



Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial

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Summary

Background Poly(ADP-ribose) polymerase (PARP) inhibitors have antitumour activity against metastatic castration-resistant prostate cancers with DNA damage response (DDR) alterations in genes involved directly or indirectly in homologous recombination repair (HRR). In this study, we assessed the PARP inhibitor talazoparib in metastatic castration-resistant prostate cancers with DDR-HRR alterations.

Methods In this open-label, phase 2 trial (TALAPRO-1), participants were recruited from 43 hospitals, cancer centres, and medical centres in Australia, Austria, Belgium, Brazil, France, Germany, Hungary, Italy, the Netherlands, Poland, Spain, South Korea, the UK, and the USA. Patients were eligible if they were men aged 18 years or older with progressive, metastatic, castration-resistant prostate cancers of adenocarcinoma histology, measurable soft-tissue disease (per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]), an Eastern Cooperative Oncology Group performance status of 0–2, DDR-HRR gene alterations reported to sensitise to PARP inhibitors (ie, *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*), had received one or two taxane-based chemotherapy regimens for metastatic disease, and progressed on enzalutamide or abiraterone, or both, for metastatic castration-resistant prostate cancers. Eligible patients were given oral talazoparib (1 mg per day; or 0.75 mg per day in patients with moderate renal impairment) until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent, or death. The primary endpoint was confirmed objective response rate, defined as best overall soft-tissue response of complete or partial response per RECIST 1.1, by blinded independent central review. The primary endpoint was assessed in patients who received study drug, had measurable soft-tissue disease, and had a gene alteration in one of the predefined DDR-HRR genes. Safety was assessed in all patients who received at least one dose of the study drug. This study is registered with ClinicalTrials.gov, NCT03148795, and is ongoing.

Findings Between Oct 18, 2017, and March 20, 2020, 128 patients were enrolled, of whom 127 received at least one dose of talazoparib (safety population) and 104 had measurable soft-tissue disease (antitumour activity population). Data cutoff for this analysis was Sept 4, 2020. After a median follow-up of 16.4 months (IQR 11.1–22.1), the objective response rate was 29.8% (31 of 104 patients; 95% CI 21.2–39.6). The most common grade 3–4 treatment-emergent adverse events were anaemia (39 [31%] of 127 patients), thrombocytopenia (11 [9%]), and neutropenia (ten [8%]). Serious treatment-emergent adverse events were reported in 43 (34%) patients. There were no treatment-related deaths.

Interpretation Talazoparib showed durable antitumour activity in men with advanced metastatic castration-resistant prostate cancers with DDR-HRR gene alterations who had been heavily pretreated. The favourable benefit–risk profile supports the study of talazoparib in larger, randomised clinical trials, including in patients with non-*BRCA* alterations.

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Introduction

The poly(ADP-ribose) polymerase (PARP) enzymes PARP1 and PARP2 are key components of the DNA damage response (DDR) mechanism.¹ PARP inhibitors selectively kill specific cancer cells via so-called synthetic lethality, a mechanism whereby deficiency in function of one gene or gene product has little effect alone but is toxic in combination with deficiency in function of a second gene or gene product.¹ PARP inhibition is synthetically lethal in cells with homologous deletions or deleterious alterations, or both, in

DDR genes involved either directly or indirectly in homologous recombination repair (HRR).¹ Germline or somatic DDR alterations occur in 23–27% of men with prostate cancer,^{2,3} and are associated with worse outcomes.^{4–6}

Talazoparib potentially inhibits PARP catalytic activity and is the most efficient PARP inhibitor at trapping PARP1 and PARP2 on DNA single-strand break sites, preventing DNA replication and transcription, and leading to double-strand DNA breaks and cell death.^{7–10} Talazoparib is approved for treating germline *BRCA1*-mutated and

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Research in context

Evidence before this study

In the planning phase for TALAPRO-1, we searched PubMed in late 2015 to early 2016 for relevant preclinical or clinical research published on so-called BRCAness, DNA damage response, DNA damage repair (DDR), homologous recombination repair (HRR), synthetic lethality, poly(ADP-ribose) polymerase (PARP) inhibitors, and advanced prostate cancer. Prostate cancer remains the second most common cause of cancer-related death in men, with no curative treatment options available once patients develop metastatic castration-resistant prostate cancer. At study initiation, treatment options for men with metastatic castration-resistant prostate cancers included novel hormonal therapies (eg, enzalutamide, abiraterone), taxanes (docetaxel, cabazitaxel), radium-223, and sipuleucel-T. An unmet medical need remains for men with metastatic castration-resistant prostate cancers who have already received novel hormone therapy and taxane-based chemotherapy; some of these tumours carry alterations in DDR genes involved directly or indirectly in HRR that can sensitise to PARP inhibitors. Those alterations have been linked to worse prognosis. Several PARP inhibitors are being assessed for the treatment of metastatic castration-resistant prostate cancers with defective HRR gene alterations. The toxicity profile and efficacy or duration of sensitivity to PARP inhibitors might differ depending on specific HRR gene alterations; therefore, continued research with PARP inhibitors is warranted.

Added value of this study

To our knowledge, this study is the first international phase 2 trial to assess the antitumour activity and tolerability of

talazoparib in men with metastatic castration-resistant prostate cancers with alterations in DDR genes involved in HRR who have been heavily pretreated. Antitumour activity was most notable against tumours with *BRCA2* alterations, although partial or complete responses, stable disease, and prostate-specific antigen responses were also seen in tumours with alterations in *BRCA1*, *PALB2*, and *ATM*, which affirms that PARP inhibition has antitumour activity beyond the *BRCA1* and *BRCA2* subset. Our finding that homozygous loss is associated with enhanced antitumour activity might be crucial to interpreting antitumour activity results in gene-by-gene analyses from prostate cancer PARP inhibitor studies using multi-gene panels, including the TALAPRO-1 study.

Implications of all the available evidence

These data suggest that talazoparib has durable antitumour activity against lethal prostate cancers with various DNA repair defects that directly or indirectly impact HRR. This antitumour activity was observed even in men with very advanced prostate cancer who have exhausted most available treatment options. The favourable benefit-risk profile of talazoparib monotherapy against metastatic castration-resistant prostate cancers with alterations in DDR genes either directly or indirectly involved in HRR in men previously treated with taxanes and novel hormone therapy supports the study of talazoparib in larger, randomised clinical trials, including in men with non-*BRCA* alterations.

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BRCA2-mutated human epidermal growth factor receptor 2 (*HER2*, *ErbB-2*) negative metastatic or locally advanced breast cancer.^{11,12} To our knowledge, TALAPRO-1 is the first international phase 2 trial to assess the antitumour activity and tolerability of talazoparib monotherapy in men with metastatic castration-resistant prostate cancers and HRR gene alterations who have been heavily pretreated.

Methods

Study design and participants

TALAPRO-1 is an open-label, phase 2 trial that enrolled patients at 43 hospitals, cancer centres, and medical centres in 14 countries (Australia, Austria, Belgium, Brazil, France, Germany, Hungary, Italy, the Netherlands, Poland, Spain, South Korea, the UK, and the USA). Patients were eligible if they were men aged 18 years or older with progressive metastatic castration-resistant prostate cancers of adenocarcinoma histology. Progressive disease was defined as a minimum of three increasing prostate-specific antigen (PSA) values with an interval of at least 1 week between readings, soft-tissue disease progression as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or bone disease progression

defined by Prostate Cancer Working Group 3 criteria¹³ with two or more new metastatic lesions on bone scan. The screening central laboratory PSA value needed to be 2 µg/L or higher if the candidate was qualifying solely by PSA progression. Study inclusion criteria were amended after initiation. The original study design allowed the enrolment of patients with measurable and non-measurable disease in two overlapping cohorts: cohort A, which included patients with alterations in HRR likely to sensitise to PARP inhibition, and cohort B, which included patients with DNA defects in an expanded panel of genes that are likely to, or might, sensitise to PARP inhibition. With the approval of protocol amendment three on Feb 15, 2018, enrolment was restricted to patients with measurable disease and with DNA alterations likely to sensitise to PARP inhibition, which originally comprised a panel of 13 genes. *FANCD2* and *FANCI* did not pass subsequent validation requirements, leaving the following panel of 11 HRR genes that were used in the analyses: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, and *RAD51C*. More information is in the appendix (p 3). Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; bilateral orchiectomy or ongoing androgen deprivation

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therapy with a gonadotropin-releasing hormone agonist or antagonist, with serum testosterone of 50 ng/dL or less (≤ 1.73 nmol/L) at screening; stable bisphosphonate or denosumab dose for at least 4 weeks for patients receiving these therapies; estimated life expectancy of at least 6 months (as assessed by investigator); and previous treatment with one or two chemotherapy regimens (≥ 1 taxane-based) in the metastatic setting (castration-sensitive or castration-resistant prostate cancer; patients could have received radium-223 or cabazitaxel, or both) and progressed on at least one novel hormone therapy (enzalutamide, abiraterone, or both) given for metastatic castration-resistant prostate cancers. A list of key eligibility criteria is in the appendix (p 4) and a full list in the protocol (appendix).

This study followed Good Clinical Practice standards, the Declaration of Helsinki, and the International Conference on Harmonisation. The Institutional Review Board or Ethics Committee at each study site approved the protocol. All patients provided signed informed consent.

