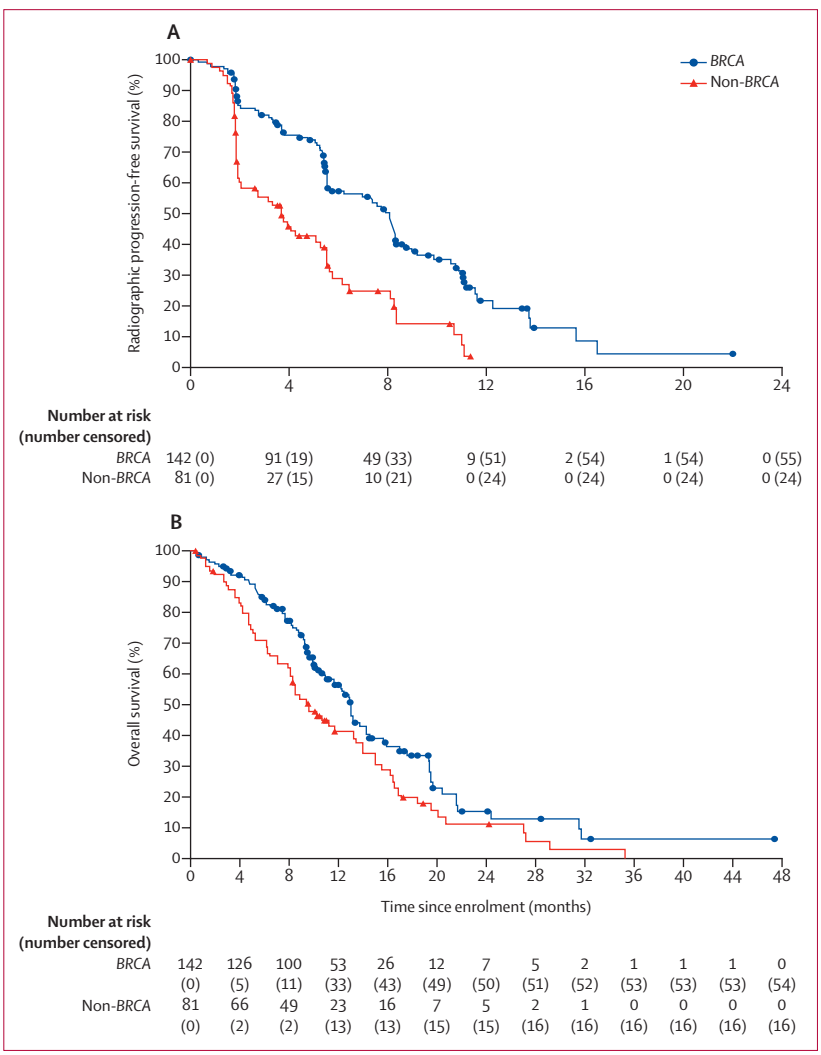

Figure 2: **Radiographic progression-free survival (A) and overall survival (B) in the *BRCA* and non-*BRCA* cohorts**
Symbols represent censored patients.

	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	154 (53%)	15 (5%)	0	0
Vomiting	101 (35%)	10 (3%)	0	0
Constipation	95 (33%)	5 (2%)	1 (<1%)	0
Fatigue	87 (30%)	19 (7%)	0	0
Decreased appetite	85 (29%)	8 (3%)	0	0
Anaemia	61 (21%)	92 (32%)	2 (1%)	1 (<1%)
Thrombocytopenia	52 (18%)	24 (8%)	23 (8%)	0
Back pain	51 (18%)	13 (4%)	0	0
Arthralgia	38 (13%)	6 (2%)	0	0
Asthenia	37 (13%)	11 (4%)	0	0
Neutropenia	27 (9%)	17 (6%)	11 (4%)	0
Bone pain	23 (8%)	9 (3%)	0	0
Hypertension	22 (8%)	12 (4%)	0	0
Blood alkaline phosphatase increased	15 (5%)	11 (4%)	0	0
Stomatitis	15 (5%)	6 (2%)	0	0
Leukopenia	14 (5%)	11 (4%)	3 (1%)	0
γ-glutamyl transferase increased	13 (4%)	11 (4%)	1 (<1%)	0
Lymphopenia	11 (4%)	12 (4%)	1 (<1%)	0
Hypophosphataemia	7 (2%)	6 (2%)	1 (<1%)	0
Spinal cord compression	1 (<1%)	7 (2%)	0	0
General physical health deterioration	1 (<1%)	7 (2%)	1 (<1%)	4 (1%)

