



Talazoparib plus enzalutamide in men with HRR-deficient metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial

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Summary

Background Metastatic castration-resistant prostate cancer remains incurable and is particularly aggressive in patients with alterations in DNA damage repair genes involved directly or indirectly in homologous recombination repair (HRR). In the primary analysis of TALAPRO-2, talazoparib plus enzalutamide significantly improved radiographic progression-free survival (rPFS) versus enzalutamide plus placebo in patients with metastatic castration-resistant prostate cancer harbouring HRR gene alterations. At primary analysis, overall survival was immature. Here we report final prespecified overall survival analysis, updated rPFS, safety, and patient-reported outcomes in the HRR-deficient cohort of TALAPRO-2.

Methods TALAPRO-2 is an ongoing international, randomised, double-blind, placebo-controlled phase 3 trial. The HRR-deficient cohort included randomly assigned patients from 142 hospitals, cancer centres, and medical centres in 26 countries; the study included men aged at least 18 years (≥ 20 years in Japan) with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer, progressive disease at study entry, and no previous life-prolonging systemic therapy for castration-resistant prostate cancer, but were receiving ongoing androgen deprivation therapy. Patients were prospectively assessed for tumour HRR gene alterations and randomly assigned (1:1) to once-daily oral talazoparib 0.5 mg plus enzalutamide 160 mg or enzalutamide plus placebo stratified by prior treatment (yes vs no) for castration-sensitive disease. The sponsor, patients, and investigators were masked to talazoparib or placebo, whereas enzalutamide was open label. The primary endpoint was rPFS (time from randomisation to radiographic progression or death, whichever occurred first) by blinded independent central review, and overall survival (time from randomisation to death due to any cause) was a key alpha-protected secondary endpoint, both assessed in the intention-to-treat population. Follow-up for overall survival was intended to continue until the planned final analysis. For statistical significance at the final overall survival analysis, the two-sided p value from the stratified log-rank test needed to be 0.024 or less based on a group sequential design with O'Brien–Fleming spending function. Safety was assessed in patients who had received at least one study drug dose. The trial is registered with ClinicalTrials.gov, NCT03395197.

Findings Between Dec 18, 2018, and Jan 20, 2022, 399 patients with HRR-deficient metastatic castration-resistant prostate cancer were randomly assigned (200 [50%] to talazoparib plus enzalutamide and 199 [50%] to enzalutamide plus placebo). At a median follow-up of 44.2 months (IQR 36.0–50.8), treatment with talazoparib plus enzalutamide resulted in a statistically significant improvement in overall survival versus enzalutamide (hazard ratio [HR] 0.62 [95% CI 0.48–0.81]; two-sided $p=0.0005$); median overall survival 45.1 months (95% CI 35.4–not reached) in the talazoparib group versus 31.1 months (27.3–35.4) in the control group. In the subgroup of patients with *BRCA1/2* alterations ($n=155$ [39%]), median overall survival was not reached for talazoparib plus enzalutamide versus 28.5 months for enzalutamide (HR 0.50 [95% CI 0.32–0.78]; $p=0.0017$); 4-year overall survival rates were 53% in the talazoparib group versus 23% in the control group. In patients without *BRCA1/2* alterations ($n=244$ [61%]), median overall survival was 42.4 months for talazoparib plus enzalutamide versus 32.6 months for enzalutamide (HR 0.73 [95% CI 0.52–1.02]; $p=0.066$). Updated rPFS favoured talazoparib plus enzalutamide versus enzalutamide (HR 0.47 [95% CI 0.36–0.61]; $p<0.0001$; median rPFS 30.7 vs 12.3 months). No new safety signals were identified; most common adverse events of grade 3 or higher with talazoparib plus enzalutamide were anaemia (86 [43%] patients) and neutropenia (39 [20%] patients).

Interpretation Talazoparib plus enzalutamide resulted in statistically significant and clinically meaningful improvement in survival versus enzalutamide plus placebo, further supporting this combination as a standard of care in HRR-deficient metastatic castration-resistant prostate cancer.