Procedures

Potentially eligible patients were screened for the prespecified alterations in DDR genes involved directly or indirectly in HRR (ie, DDR-HRR genes) that are likely to sensitise to PARP inhibition using tumour tissue analysis (FoundationOne CDx next-generation sequencing, Illumina HiSeq 4000 platform at Foundation Medicine, Cambridge, MA, USA) or, if enrolled under protocol amendment one (March 31, 2017; amendment allowed the entry of men without measurable disease), for HRR deficiencies assessed using an expanded DNA damage repair panel of genes likely to or that might sensitise to PARP inhibition. The gene or genes altered were reported using FoundationOne CDx results generated either on screening for the study or using historical medical records.

Patients were given oral talazoparib 1 mg per day (or 0.75 mg per day for patients with moderate renal impairment, defined as an estimated glomerular filtration rate of 30–59 mL/min per 1.73 m²), with dose modification or appropriate supportive care, or both, given for recovery from grade 3 or 4 adverse events (appendix pp 5–8). Talazoparib was continued until progression, as determined on radiographic imaging, unacceptable toxicity, investigator decision, withdrawal of consent, or death. Increased PSA or circulating tumour cell counts alone were not a reason for discontinuing talazoparib.

Radiographic assessments (CT [preferred] or MRI of the abdomen and pelvis, CT of chest, and whole-body radionuclide bone scan) were done every 8 weeks during the first 24 weeks, then every 12 weeks thereafter. Soft-tissue responses were confirmed at least 4 weeks after the response was identified with CT or MRI, per RECIST 1.1 with no evidence of confirmed bone progression per Prostate Cancer Working Group 3 criteria on repeat bone scan at least 6 weeks later, per independent central review. Clinical laboratory tests and assessments of safety were

done at screening and at each scheduled visit (every 2 weeks up to week 9, every 4 weeks up to week 25, then every 12 weeks thereafter [haematology and serum chemistry every 8 weeks] while on study drug). Safety assessments included investigator-assessed adverse events, physical examinations, vital signs, clinical laboratory tests, incidence of dose modifications, and permanent treatment discontinuation due to adverse events.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 23.0) and classified by severity using the Common Terminology Criteria for Adverse Events (version 4.03).

Routine clinical laboratory tests (haematology [using electronic cell counter], serum chemistry [using an automated chemistry analyser]) were done according to protocol-defined timelines by the central laboratory (Global Q2 Solutions, a Quintiles Quest Joint Venture, Affiliate Labs, Morrisville, NC, USA) but could also be collected at any time at the investigator's discretion or to monitor adverse events or determine if dosing modifications were required. Circulating tumour cell counts were done using the CELLSEARCH platform at The Institute of Cancer Research, Sutton, UK. Local safety laboratory assessments could also be done but were not to replace central laboratory assessments. Haematology assessments included haematocrit, haemoglobin, mean corpuscular volume, red blood cell count, platelet count, white blood cell count and differential, total neutrophils, lymphocytes, monocytes, eosinophils, and basophils; chemistry assessments included albumin, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen, creatinine, glucose (non-fasting), bicarbonate, calcium (and calcium albumin corrected), chloride, magnesium, phosphate, potassium, sodium, lactate dehydrogenase, and PSA.

Germline versus somatic categorisation of alterations was based on comparison of tumour and matched saliva DNA sequences, and zygosity of alterations was predicted centrally using the somatic-germline-zygosity computational algorithm.¹⁴ When patients had multiple alterations of the 11 predefined DDR-HRR genes, for purposes of subject-level categorisation, homozygous status was considered to be dominant to heterozygous status, and germline origin was considered to be dominant to somatic origin. Baseline saliva samples were sequenced using the Ambry CustomNext-Cancer panel (Ambry Genetics, Aliso Viejo, CA, USA), which included nine of the 11 genes; *ATR* and *FANCA* were not present in the germline panel. Serial circulating tumour cells, circulating tumour DNA, and protein biomarker samples were also collected. Circulating tumour DNA analyses will be reported separately. Tumour HRR gene alterations were designated as being of germline (also present in saliva), somatic (tumour only), or unknown origin (core gene not represented in the nine-gene germline panel or saliva

sample not available or evaluable). This analysis was confined to short variants (ie, single-nucleotide variants or short insertions or deletions). We did a similar analysis using zygosity as assessed using the somatic-germline-zygosity computational algorithm, which predicts whether alterations are homozygous or hemizygous (hereafter referred to as homozygous) or heterozygous, with analysis limited to short variants and tumours with adequate tumour purity.¹⁴

Outcomes

The primary endpoint was confirmed objective response rate, defined as best overall soft-tissue response of complete or partial response per RECIST 1.1 as assessed by blinded independent central review and investigator assessment. Secondary endpoints were time to objective response (defined as time from the first dose of talazoparib to first objective evidence of soft-tissue response with no evidence of confirmed bone disease progression per Prostate Cancer Working Group 3 criteria according to blinded independent central review and investigator assessment), duration of objective response (defined as time from first objective response to first objective evidence of radiographic progression or death due to any cause per blinded independent central review and investigator assessment), proportion of patients with a decrease in PSA of 50% or more from baseline, time to PSA progression (the time from first dose of talazoparib to the date of a $\geq 25\%$ increase in PSA with an absolute increase of ≥ 2 $\mu\text{g/L}$ [2 ng/mL], confirmed by a second consecutive PSA value at ≥ 3 weeks later), proportion of patients with conversion of circulating tumour cell count (proportion with a decrease from baseline of ≥ 5 to < 5 cells per 7.5 mL blood or a decrease from ≥ 1 to 0 cells per 7.5 mL blood at any time, or any increase from < 5 cells per 7.5 mL blood), radiographic progression-free survival (time from the first dose of talazoparib to progression in soft tissue as determined by radiography per RECIST 1.1, per blinded independent central review and investigator assessment, in bone as per Prostate Cancer Working Group 3 criteria and independent central review, or death due to any cause, whichever occurred first), overall survival (time from first dose of talazoparib to death due to any cause), safety, patient-reported outcomes (time to deterioration in patient-reported pain, as assessed by the Brief Pain Inventory Short Form [BPI-SF]; change from baseline in patient-reported pain as per BPI-SF, and change from baseline in patient-reported outcome general health status, as assessed by the EQ-5D-5L; all to be reported separately), and pharmacokinetics of talazoparib (including pre-dose trough and post-dose plasma concentrations; to be reported separately).

Potential biomarkers (including HRR gene alteration group, HRR gene alteration origin [germline vs somatic], and zygosity) of response (including confirmed objective response rate, time to objective response, duration of

response, reduction in tumour burden, PSA, and radiographic progression-free survival) were exploratory endpoints.

Statistical analysis

The primary aim of TALAPRO-1 was to assess the anti-tumour activity of talazoparib in terms of objective response rate. A planned sample size of at least 100 patients was sufficient to show that if the observed best objective response rate was at least 23%, the lower bound of the corresponding exact two-sided 95% CI would be higher than 15.2%.

Prespecified interim analyses for safety and antitumour activity were planned: after 20 patients who were HRR deficient with measurable disease had completed 8 weeks of treatment; after 20 patients with *BRCA1*, *BRCA2*, or *PALB2* alterations and measurable disease had received study treatment for at least 16 weeks or were no longer being followed up (eg, had withdrawn consent, discontinued from the study, died, or were otherwise lost to follow-up); and after 60 patients who were HRR deficient and had measurable disease had completed at least 6 months of study treatment or were otherwise no longer being followed up (eg, had withdrawn consent, discontinued from the study, died, or were otherwise lost to follow-up). These analyses are not reported here. We did a final analysis, reported herein, after 100 patients who were HRR deficient and had measurable disease had completed at least 6 months of study treatment or were otherwise no longer being followed up (eg, had withdrawn consent, discontinued from the study, died, or were otherwise lost to follow-up).

The population of patients evaluable for antitumour activity was defined as all enrolled patients who had measurable soft-tissue disease at screening per investigator assessment, had alterations in a gene within the 11 predefined DDR-HRR genes, and had received at least one dose of talazoparib. Patients with measurable disease at baseline and at least one valid assessment after baseline, per blinded independent central review, were assessed for best change from baseline in the sum of the diameter of the target lesions (as part of the objective response rate outcome). Post hoc, we analysed all antitumour activity endpoints by HRR gene alteration group (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, and the other genes in the predefined panel of 11 DDR-HRR genes), in which we separated all patients by DDR-HRR gene alteration using a hierarchical strategy, with *BRCA1* or *BRCA2* ranked above *PALB2*, *PALB2* ranked above *ATM*, and *ATM* ranked above all other alterations. For analyses, we grouped together the *BRCA1* and *BRCA2* groups due to the low number of patients with *BRCA1* alterations and we anticipated similar functional effect of these two alterations on HRR on the basis of the scientific literature. We implemented this strategy post hoc on the basis of the latest understanding of the likely relative importance of these genes.¹⁵ We used the Brookmeyer and Crowley method to calculate 95% CIs

of median radiographic progression-free survival and overall survival. We also analysed objective response rates for single and co-occurring alterations and by alteration origin separately using the two-sided Fisher's exact test and calculated odds ratios (ORs) for objective response. In an exploratory analysis of the association of overall and objective response with zygosity, an OR of more than 1 indicated a better outcome for homozygous compared with heterozygous status. We calculated the exact CI and the p value on the basis of the Fisher's exact test.