Data are shown as n (%). A total of 288 patients had one or more recorded treatment-emergent adverse events. Data are presented for grade 1–2 treatment-emergent adverse events with a combined incidence of ≥20% or any higher-grade (grade 3–5) treatment-emergent adverse events with an incidence of ≥2%.

Table 4: **Treatment-emergent adverse events in the safety analysis set (n=289)**

Discussion

The results of this multicentre, open-label, phase 2 study establish the anti-tumour activity of niraparib in patients with metastatic castration-resistant prostate cancer and DRDs who have progressed on both androgen signalling inhibitors and taxanes. Treatment with niraparib was manageable, and adverse events observed were consistent with the known safety profile of niraparib, with no new safety signals.

The activity of niraparib in the measurable *BRCA* cohort is notable given the heavily pretreated, end-stage patient population with few therapeutic options. These findings are especially remarkable considering the high percentage of patients with visceral metastasis, in particular to the liver, which is strongly associated with poor survival;[25] the high percentage of patients with three or more lines of previous therapy; and that some patients in the *BRCA* cohort even achieved a complete response. Further evidence of benefit was shown by the proportion of patients experiencing stabilisation of disease for more than 6 months in both the *BRCA* and non-*BRCA* cohorts, which is a clinically meaningful finding given this heavily pretreated advanced disease state. Also notable was that patients in both cohorts, some with multiple poor prognostic features, continued to derive clinical benefit from niraparib after radiographic progression (in line with the importance of considering the totality of a patient's disease before discontinuing a drug rather than strictly at the first evidence of progression in any site, as recommended by PCWG3[21]). Objective response rate, median radiographic progression-free survival and overall survival, and composite response rate were greater in the *BRCA* cohort than in the non-*BRCA* cohort, including a median radiographic progression-free survival time that was approximately double that in the non-*BRCA* cohort. Interestingly, our exploratory endpoint of composite response rate was largely similar between the subgroups of patients with measurable versus non-measurable disease in both cohorts (particularly in the *BRCA* cohort). Taken together, these results extend the evidence on the activity of PARP inhibitors in patients with metastatic castration-resistant prostate cancer and DRD-altered tumours whose disease has progressed on approved life-prolonging therapies, and also highlight the importance of biological profiling of an individual patient's disease in metastatic castration-resistant prostate cancer.[8,21] Of note, to our knowledge, this trial is the first to prospectively test the CTC0 endpoint, which has been shown to strongly associate with survival.[22]

The dose of niraparib used in this study (300 mg oral; once daily dosing) was chosen based on the previously evaluated pharmacokinetics, clinical activity, and safety profile of niraparib and is the approved dose for patients with ovarian cancer.[17,26] As expected, grade 3 or worse treatment-emergent adverse events were largely haematological and manageable with supportive measures (such as blood transfusions and growth factor treatment), dose interruptions, and dose reductions. Rates of treatment interruptions and reductions were higher than the previously reported rates for other PARP inhibitors.[9–13] This finding is consistent with the more advanced disease stage of patients in the GALAHAD trial, who had all progressed on androgen signalling inhibitor therapy and taxane chemotherapy and also tended to be on later lines of therapy, with the majority having received three or more lines of previous therapy. Moreover, the present study applied more stringent dose interruption criteria (for example, skipping a dose was also considered a dose interruption). Thus, the finding that at least half of the patients in both the *BRCA* and non-*BRCA* cohorts maintained the full dose (300 mg) of niraparib throughout the study supports the overall tolerability of this regimen. Relative dose intensity was also generally high, including in the primary efficacy cohort, and was higher for those who had an objective response in that cohort compared with those who did not.

The clinical activity of niraparib shown in this study's specific patient population (noting particular activity observed in the *BRCA* cohort) can be further contextualised by results of studies of other PARP inhibitors that point to a benefit for both minimally and heavily pretreated patients with metastatic castration-resistant prostate cancer and particular DRD alterations. Of note, in the phase 3 PROfound study that evaluated patients treated with the PARP inhibitor olaparib versus those treated with the

physician's choice of an androgen signalling inhibitor, olaparib treatment resulted in a median radiographic progression-free survival of 7·4 months versus 3·6 months (hazard ratio 0·34, 95% CI 0·25–0·47; p<0·001), median overall survival of 19·1 months versus 14·7 months (0·69, 0·50–0·97; p=0·02 at final analysis), and confirmed objective response rate of 33% (28 of 84) versus 2% (one of 43; odds ratio 20·86, 95% CI 4·18–379·18; p<0·001) compared with the control treatment in a cohort of patients with alterations in *BRCA1, BRCA2,* or *ATM*.[10,11] Rucaparib, which was investigated in the phase 2 TRITON-2 study, led to an objective response rate of 47·5% and a median time to PSA progression of 6·5 months, with a better response seen in patients with *BRCA* alterations compared with those with alterations in other genes such *ATM* or *CDK12*.[12,13] In the phase 2 TALAPRO-1 study, patients with certain gene alterations reported to sensitise to PARP inhibitors were enrolled and treated with talazoparib. The objective response rate was 29·8% (31 of 104; 95% CI 21·2–39·6) with talazoparib treatment after a median follow-up of 16·4 months.[9]

The limitations of the present study include that some patients developed progressive disease before completing their first disease evaluation, consistent with the advanced stage and aggressiveness of the disease in the enrolled population. Additionally, tissue-based assays rely on sufficient high-quality biopsy samples, which might be difficult to obtain, and further challenges ensue when archival samples are found to be unsuitable or unavailable for analysis. In this study, a commercially available tissue-based assay was initially used to select patients, but due to the aforementioned challenges, a blood-based assay was subsequently implemented, with early prescreening rates and biomarker logic finalisation then addressed during a brief study pause. As such, a notable number of patients in GALAHAD were prescreened using blood-based assay. Such assays could offer valuable data, especially for metastatic prostate cancer for which tumour biopsies are challenging to acquire and biopsies are largely limited to bone that has considerable issues with the quality of materials. However, liquid biopsies also have limitations. Given the lack of parallel next-generation sequencing of corresponding white blood cells in this study, clonal haematopoietic alterations of indeterminate potential could have presented as a biological confounding factor.[27] Additionally, blood-based assays might show false negative results in blood samples with low plasma circulating tumour DNA content, especially for mutations that are difficult to detect such as homozygous deletions. Conversely, circulating tumour DNA assays could select for patients with higher percentages of circulating tumour DNA, which was previously found to be a predictive factor for a poorer prognosis.[28] Nevertheless, the number of patients enrolled for efficacy evaluation in GALAHAD (n=223 with specifically germline pathogenic or biallelic DRD alterations, of a total of 4218 with any biomarker sample submitted) represents an incidence of DRD alterations that is within expectations. Finally, 22% of the GALAHAD study population had *TP53* alterations, which are also associated with overall poor prognosis.

Additional studies, including those designed to evaluate niraparib-based regimens in appropriate biomarker-identified populations at earlier stages of disease, are underway to expand on the present findings. The phase 3 MAGNITUDE study is evaluating niraparib in combination with abiraterone acetate plus prednisone as first-line therapy in patients with metastatic castration-resistant disease with or without DRD.[29] The phase 3 AMPLITUDE study will also evaluate niraparib in combination with abiraterone acetate plus prednisone in a biomarker-selected population with metastatic castration-sensitive disease.[30]

In conclusion, these results suggest that niraparib has promising clinical activity with a manageable safety profile when administered as a monotherapy for treatment-refractory metastatic castration-resistant prostate cancer with *BRCA* alterations or select non-*BRCA* alterations. Such findings underscore the need for and importance of molecular testing to inform management along with continued research to establish treatment paradigms with appropriately targeted therapies for patients with prostate cancer. Efforts to investigate and better understand predictive markers and signatures of both response and resistance to treatment with PARP inhibitors such as niraparib are needed to guide therapy selection and optimise treatment outcomes.