We summarised the rates of binary proportions along with two-sided exact 95% CI (Clopper-Pearson method).¹⁶ We summarised time-to-event endpoints using the Kaplan-Meier method. We did post-hoc analyses of PSA response of $\geq 30\%$, composite response (defined as objective response, PSA response of $\geq 50\%$, or circulating tumour cell conversion, or a combination of these responses) and objective response rate by blinded independent central review according to the presence of

visceral liver, visceral non-liver, visceral, and non-visceral disease (Clopper-Pearson method used for 95% CI). We did subgroup analyses of objective response rate by blinded independent central review and PSA response, with subgroups defined by ECOG performance status, geographical region, alteration type, alteration origin, zygosity, initial metastatic stage, disease site, previous taxane use, and age. Circulating tumour cell count conversion rate was defined as any decrease from 5 or more cells per 7.5 mL at baseline to less than 5 cells per 7.5 mL after baseline. Patients with a circulating tumour cell count of less than 5 cells per 7.5 mL of blood at baseline were not analysed for this conversion endpoint. We calculated the proportion of patients with a conversion to less than 5 cells per 7.5 mL along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion). As a post-hoc analysis, clinical benefit was defined as complete or partial response, or stable disease for at least 6 months from start of treatment.

We did a sensitivity analysis to assess concordance between blinded independent central review and investigator assessment using the agreement rate between best overall response in the DDR deficient measurable disease population.

The safety population was defined as all patients who received at least one dose of talazoparib, including a subset of patients with non-measurable disease who were enrolled under an early version of the protocol and HRR gene alterations that were assessed using an expanded DDR-HRR gene panel including genes likely to or that might sensitise to PARP inhibitors.

Unless otherwise specified, all data were assessed as observed and no imputation method was used for missing values. Missing dates were imputed per protocol. p values of less than 0.05 were considered to be significant. We did statistical analyses using SAS version 9.4. This study is registered with ClinicalTrials.gov (NCT03148795).

Role of the funding source

The sponsor (Pfizer/Medivation) was involved in study design, data analysis, and data interpretation, and provided funding for medical writing support. All authors, including those employed by the sponsor, contributed to data interpretation, development, writing, and approval of the manuscript.

Results

The first patient's first visit occurred on July 4, 2017, with prescreening ending on Feb 21, 2020; study enrolment officially closed on March 20, 2020. Of 1425 screened patients, 1297 did not have HRR gene alterations or did not meet other eligibility criteria (figure 1; appendix p 3). Between Oct 18, 2017, and March 20, 2020, 128 men were enrolled, of whom 23 (18%) had non-measurable disease or were not HRR deficient and one (1%) patient did not receive talazoparib, leaving 127 patients in the safety population (with both measurable and non-measurable

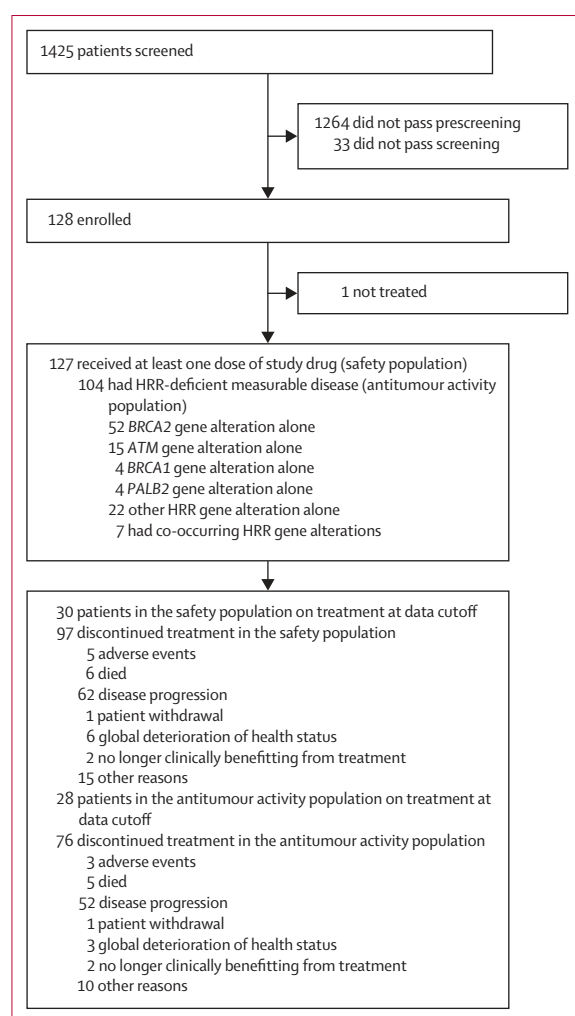


Figure 1: Trial profile

HRR=homologous recombination repair.

	Safety population (n=127)	Antitumour activity population (n=104)					
		BRCA1 or BRCA2 (n=61)*	BRCA2 (n=57)*	PALB2 (n=4)	ATM (n=17)†	Other (n=22)‡	Total (N=104)
Age, years	69.0 (63.0–74.0)	69.0 (63.0–72.0)	69.0 (46.0–83.0)	72.5 (60.5–77.0)	67.0 (61.0–73.0)	71.0 (65.0–79.0)	69.0 (63.0–73.0)
Race							
White	110 (87%)	53 (87%)	50 (88%)	3 (75%)	16 (94%)	19 (86%)	91 (88%)
Black	4 (3%)	3 (5%)	3 (5%)	0	0	0	3 (3%)
Asian	3 (2%)	0	0	0	1 (6%)	1 (5%)	2 (2%)
Not reported	10 (8%)	5 (8%)	4 (7%)	1 (25%)	0	2 (9%)	8 (8%)
Renal impairment							
Normal or mild	105 (83%)	50 (82%)	46 (81%)	4 (100%)	15 (88%)	16 (73%)	85 (82%)
Moderate	22 (17%)	11 (18%)	11 (19%)	0	2 (12%)	6 (27%)	19 (18%)
Baseline serum PSA, µg/L	103.8 (24.0–303.1)	97.4 (19.4–299.5)	97.4 (20.8–296.0)	118.7 (56.3–244.5)	178.5 (56.1–308.5)	153.5 (33.8–305.0)	118.6 (26.0–304.1)
Baseline testosterone, ng/dL	10.1 (10.1–19.9)	10.1 (10.1–15.8)	10.1 (10.1–15.0)	15.8 (10.0–33.4)	14.1 (10.1–22.2)	10.1 (10.1–20.7)	10.1 (10.1–17.7)
Baseline CTC count, cells per 7.5 mL of blood	5.0 (0.0–41.0)	5.0 (0.0–22.0)	5.0 (0.0–22.0)	13.0 (3.0–490.0)	23.0 (0.0–62.0)	3.5 (1.5–36.5)	5.0 (1.0–38.0)
Total Gleason score							
Grade group 1 (≤6)	9 (7%)	4 (7%)	4 (7%)	0	2 (12%)	3 (14%)	9 (9%)
Grade group 2 (3 + 4) and 3 (4 + 3)	39 (31%)	17 (28%)	17 (30%)	0	6 (35%)	8 (36%)	31 (30%)
Grade group 4 (8) and 5 (9–10)	78 (61%)	39 (64%)	35 (61%)	4 (100%)	9 (53%)	11 (50%)	63 (61%)
Not reported	1 (1%)	1 (2%)	1 (2%)	0	0	0	1 (1%)
Initial M stage at primary diagnosis							
M0	50 (39%)	26 (43%)	24 (42%)	0	6 (35%)	7 (32%)	39 (38%)
M1	57 (45%)	26 (43%)	25 (44%)	4 (100%)	9 (53%)	9 (41%)	48 (46%)
MX	16 (13%)	7 (11%)	6 (11%)	0	1 (6%)	5 (23%)	13 (13%)
Not reported	4 (3%)	2 (3%)	2 (4%)	0	1 (6%)	1 (5%)	4 (4%)
Disease site							
Visceral	41 (32%)	18 (30%)	17 (30%)	3 (75%)	5 (29%)	10 (45%)	36 (35%)
Non-visceral	86 (68%)	43 (70%)	40 (70%)	1 (25%)	12 (71%)	12 (55%)	68 (65%)
ECOG performance status							
0	52 (41%)	24 (39%)	22 (39%)	0	8 (47%)	9 (41%)	41 (39%)
1	63 (50%)	31 (51%)	29 (51%)	4 (100%)	8 (47%)	10 (45%)	53 (51%)
2	12 (9%)	6 (10%)	6 (11%)	0	1 (6%)	3 (14%)	10 (10%)
Previous taxane use							
Docetaxel only	65 (51%)	35 (57%)	32 (56%)	1 (25%)	9 (53%)	9 (41%)	54 (52%)
Docetaxel and cabazitaxel	61 (48%)	26 (43%)	25 (44%)	3 (75%)	8 (47%)	12 (55%)	49 (47%)
Not reported	1 (1%)	0	0	0	0	1 (5%)	1 (1%)
Previous novel hormone therapy							
Abiraterone only	45 (35%)	28 (46%)	27 (47%)	2 (50%)	3 (18%)	4 (18%)	37 (36%)
Enzalutamide only	46 (36%)	20 (33%)	19 (33%)	2 (50%)	8 (47%)	7 (32%)	37 (36%)
Abiraterone and enzalutamide	34 (27%)	12 (20%)	10 (18%)	0	6 (35%)	10 (45%)	28 (27%)
Not reported	2 (2%)	1 (2%)	1 (2%)	0	0	1 (5%)	2 (2%)

Data are median (IQR) or n (%). Patients were separated hierarchically by HRR gene alterations involved either directly or indirectly with HRR, with BRCA1 and BRCA2 ranked above PALB2, PALB2 ranked above ATM, and ATM ranked above all other alterations. CTC=circulating tumour cell. ECOG=Eastern Cooperative Oncology Group. HRR=homologous recombination repair. PSA=prostate-specific antigen. *The BRCA1 or BRCA2 and BRCA2 groups both included two patients with both BRCA2 and PALB2 alterations, one patient with both BRCA2 and ATM alterations, one patient with both BRCA2 and CHEK2 alterations, and one patient with both BRCA2 and MLH1 alterations; these patients were not counted or included in the other groups. †The ATM group included one patient with both ATM and FANCA alterations and one patient with both ATM and RAD51C alterations. ‡The other group included patients with HRR gene alterations in ATR, CHEK2, FANCA, MLH1, MRE11A, NBN, or RAD51C.