Contributors

All authors in their role as GALAHAD study investigators or Janssen Research & Development investigators contributed to study design, study conduct, data analysis, and data interpretation. All authors participated in drafting and revising the manuscript and approved the final version before submission. MRS, GEM, and XZ verified all data. All authors had full access to all data for the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MRS has received grants or contracts to their institution from Bayer, Janssen, Pfizer, AstraZeneca, and Lilly; has received consulting fees from Astellas Pharma, Novartis, Janssen, AstraZeneca, Bayer, Lilly, and Pfizer; and has participated on data safety monitoring boards, advisory boards, or both for Janssen, Pfizer, and AstraZeneca. HIS has a leadership role in Asterias Biotherapeutics; holds stock and other ownership interests in Asterias Biotherapeutics; received grants or contracts to their institution from Epic Sciences, Illumina, Menarini Silicon Biosystems, ThermoFisher, and AIQ Pharma; provided consulting to Ambry Genetics Corporation/Konica Minolta, Amgen (uncompensated), Bayer, ESSA Pharma (uncompensated), Menarini Silicon Biosystems (uncompensated), Pfizer, Sun Pharmaceuticals, and WCG Oncology; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sidney Kimmel Cancer Center—Jefferson Health; has received support for attending meetings or travel from Amgen, Bayer, ESSA Pharma, Menarini Silicon Biosystems, Epic Sciences, Pfizer, WCG Oncology, and Phosplatin; has patents planned, issued, or pending via their institution with BioNTech, Elucida Oncology, MabVax Therapeutics, and Y-mAbs Therapeutics; and has other financial or non-financial interests in Elsevier, Prostate Cancer Foundation (via institution), National Cancer Institute (via institution), Department of Defense (via institution), MabVax Therapeutics, and BioNTech. SS has received grants from Amgen, Advanced Accelerator Applications (a Novartis company), Merck Sharp & Dohme,

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KNC has received grants or contracts to their institution from Janssen, AstraZeneca, Merck, Novartis, and Point Biopharma; has received consulting fees from Astellas, AstraZeneca, Janssen, Merck Sharp & Dohme, Novartis, Point Biopharma, and Roche; and has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas, Janssen, Merck Sharp & Dohme, AstraZeneca, and Novartis. FS has received grants or contracts, consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events, and has received equipment, materials, drugs, medical writing, gifts, or other services from Janssen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Myovant, Sanofi, Novartis, and Pfizer; and has participated on data safety monitoring boards, advisory boards, or both for Janssen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Myovant, Sanofi, Novartis, and Pfizer. 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KAU has been listed as an inventor on a patent as an employee of Janssen Research & Development. KF has received consulting fees from AAA, Astellas, AstraZeneca, Bayer, Novartis, Janssen, Amgen, Pfizer, Orion, Curevac, and Sanofi; has received payment or honoraria from lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas, AstraZeneca, Bayer, Janssen, Novartis, Merck Sharp & Dohme, Bristol Myers Squibb, and Orion; and has participated on data safety monitoring boards, advisory boards, or both for Astellas, AstraZeneca, Bayer, Novartis, Janssen, Amgen, Pfizer, Sanofi, Orion, and Curevac. OS declares no competing interests.

Data sharing

The full study protocol is available in the appendix. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access Project site at http://yoda.yale.edu. De-identified patient-level data will be made available to qualified researchers upon request, after signing of a data transfer agreement with Janssen Research & Development. Requests for data sharing, including a research proposal, can also be made to the corresponding author.

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References

1 Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur Urol* 2020; **77:** 508–47.

2 Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* 2021; **385:** 1091–103.

3 Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016; **375:** 443–53.