Table 1: Baseline patient characteristics in the safety population and in the antitumour activity population (overall and by HRR gene alteration group)

disease) and 104 patients in the antitumour activity population (with HRR deficient measurable disease only; figure 1). Baseline patient characteristics in the safety and antitumour activity populations were similar (table 1).

Median follow-up was 16.4 months (IQR 11.1–22.1). Data cutoff for these analyses was Sept 4, 2020.

Of 104 patients in the antitumour activity population, four (4%) had a BRCA1 alteration alone, 52 (50%) had a

	BRCA1 or BRCA2 (n=61)*	BRCA2 (n=57)*	PALB2 (n=4)	ATM (n=17)†	Other (n=22)‡	Total (N=104)
Best overall response§						
Confirmed complete response	6/61 (10%)	6/57 (11%)	0/4 (0%)	1/17 (6%)	0/22 (0%)	7/104 (7%)
Confirmed partial response	22/61 (36%)	20/57 (35%)	1/4 (25%)	1/17 (6%)	0/22 (0%)	24/104 (23%)
Stable disease (any duration)	21/61 (34%)	19/57 (33%)	2/4 (50%)	6/17 (35%)	8/22 (36%)	37/104 (36%)
Stable disease for ≥6 months	6/61 (10%)	6/57 (11%)	0/4 (0%)	2/17 (12%)	0/22 (0%)	8/104 (8%)
Non-complete response or non-progressive disease	4/61 (7%)	4/57 (7%)	0/4 (0%)	0/17 (0%)	0/22 (0%)	4/104 (4%)
Progressive disease	4/61 (7%)	4/57 (7%)	0/4 (0%)	8/17 (47%)	10/22 (46%)	22/104 (21%)
Not evaluable	4/61 (7%)	4/57 (7%)	1/4 (25%)	1/17 (6%)	4/22 (18%)	10/104 (10%)
Objective response§	28/61 (46%)	26/57 (46%)	1/4 (25%)	2/17 (12%)	0/22 (0%)	31/104 (30%)
PSA response of ≥30% (post hoc)¶	43/61 (70%)	41/57 (72%)	3/4 (75%)	2/17 (12%)	2/22 (9%)	50/104 (48%)
PSA response of ≥50%						
In all patients with a baseline and at least one post-baseline PSA assessment	39/59 (66%)	37/55 (67%)	3/4 (75%)	1/15 (7%)	1/18 (6%)	44/96 (46%)
In all patients with a baseline PSA assessment	39/61 (64%)	37/57 (65%)	3/4 (75%)	1/17 (6%)	1/22 (5%)	44/104 (42%)
CTC conversion from ≥5 to <5 cells per 7.5 mL of blood	17/21 (81%)	17/21 (81%)	0/1 (0%)	3/6 (50%)	1/5 (20%)	21/33 (64%)
Median radiographic progression-free survival, months (95% CI)**	11.2 (7.5–19.2)	11.2 (7.5–19.2)	5.6 (3.7–7.4)	3.5 (1.7–8.3)	1.8 (1.7–3.7)	5.6 (3.7–8.8)
Composite response (post hoc)††	44/61 (72%)	42/57 (74%)	3/4 (75%)	4/17 (24%)	2/22 (9%)	53/104 (51%)
Clinical benefit rate (post hoc)‡‡	34/61 (56%)	32/57 (56%)	1/4 (25%)	4/17 (24%)	0/22 (0%)	39/104 (38%)

Data are n/N (%), unless otherwise stated. For all endpoints, patients were separated hierarchically by HRR gene alterations involved either directly or indirectly in HRR with BRCA1 and BRCA2 ranked above PALB2, PALB2 ranked above ATM, and ATM ranked above all other alterations. CTC=circulating tumour cells. HRR=homologous recombination repair. PSA=prostate-specific antigen. *The BRCA1 or BRCA2 and BRCA2 groups included two patients with both BRCA2 and PALB2 alterations, one patient with both BRCA2 and ATM alterations, one patient with both BRCA2 and CHEK2 alterations, and one patient with both BRCA2 and MLH1 alterations. †The ATM group included one patient with both ATM and FANCA alterations and one patient with both ATM and RAD51C alterations. ‡The other group included patients with HRR gene alterations in ATR, CHEK2, FANCA, MLH1, MRE11A, NBN, or RAD51C. §Only includes patients with measurable disease per investigator assessment. ¶PSA response in patients with a baseline PSA assessment. ||Patients with a CTC count of ≥5 cells per 7.5 mL of blood at study entry that decreased to <5 cells per 7.5 mL of blood anytime during the study; only includes patients with a baseline CTC assessment and ≥1 post-baseline CTC assessment. **Based on the Brookmeyer and Crowley method. ††Defined as patients with objective response, PSA response of ≥50%, or CTC conversion, or a combination of these responses. ‡‡Defined as patients with complete response, partial response, or stable disease for ≥6 months from treatment start.

Table 2: Antitumour activity assessments overall and by HRR gene alteration group, by blinded independent central review, in the antitumour activity population

BRCA2 gene alteration alone, 15 (14%) had an ATM alteration alone, four (4%) had a PALB2 alteration alone, and 22 (21%) had other HRR gene alterations (three or fewer participants had each of the other gene alterations, except CHEK2 [n=9] and MLH1 [n=4]). Seven (7%) patients had co-occurring HRR gene alterations (appendix p 19). Table 1 shows the number of patients in each subgroup when separated by the predefined hierarchy. Similar rates of HRR gene alterations were seen in the safety population (data not shown).

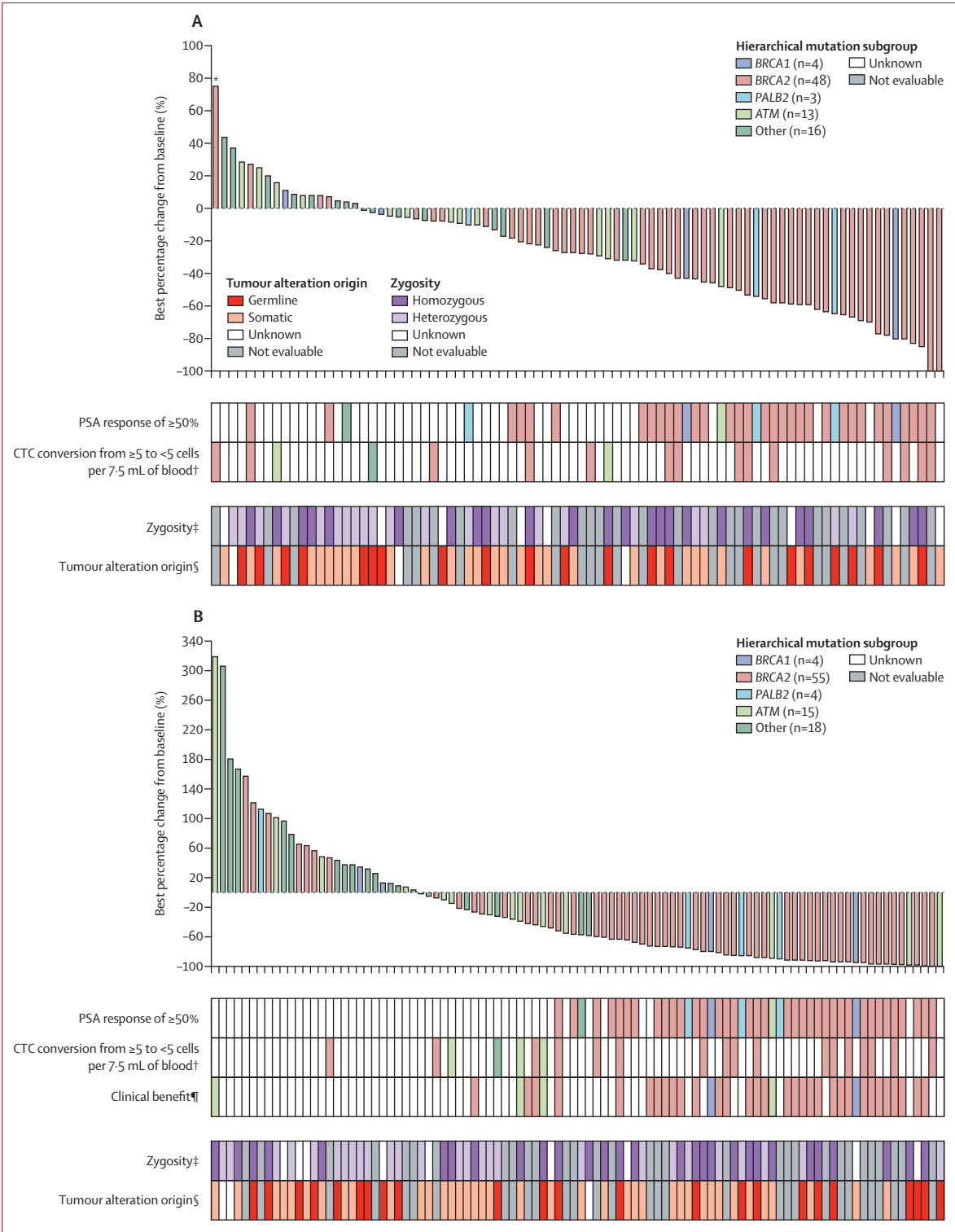
Median duration of talazoparib treatment was 6.1 months (IQR 3.6–10.8) in the safety population and 6.2 months (3.6–9.9) in the antitumour activity population.

In the antitumour activity population, confirmed objective response rate by blinded independent central review was 29.8% (95% CI 21.2–39.6), with a response occurring in 31 of 104 patients (table 2). Confirmed objective response by blinded independent central review by hierarchical separation of HRR gene alteration group (post-hoc analysis) was seen in 26 (46%) of 57 patients with BRCA2 alterations, two (50%) of four with BRCA1

alterations, one (25%) of four with PALB2 alterations, and two (12%) of 17 with ATM alterations (table 2). Objective response rate by individual gene alteration (post hoc) is shown in the appendix (p 9). Prespecified subgroup analyses for objective response rate by blinded independent central review are shown in the appendix (p 20). In post-hoc analyses, confirmed objective response by blinded independent central review was observed in 26 (38%) of 68 patients with non-visceral disease and in five (14%) of 36 patients with visceral disease. In the 36 patients with visceral disease, an objective response by blinded independent central review was observed in one (5%) of 20 patients with liver disease and four (25%) of 16 with non-liver disease. Confirmed objective response rate by investigator assessment in the antitumour activity population was 30.8% (95% CI 22.1–40.6), with responses recorded in 32 of 104 patients (appendix pp 10–11). The agreement for objective response was 86.9% (53 of 61 patients) for the BRCA1 and BRCA2 population and 89.4% overall (93 of 104 patients).

Best change from baseline in sum of diameters for target lesions (blinded independent central review), PSA

assessment, and circulating tumour cell counts by HRR gene alteration (post-hoc analyses) for the antitumour activity population are shown in figure 2. Most patients in the antitumour activity population with both baseline and post-baseline assessments showed a reduction in tumour burden (67 [80%] of 84 patients), PSA level (69 [72%]



(Figure 2 continues on next page)

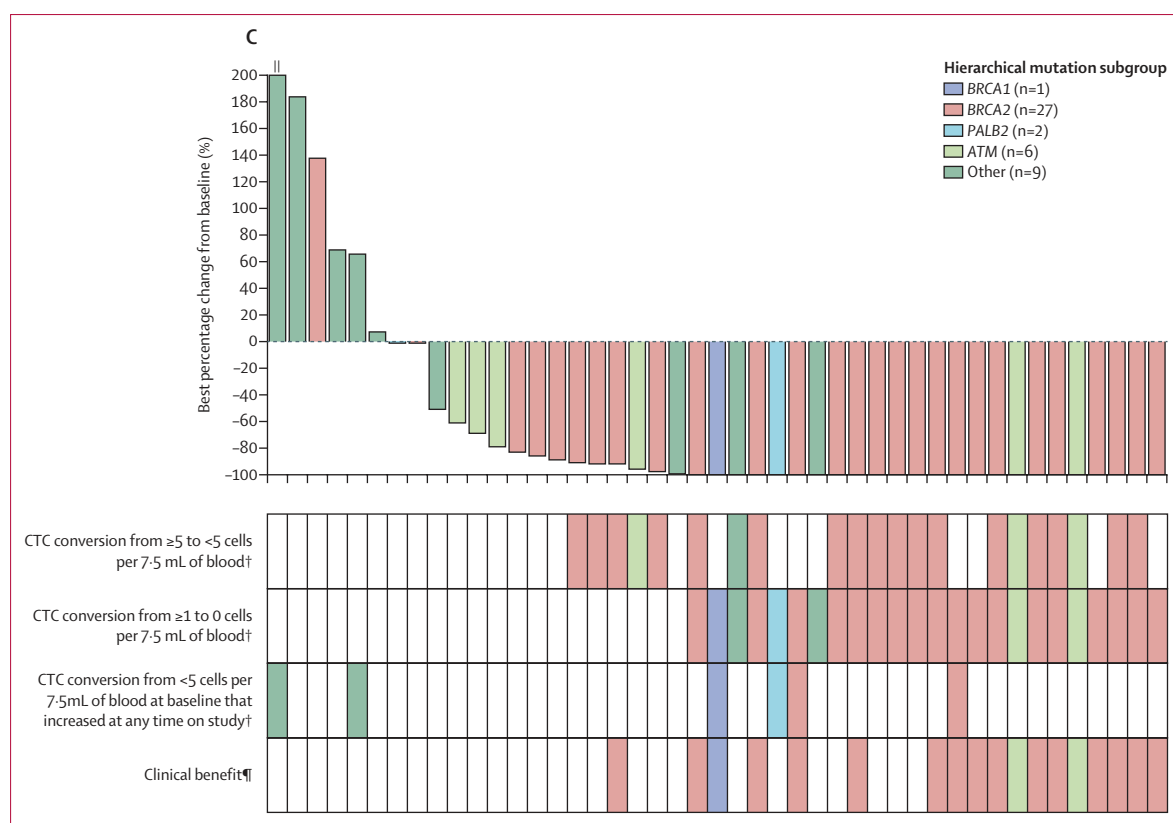


Figure 2: Best change from baseline in sum of diameters for target lesions by blinded independent central review (A), PSA assessment (B), and CTC count (C) in the antitumour activity population

Tumour alteration origin and zygosity were based on tumour tissue samples recorded under the latest screening attempt and assessable for only short variants. All analyses exclude patients who did not have baseline or post-baseline assessments. 84 participants were evaluable for sum of diameter for target lesions, 96 patients were evaluable for PSA assessment, and 45 were evaluable for CTC count. The other group includes alterations in *ATR*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, and *RAD51C*. CTC=circulating tumour cell. HRR=homologous recombination repair. PSA=prostate-specific antigen. *This patient had a *BRCA2* rearrangement along with a number of other non-HRR alterations associated with prostate cancer pathobiology or negative prognosis, or both, including but not limited to *AR* amplification, *TP53* alteration, and *HGF* amplification. †Only includes patients with a baseline CTC assessment and at least one post-baseline CTC assessment. ‡Predicted DDR-HRR gene mutational zygosity. §Patient DDR-HRR alteration origin was based on comparison of tumour with saliva variants. ¶Defined as complete response, partial response, or stable disease for at least 6 months from treatment start. ||Bar reaches 2600% but is truncated for display purposes.

of 96), and circulating tumour cell count (37 [82%] of 45), with the highest rates observed in patients with *BRCA1* or *BRCA2* alterations (47 [90%] of 52 patients for tumour burden, 50 [85%] of 59 for PSA, and 26 [93%] of 28 for circulating tumour cell count). Most evaluable patients with *PALB2* or *ATM* alterations also had a reduction in tumour burden, PSA level, and circulating tumour cell counts (figure 2). In exploratory analyses, the occurrence of some degree of reduction in tumour burden and PSA was independent of the DDR-HRR gene alteration, having germline or somatic origin, or its zygosity (figure 2). However, decreases in tumour size or PSA of 30% or more were primarily observed with homozygous alterations (figure 2). Prespecified subgroup analyses for PSA response are in the appendix (p 20). Post-hoc analyses of PSA response and circulating tumour cell conversion by hierarchical separation of HRR gene alteration group are in table 2. Post-hoc analyses of the rate of composite response and clinical benefit are shown in table 2.

Time to response and duration of response for patients with confirmed complete or partial responses by blinded independent central review are shown in figure 3A, and by investigator assessment are in the appendix (p 22), and durations of stable disease are shown in figure 3B. In the antitumour activity population, median time to objective response was 3.4 months (IQR 1.8–5.4) and median duration of response was 12.8 months (95% CI 6.5 to not evaluable; 12 patients had an ongoing response at data cutoff). Time to response and duration of response per HRR gene alteration group (post-hoc analyses) by blinded independent central review and investigator assessment are presented in the appendix (pp 12–13).

63 radiographic progression-free survival events occurred. Median radiographic progression-free survival by blinded independent central review is shown in figure 4 and by HRR gene alteration (post-hoc analyses) in the appendix (p 23). Similar results were observed for median radiographic progression-free survival by