4 Tukachinsky H, Madison RW, Chung JH, et al. Genomic analysis of circulating tumor DNA in 3,334 patients with advanced prostate cancer identifies targetable BRCA alterations and AR resistance mechanisms. *Clin Cancer Res* 2021; **27:** 3094–105.

5 Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015; **161:** 1215–28.

6 Schiewer MJ, Knudsen KE. DNA damage response in prostate cancer. *Cold Spring Harb Perspect Med* 2019; **9:** a030486.

7 Warner EW, Yip SM, Chi KN, Wyatt AW. DNA repair defects in prostate cancer: impact for screening, prognostication and treatment. *BJU Int* 2019; **123:** 769–76.

8 Ratta R, Guida A, Scotté F, et al. PARP inhibitors as a new therapeutic option in metastatic prostate cancer: a systematic review. *Prostate Cancer Prostatic Dis* 2020; **23:** 549–60.

9 de Bono JS, Mehra N, Scagliotti GV, et al. Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial. *Lancet Oncol* 2021; **22:** 1250–64.

10 de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 2020; **382:** 2091–102.

11 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.

12 Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. *Clin Cancer Res* 2020; **26:** 2487–96.

13 Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J Clin Oncol* 2020; **38:** 3763–72.

14 AstraZeneca. Lynparza film-coated tablets—summary of product characteristics. 2019. https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf. (accessed Aug 23, 2021).

15 AstraZeneca. LYNPARZA® (olaparib) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals, 2020.

16 Clovis Oncology. RUBRACA® (rucaparib) package insert. Boulder, CO: Clovis Oncology, 2020.

17 Washington CR, Moore KN. PARP inhibitors in the treatment of ovarian cancer: a review. *Curr Opin Obstet Gynecol* 2021; **33:** 1–6.

18 Tesaro. ZEJULA™ (niraparib) package insert. Waltham, MA: Tesaro, 2017.

19 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

20 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.

21 US Food and Drug Administration. Premarket approval (PMA): FoundationOne CDx. 2017. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=p170019 (accessed Aug 23, 2021).

22 Heller G, McCormack R, Kheoh T, et al. Circulating tumor cell number as a response measure of prolonged survival for metastatic castration-resistant prostate cancer: a comparison with prostate-specific antigen across five randomized phase III clinical trials. *J Clin Oncol* 2018; **36:** 572–80.

23 Lorente D, Olmos D, Mateo J, et al. Decline in circulating tumor cell count and treatment outcome in advanced prostate cancer. *Eur Urol* 2016; **70:** 985–92.

24 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10:** 1–10.

25 Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2014; **32:** 671–77.

26 Jones P, Wilcoxen K, Rowley M, Toniatti C. Niraparib: a poly(ADP-ribose) polymerase (PARP) inhibitor for the treatment of tumors with defective homologous recombination. *J Med Chem* 2015; **58:** 3302–14.

27 Jensen K, Konnick EQ, Schweizer MT, et al. Association of clonal hematopoiesis in DNA repair genes with prostate cancer plasma cell-free DNA testing interference. *JAMA Oncol* 2021; **7:** 107–10.

28 Maurice-Dror C, Fonseca N, Herberts C, Fan W, Wyatt AW, Chi KN. Circulating tumor DNA fraction (ctDNA%) to independently predict for clinical outcomes in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *Proc Am Soc Clin Oncol* 2021; **39** (suppl 15)**:** 5049.

29 Chi KN, Rathkopf DE, Attard G, et al. A phase III randomized, placebo-controlled, double-blind study of niraparib plus abiraterone acetate and prednisone versus abiraterone acetate and prednisone in patients with metastatic prostate cancer (NCT03748641). *Proc Am Soc Clin Oncol* 2020; **38** (suppl 6)**:** TPS257.

30 Rathkopf DE, Chi KN, Olmos D, et al. AMPLITUDE: a study of niraparib in combination with abiraterone acetate plus prednisone (AAP) versus AAP for the treatment of patients with deleterious germline or somatic homologous recombination repair (HRR) gene-altered metastatic castration-sensitive prostate cancer (mCSPC). *Proc Am Soc Clin Oncol* 2021; **39** (suppl 6)**:** TPS176.