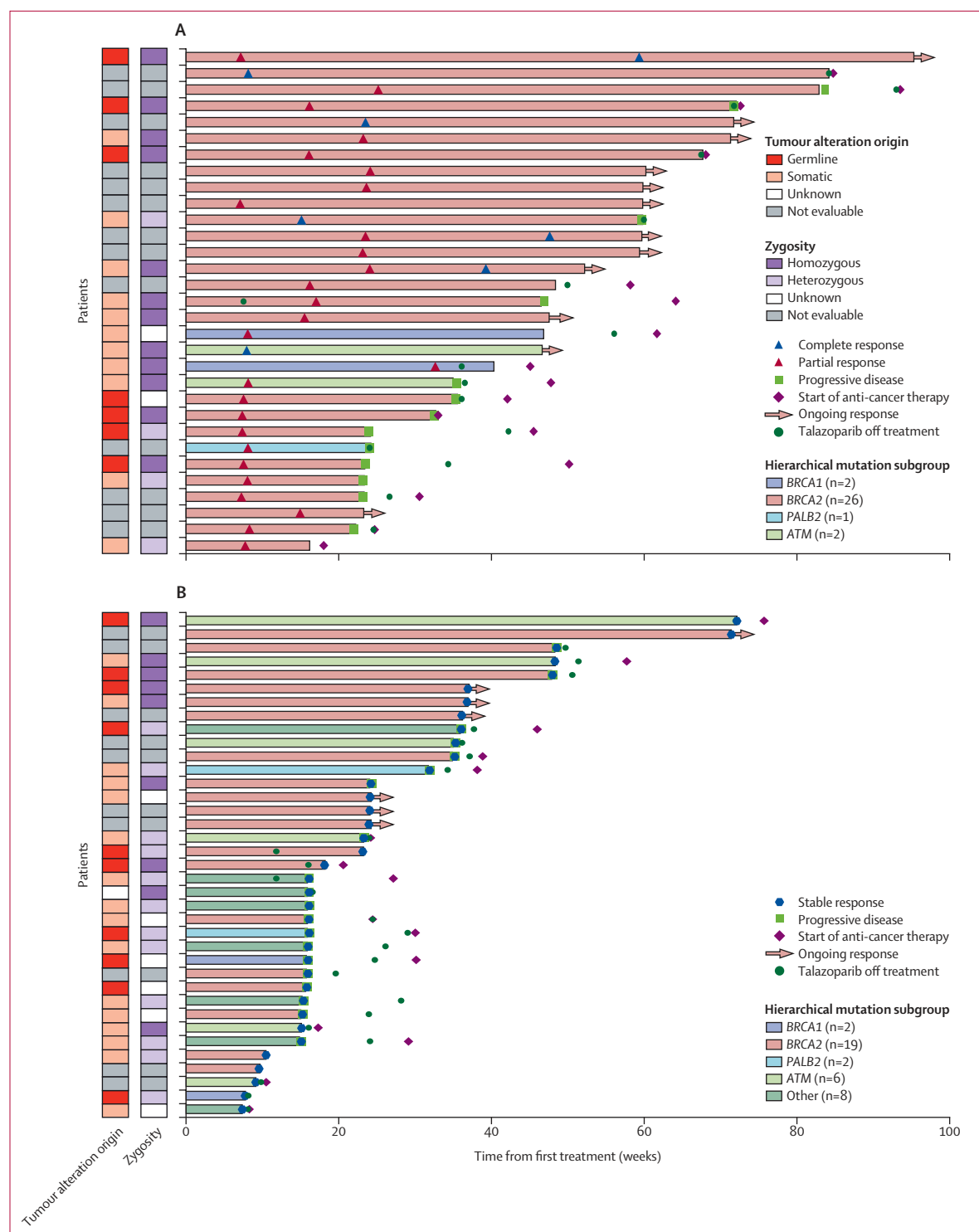


Figure 3: Time to response and duration of response by blinded independent central review in patients with confirmed complete response or partial response (n=31; A), and time to stable disease and duration of stable disease in patients with stable disease (n=37; B) in the antitumour activity population

Tumour alteration origin and zygosity were based on tumour tissue samples recorded under the latest screening attempt and assessable only for short variants. Some patients were not evaluable for tumour alteration origin and zygosity due to type of alteration (only short variants were amenable to these analyses; hence, rearrangements and copy number alterations were excluded), paucity of matched saliva data (tumour alteration origin), or inadequate tumour purity (zygosity), or a combination of these factors. HRR gene alteration origins are shown for patients evaluable for both germline (saliva) and tumour HRR gene alteration. Alteration zygosity of the 11 predefined DDR-HRR genes was predicted by somatic-germline-zygosity analysis of tumours with adequate purity. The other group includes alterations in *ATR*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, or *RAD51C*. HRR=homologous recombination repair.

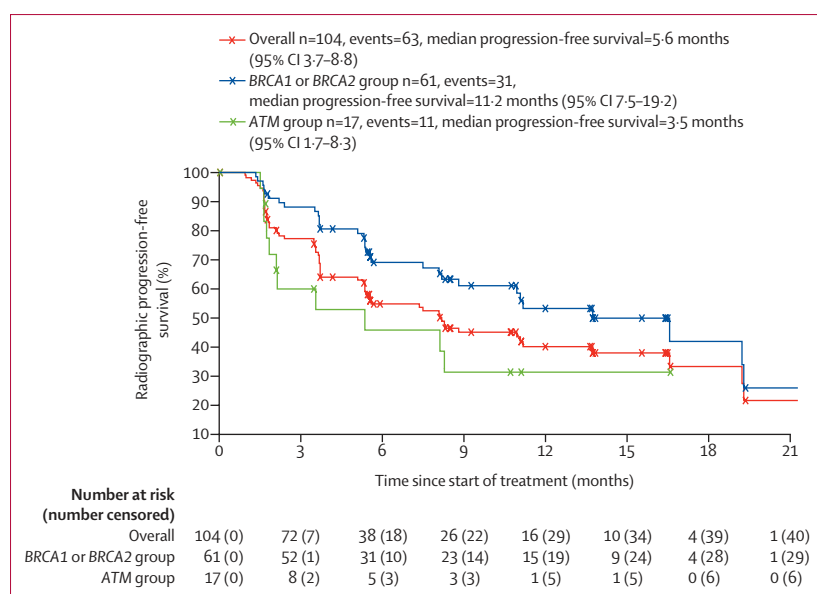


Figure 4: Radiographic progression-free survival by HRR gene altered (blinded independent central review; antitumour activity population)

We present data for BRCA1 or BRCA2 and ATM alterations because of their mutational prevalence, potential differential biology, and variation of response (appendix p 9). HRR=homologous recombination repair.

investigator assessment (appendix p 24). Median overall survival was 16.4 months (95% CI 12.2–19.9; appendix p 25) and median time to PSA progression was 9.2 months (5.6–11.1; appendix p 26). Post-hoc results by HRR gene alteration group are shown in the appendix (pp 23–26).

In exploratory analyses, 71 men in the antitumour activity population were assessable for germline and somatic tumour HRR gene alterations, of whom 25 (35%) had alterations of germline origin, 44 (62%) had alterations of somatic origin, and five (7%) had alterations of unknown origin (*ATR* and *FANCA* were not present in the germline panel). The most common alterations were *BRCA2* (13 germline, 19 somatic) and *ATM* (four germline, 11 somatic; appendix p 15). Objective responses were observed in seven (28%) of 25 men with tumours with HRR gene alterations of germline origin and in 11 (26%) of 43 men with tumours with HRR gene alterations of only somatic origin ($p=1.0$, two-sided Fisher's exact test).

92 men in the antitumour activity population had data to allow assessment of zygosity, among whom tumour HRR gene alterations were predicted to have a loss of heterozygosity in 30 (33%) men, heterozygous in 30 (33%) men, and with zygosity non-evaluable in 32 (35%) men. Objective response in tumours with HRR gene alterations with loss of heterozygosity was observed in 12 (40%) of 30 men and for those categorised as heterozygous was observed in four (13%) of 30 men (OR 4.33 [95% CI 1.06–20.94]; $p=0.039$). Objective response in tumours with evaluable *BRCA2* gene alterations with loss of heterozygosity was observed in nine (50%) of 18 men and for those categorised as

heterozygous was observed in four (44%) of nine men (OR 1.25 [0.19–8.55; $p=1.00$]). Although the number of tumours with *ATM* alterations was relatively low, tumour size reductions were typically associated with homozygous alterations (figure 2A).

In the safety population, 121 (95%) of 127 men reported any all-cause treatment-emergent adverse event (table 3). Anaemia, nausea, decreased appetite, and asthenia were the most common all-grade treatment-emergent adverse events (table 3). The most common grade 3–4 treatment-emergent adverse events (ie, occurred in $\geq 5\%$ patients) were anaemia (in 39 [31%] of 127), thrombocytopenia (11 [9%]), and neutropenia (ten [8%]; table 3); no grade 4 anaemia or neutropenia events were observed. 41 (32%) patients reported grade 3 and five (4%) patients reported grade 4 haematological treatment-emergent adverse events, and 40 (32%) grade 3 events and four (3%) grade 4 events were considered to be treatment related by the investigators. All-cause serious treatment-emergent adverse events were reported in 43 (34%) of 127 patients (appendix p 17). The most common all-cause serious adverse events (ie, that occurred in more than one patient) were pulmonary embolism (eight [6%]), anaemia (five [4%]), disease progression (four [3%]), urinary tract infection (three [2%]), pneumonia (three [2%]), and general physical health deterioration, pain, pyrexia, subdural haematoma, and platelet count decreased (each occurred in two [2%] patients). 11 (9%) patients reported treatment-related serious adverse events, which were anaemia (five [4%]), decreased platelet count (two [2%]), and asthenia, pyrexia, decreased white blood cell count, pulmonary embolism, and overdose (each one [1%] patient; a patient could report more than one adverse event). 69 all-cause deaths occurred, of which 59 (86%) were due to disease progression, two (3%) were not related to study treatment, three (4%) were reported as due to other reasons, and five (7%) were reported as due to unknown causes. Multiple causes of death could be reported for each participant. No deaths were related to talazoparib. No patients had myelodysplastic syndrome or acute myeloid leukaemia (known treatment-emergent adverse events among patients with solid tumours given talazoparib¹¹) while on study or by the end of follow-up.

All-cause treatment-emergent adverse events led to dose reductions in 33 (26%) of 127 patients and dose interruptions in 47 (37%) patients. The most common treatment-emergent adverse events leading to dose reductions were anaemia (28 [22%] of 127 patients), decreased platelet count (six [5%]), decreased neutrophil count (four [3%]), and decreased white blood cell count (three [2%]). The most common treatment-emergent adverse events leading to dose interruptions were anaemia (24 [19%]), decreased platelet count (14 [11%]), decreased neutrophil count (ten [8%]), and decreased appetite (six [5%]). 44 (35%) patients were given at least one blood transfusion (appendix p 16). All-cause treatment-emergent adverse events leading to permanent

	Grade 1-2	Grade 3	Grade 4
Any treatment-emergent adverse event	50 (39%)	57 (45%)	4 (3%)
Non-haematological			
Nausea	39 (31%)	3 (2%)	0
Decreased appetite	32 (25%)	4 (3%)	0
Asthenia	25 (20%)	5 (4%)	0
Fatigue	23 (18%)	2 (2%)	0
Constipation	22 (17%)	1 (1%)	0
Diarrhoea	21 (17%)	0	0
Peripheral oedema	20 (16%)	1 (1%)	0
Back pain	16 (13%)	1 (1%)	0
Dyspnoea	15 (12%)	2 (2%)	0
Vomiting	15 (12%)	2 (2%)	0
Dizziness	15 (12%)	0	0
Pain in extremity	10 (8%)	2 (2%)	0
Arthralgia	9 (7%)	1 (1%)	0
Bone pain	8 (6%)	1 (1%)	0
Fall	8 (6%)	1 (1%)	0
Haematuria	8 (6%)	1 (1%)	0
Headache	8 (6%)	1 (1%)	0
Musculoskeletal pain	6 (5%)	3 (2%)	0
Urinary tract infection	7 (6%)	2 (2%)	0
AST increased	6 (5%)	2 (2%)	0
Paraesthesia	7 (6%)	1 (1%)	0
Pulmonary embolism	1 (1%)	6 (5%)	0
ALT increased	6 (5%)	1 (1%)	0
Dysuria	6 (5%)	1 (1%)	0
Hypertension	3 (2%)	4 (3%)	0
Pain	6 (5%)	1 (1%)	0
Chest pain	5 (4%)	1 (1%)	0
Hypotension	5 (4%)	1 (1%)	0
Blood ALP increased	4 (3%)	1 (1%)	0
Cancer pain	2 (2%)	3 (2%)	0
γ-Glutamyltransferase increased	2 (2%)	2 (2%)	1 (1%)
Abdominal pain	3 (2%)	1 (1%)	0
Disease progression	0	0	0
Hyponatraemia	2 (2%)	2 (2%)	0
Bronchitis	2 (2%)	1 (1%)	0
Hypophosphataemia	2 (2%)	1 (1%)	0
Muscular weakness	2 (2%)	1 (1%)	0
Pneumonia	0	3 (2%)	0
Toothache	2 (2%)	1 (1%)	0
Blood potassium increased	1 (1%)	1 (1%)	0

(Table 3 continues in next column)

	Grade 1-2	Grade 3	Grade 4
(Continued from previous column)			
Cataract	1 (1%)	1 (1%)	0
Ecchymosis	1 (1%)	1 (1%)	0
General physical health deterioration	0	1 (1%)	0
Hypomagnesaemia	1 (1%)	1 (1%)	0
Spinal cord compression	1 (1%)	1 (1%)	0
Subdural haematoma	0	1 (1%)	0
Blood bilirubin increased	0	1 (1%)	0
Cardiorespiratory arrest	0	0	0
Condition aggravated	0	1 (1%)	0
Gastrointestinal infection	0	1 (1%)	0
Third nerve paresis	0	1 (1%)	0
Lymphangitis carcinomatosa	0	1 (1%)	0
Malignant neoplasm progression	0	0	0
Metastases to meninges	0	1 (1%)	0
Neoplasm progression	0	0	0
Pancreatic carcinoma	0	1 (1%)	0
Parotitis	0	1 (1%)	0
Penile pain	0	1 (1%)	0
Proctitis	0	1 (1%)	0
Radicular pain	0	1 (1%)	0
SARS-CoV-2 positive test	0	1 (1%)	0
Sepsis	0	0	1 (1%)
Haematological			
Any	22 (17%)	41 (32%)	5 (4%)
Anaemia	23 (18%)	39 (31%)	0
Thrombocytopenia	13 (10%)	7 (6%)	4 (3%)
Neutropenia	11 (9%)	10 (8%)	0
Leukopenia	12 (9%)	1 (1%)	0
Lymphopenia	4 (3%)	4 (3%)	2 (2%)

Data are n (%). Data are for events reported in at least 10% of patients for grade 1-2 events and all events for grades 3 and 4. Included data up to 28 days after the last dose of talazoparib, or before new systemic (ie, not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first. Ten grade 5 treatment emergent adverse events (ie, deaths) occurred: one due to pulmonary embolism, four due to disease progression, one due to general physical health deterioration, one due to subdural haematoma, one due to cardiorespiratory arrest, one due to malignant neoplasm progression, and one due to neoplasm progression. MedDRA version 23.0 coding dictionary applied. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. MedDRA=Medical Dictionary for Regulatory Activities.

Table 3: All-cause treatment-emergent adverse events in the safety population (n=127)

Discussion

TALAPRO-1 is an open-label, phase 2 trial of single-agent talazoparib in men with metastatic castration-resistant prostate cancers with alterations of DDR genes involved directly or indirectly in HRR and who have been heavily pretreated with novel hormone therapy and taxane chemotherapy. In this population, talazoparib had robust antitumour activity, which was most notable and durable against tumours with *BRCA1* or *BRCA2* gene alterations. Responses were also confirmed in patients with tumours

discontinuation of talazoparib were reported in 15 (12%) of 127 patients; of these discontinuations, three (20%) were due to haematological treatment-emergent adverse events (two due to decreased platelet count and one due to decreased white blood cell count), and one (7%) was due to a gastrointestinal treatment-emergent adverse event (vomiting). A complete list of adverse events leading to discontinuation of talazoparib is in the appendix (p 18).

with alterations in *PALB2* alone and *ATM* alone. Stable disease of any duration was observed in patients with alterations in *PALB2*, *ATM*, and other rarer HRR genes (*ATR*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, and *RAD51C*).

The results we report here are similar to those reported in other PARP inhibitor trials. In the phase 3 PROfound trial (NCT02987543) assessing olaparib monotherapy versus enzalutamide or abiraterone in men with metastatic castration-resistant prostate cancers with an HRR gene alteration previously treated with novel hormone therapy—an earlier disease setting than TALAPRO-1—the objective response rate in patients with *BRCA1*, *BRCA2*, or *ATM* alterations was 33·3% (28 of 84 patients) for olaparib versus 2·3% (one of 43 patients) in the control group.¹⁷ Progression-free survival and overall survival were longer with olaparib than with control (median progression-free survival: 7·4 months vs 3·6 months; median overall survival: 19·1 months vs 14·7 months).^{17,18} In the phase 2 TRITON2 trial of rucaparib (NCT02952534), patients with metastatic castration-resistant prostate cancer with HRR gene alterations and previously treated with novel hormone therapy and taxane chemotherapy had objective response rates by gene subgroup of 43·5% (27 of 62 patients) for *BRCA1* or *BRCA2*, 10·5% (two of 19 patients) for *ATM*, 11·1% (one of nine patients) for *CHEK2*, and 0% (none of ten patients) for *CDK12*.^{19,20} Median radiographic progression-free survival in men with *BRCA1* or *BRCA2* mutations was 9·0 months (95% CI 8·3–13·5) and estimated 12-month overall survival was 73·0% (95% CI 62·9–80·7).²⁰ In the phase 2 Galahad trial of niraparib (NCT02854436), involving men with metastatic castration-resistant prostate cancers with bi-allelic DNA-repair gene defects who had been previously treated with novel hormone therapy and taxane chemotherapy, the objective response rate was 41·4% for the *BRCA1* or *BRCA2* subgroup.²¹ Although antitumour activity data from these trials seem to be similar, there are important distinctions that should be considered when comparing these data, including the method of determining genomic alteration, type of DDR-HRR gene alterations eligible for enrolment, previous treatment requirements, and a requirement for measurable soft-tissue disease at study entry.

The safety profile observed so far in TALAPRO-1 is consistent with the established safety profile of talazoparib.^{22–24} The most commonly reported all-grade adverse events included anaemia, nausea, decreased appetite, and asthenia. Dose reduction of talazoparib due to adverse events occurred in 33 (26%) of 127 patients and permanent treatment discontinuation due to adverse events occurred in 15 (12%) patients, although rarely for haematological adverse events (three [2%] patients).

A previous study suggested that only a small number of patients with *ATM*-mutated metastatic castration-resistant prostate cancers derive benefit from PARP inhibitors.¹⁹ Another study reported complete loss of *ATM* occurring in 68 (11%) of 631 patients with advanced

prostate cancers was associated with increased genomic instability and variable sensitivity to PARP inhibitors.²⁵ We found that some men with *ATM*-altered metastatic castration-resistant prostate cancers benefitted from talazoparib with PSA responses and stable disease. Further studies are needed to assess whether or not the superior PARP trapping of talazoparib in comparison with other PARP inhibitor enhances its antitumour activity against tumours bearing *ATM* alterations.

In exploratory analyses, we found that tumours bearing HRR gene alterations with loss of heterozygosity were more sensitive to talazoparib than heterozygous altered tumours. This observation is consistent with reports that tumours with bi-allelic *BRCA1* or *BRCA2* alterations have higher homologous recombination deficiency scores than tumours without, including for prostate cancer, making them more susceptible to PARP inhibitors.^{26,27} In TALAPRO-1, the objective response rates in men with tumours with homozygous or heterozygous *BRCA2* alterations were encouraging (nine [50%] of 18 with homozygous and four [44%] of nine with heterozygous *BRCA2* alterations). The one patient who responded in the *PALB2* group was not evaluable for zygosity, although of the two patients who responded in the *ATM* group both exhibited homozygous alterations. The overall number of *ATM*-altered tumours was low and tumour size reduction was typically associated with homozygous *ATM* alterations. The association with a better outcome for patients with homozygous alterations versus those with heterozygous alterations could help explain the differential response among patients with alterations in different HRR genes. Loss of heterozygosity has been observed in approximately 70% of *BRCA1*-mutant and *BRCA2*-mutant prostate tumours,^{26,28} and in approximately half of *ATM*-mutant prostate tumours.²⁹ *PALB2* physically tethers *BRCA1* to *BRCA2* during HRR, and *PALB2* bi-allelic inactivation or loss is associated with homologous recombination deficiency that is similar to *BRCA2* loss; hence, *PALB2* alterations potentially have functional equivalence to *BRCA1* or *BRCA2* alterations in sensitisation to PARP inhibition.³⁰ *ATM* alterations have more complex effects on HRR than *BRCA* and *PALB2* alterations, and *ATM* is also implicated in replication fork stability and cell cycle progression.³¹ We found that germline versus somatic origin of HRR alterations had no association with response, which is consistent with other results.²⁰

Our study has several limitations, including the absence of a control group and potential investigator bias due to the open-label design. The trial was not designed to assess differences across the HRR gene alteration subgroups and, given the absence of a control group, whether differences between such subgroups are due to differences in treatment effect or in prognosis cannot be determined. Investigator bias was addressed by using blinded independent central review to assess objective response as the primary endpoint. Other limitations include the small

sample size, the heterogeneity of the study population with respect to the different number and types of treatment received before talazoparib, and the potential that we did not identify all qualifying tumour HRR gene alterations. Another limitation is that the exploratory analysis of alteration origin and zygosity prediction could only be done for short variants; therefore, these results need be confirmed in future appropriately powered studies. Notably, fewer patients were evaluable for circulating tumour cell conversion than for other biomarkers like PSA, reflecting logistical challenges related to real-time shipment of these time-sensitive samples, coupled with shipping delays and a laboratory closure due to the COVID-19 pandemic.

In summary, the benefit–risk profile in TALAPRO-1 suggests that talazoparib might provide an effective therapy for advanced metastatic castration-resistant prostate cancers with DDR alterations either directly or indirectly associated with HRR. We found evidence of durable antitumour activity with a favourable benefit–risk profile in men who had been pretreated with novel hormone therapy and taxane chemotherapy. These results support further assessment of talazoparib in the ongoing phase 3 TALAPRO-2 trial (NCT03395197) comparing talazoparib plus enzalutamide as a first-line treatment in men with advanced metastatic castration-resistant prostate cancers with or without HRR gene alterations³² and the recruiting phase 3 TALAPRO-3 trial (NCT04821622) of talazoparib plus enzalutamide in men with metastatic castration-sensitive prostate cancer with HRR gene alterations.

Contributors

JSdB contributed to the literature searches, study design, data collection, data analysis, data interpretation, development of figures, and writing, reviewing, and approving of the manuscript. NM, GVS, EC, ASte, FS, CB, and IMvO contributed to data collection, data interpretation, and writing, reviewing, and approving of the manuscript. TD contributed to data collection and analysis, and writing, review, editing, and approving of the manuscript. ASti contributed to data validation, including accessing underlying data, investigation, resources, recruited patients, data visualisation, and writing, review, editing, and approving of the manuscript. MTF contributed to data interpretation and writing, reviewing, and approving of the manuscript. CSH contributed to the literature searches, study design, data interpretation, and writing, reviewing, and approving of the manuscript. ADL contributed to the study design, data analysis, data interpretation, development of figures, and writing, reviewing, and approving of the manuscript. MM contributed to the data analysis, data interpretation, and reviewing and approving of the manuscript. H-CC contributed to the study statistical design, data analysis, data interpretation, writing and approving of the manuscript, and verifying the underlying data. CGH contributed to the study design, data analysis, data interpretation, writing and approving of the manuscript, and verifying the underlying data. AC contributed to the study design, data analysis, data interpretation, and writing and approving of the manuscript. KF contributed to the study design, data interpretation, and reviewing and approving of the manuscript. All authors had full access to the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. All authors had access to all the original data tables and figures used in the paper and JSdB was responsible for reviewing all the data to go into the formal clinical study report, signing the clinical study report signatory page that was sent to regulators, and the tables and figures from the manuscript.

Declaration of interests

JSdB reports consulting fees from Astellas Pharma, AstraZeneca, Bayer, BioXcel Therapeutics, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eisai, Genmab, GSK, Janssen Oncology, Menarini Silicon Biosystems, Merck Serono, MSD, Orion Pharma GmbH, Pfizer, Roche/Genentech, Sanofi, Sierra Oncology, and Taiho Pharmaceutical; funding or support to his institution for laboratory and clinical work from Astex Pharmaceuticals, AstraZeneca, Bayer, Celgene, Cellcentric, Daiichi Sankyo, Genentech, GSK, MedImmune, Medivation, Merck Serono, MSD, Orion Pharma GmbH, Sanofi, Sierra Oncology, and Taiho Pharmaceutical; honoraria from Astellas Pharma, AstraZeneca, BioXcel Therapeutics, Daiichi Sankyo, Janssen Oncology, Menarini Silicon Biosystems, Pfizer, Roche/Genentech, Sanofi, and Sierra Oncology; travel, accommodation, and expenses from Astellas Pharma, AstraZeneca, Genmab, GSK, Orion Pharma GmbH, Qiagen, Sanofi, Taiho Pharmaceutical, and Vertex; and is named as an inventor, with no financial interest, on a patent (number 8,822,438). NM reports consulting fees from Astellas Pharma, Bristol-Myers Squibb, Genzyme, Janssen-Cilag, MSD Oncology, and Roche; funding or clinical trial and laboratory research support to his institution from Astellas Pharma, Janssen-Cilag, Pfizer, Roche/Genentech, and Sanofi; and accommodation and expenses from Astellas Pharma, Bristol-Myers Squibb, MSD Oncology, and Roche. GVS reports payment or honoraria from AstraZeneca, Eli Lilly, MSD, Pfizer, Roche, Johnson & Johnson, and Takeda; consulting fees from Eli Lilly, BeiGene, and AstraZeneca; institutional grants or contracts from MSD and Tesaro; support for attending meetings and travel from Bayer; and is a past president of the International Association for the Study of Lung Cancer. EC reports consulting fees to her institution from Astellas Pharma, AstraZeneca, Bayer, Clovis, Janssen, MSD, and Pfizer; payment or honoraria to herself from Astellas Pharma, AstraZeneca, Bayer, Clovis, Janssen, Pfizer, and Roche; grants or contracts to her institution from AstraZeneca, Bayer, Janssen, and Synlab; support for attending meetings and travel from AstraZeneca, Bayer, and Janssen; and is an unpaid member of the European Society for Medical Oncology faculty. TD reports participation on a Data Monitoring Safety Board or Advisory Board for Advanced Accelerator Applications, Bayer, Bristol-Myers Squibb, Exelixis, and Janssen. ASte reports consulting fees (personal) from Ipsen Pharma, Janssen, and Roche; participation on a Data Safety Monitoring Board or Advisory Board for Astellas Pharma, AstraZeneca, Ferring, and Synergo; and research grant funding from Amgen, Ipsen Pharma, and Karl Storz AG. CSH reports consulting fees from AstraZeneca, Bayer, Blue Earth Diagnostics, Clovis Oncology, Ferring, Hinova Pharmaceuticals, Janssen, and Pfizer; funding for research work to her institution from Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, Clovis Oncology, eFFECTOR Therapeutics, Emergent BioSolutions, Ferring, Medivation, Pfizer, and Roche; honoraria from Astellas Pharma; and accommodation and expenses from Bayer, Blue Earth Diagnostics, Clovis Oncology, Ferring, Hinova Pharmaceuticals, Janssen Oncology, and Pfizer. FS reports consulting fees to himself from Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Myovant, Novartis, Pfizer, and Sanofi; grants or contracts to his institution from Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Myovant, Novartis, Pfizer, and Sanofi; and payment or honoraria from Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Myovant, Novartis, Janssen, Pfizer, and Sanofi. CB reports consulting fees from Astellas Pharma, Janssen, Merck, and Pfizer. IMvO reports consulting fees from Astellas Pharma, Bayer, Janssen, and MSD/AstraZeneca; grants or contracts from Astellas Pharma, Bayer, Janssen, and MSD/AstraZeneca; payment or honoraria from Astellas Pharma, Bayer, Janssen, and MSD/AstraZeneca; and support for attending meetings and travel from Astellas Pharma. ADL, MM, H-CC, CGH, and AC are employees of Pfizer and hold Pfizer stock and stock options. KF reports payment or honoraria to his institution from Astellas Pharma, Bayer, Janssen, and Sanofi, and participation on a Data Monitoring Safety Board or Advisory Board to his institution for Amgen, Astellas Pharma, AstraZeneca, Bayer, Clovis, Janssen, Pfizer, and Sanofi. ASti and MTF declare no competing interests.

Data sharing

Upon request, and subject to specific criteria, conditions, and exceptions, which are available online, Pfizer will provide access to individual de-identified participant-level data from Pfizer-sponsored global

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interventional clinical studies conducted for medicines, vaccines, and medical devices for indications that have been approved in the USA or Europe and in programmes that have been terminated (eg, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data can be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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