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Research in context

Evidence before this study

Before the TALAPRO-2 trial was started in December, 2017, we searched PubMed for relevant preclinical or clinical research published on DNA damage repair, homologous recombination repair (HRR), so-called BRCAness, novel hormonal therapies or androgen receptor pathway inhibitors (ARPIs), androgen receptor signalling inhibition, poly(ADP) ribose polymerase (PARP) inhibitors, and advanced prostate cancer. The worldwide incidence of prostate cancer is rising, and metastatic castration-resistant prostate cancer remains a lethal disease despite approvals of new agents. Therapies targeting androgen receptor signalling together with androgen deprivation therapy are the mainstay of standard of care for first-line treatment of metastatic castration-resistant prostate cancer. The prognosis is particularly poor for patients with metastatic castration-resistant prostate cancer harbouring HRR gene alterations. Since 2017, results from phase 2/3 investigational trials of PARP inhibitor monotherapy (olaparib, rucaparib, and talazoparib) have indicated efficacy of these agents in patients with BRCA-altered or HRR-altered (including BRCA) metastatic castration-resistant prostate cancer who had previously received treatment for metastatic castration-resistant prostate cancer. Two randomised phase 3 trials, PROpel (NCT03732820) and MAGNITUDE (NCT03748641), which were conducted in parallel with the current study, investigated the combination of a PARP inhibitor (olaparib and niraparib, respectively) with the androgen biosynthesis inhibitor abiraterone acetate plus prednisone (or prednisolone in PROpel; AAP) as first-line treatment for metastatic castration-resistant prostate cancer versus AAP plus placebo. Results from the primary analysis of MAGNITUDE showed improved radiographic progression-free survival (rPFS) with niraparib plus AAP versus AAP plus placebo in patients with HRR-altered metastatic castration-resistant prostate cancer. In exploratory subgroup analysis of PROpel, rPFS benefit was noted with olaparib plus AAP versus AAP plus placebo in patients with HRR-altered metastatic castration-resistant prostate cancer. Results from the final overall survival analysis of PROpel and the interim and final analyses of MAGNITUDE showed differences in overall survival benefits for the combination versus AAP alone. In the subgroup of patients with HRR gene alterations in PROpel, olaparib plus AAP showed overall survival benefit versus AAP alone, although these analyses were not powered for statistical significance. The second interim analysis of the HRR-deficient cohort in MAGNITUDE showed no overall survival benefit for niraparib plus AAP versus AAP alone in patients with HRR gene alterations.

Added value of this study

The previously reported primary analysis of the prospectively assessed HRR-deficient cohort of TALAPRO-2 showed a statistically significant improvement in rPFS with talazoparib plus enzalutamide compared with enzalutamide plus placebo, as well as improvements in other secondary endpoints. In this prespecified analysis of the key alpha-protected secondary endpoint of overall survival of TALAPRO-2, talazoparib plus enzalutamide resulted in a statistically significant and clinically meaningful improvement in overall survival versus enzalutamide plus placebo in patients with metastatic castration-resistant prostate cancer harbouring tumour HRR gene alterations. Additionally, exploratory analyses indicated benefit of the talazoparib plus enzalutamide combination in subgroups of patients with or without tumour BRCA1/2 alterations, which extends the evidence of PARP inhibitor plus ARPI efficacy beyond BRCA1/2 alterations to non-BRCA1/2 HRR gene alterations. Exploratory post-hoc analyses reveal efficacy benefits across multiple individual HRR gene alteration subgroups, including among patients with tumour CDK12m, for whom PARP inhibitors had previously shown little benefit. No new safety signals were reported with long-term follow-up. These results add to our understanding of the efficacy of talazoparib plus enzalutamide in patients with metastatic castration-resistant prostate cancer harbouring tumour HRR gene alterations.

Implications of all the available evidence

As described previously, the overall survival results from the PROpel and MAGNITUDE trials differ from those reported in TALAPRO-2, the reasons for which are yet to be understood but might be related to differences in the characteristics of the individual PARP inhibitors (eg, PARP trapping ability) or the ARPI partner, the trial design (retrospectively or prospectively assessed HRR gene alterations), or differences in the dosing of these agents. Together with the results from the unselected cohort (reported separately), these data indicate that TALAPRO-2 is the only phase 3 trial to date to show statistically significant overall survival improvement with a PARP inhibitor plus ARPI combination versus an ARPI alone in patients with metastatic castration-resistant prostate cancer harbouring prospectively assessed tumour HRR gene alterations, as well as in unselected patients with metastatic castration-resistant prostate cancer. These data further establish the combination of talazoparib plus enzalutamide as a standard of care for patients with metastatic castration-resistant prostate cancer harbouring tumour HRR gene alterations.

Introduction

The annual incidence of prostate cancer in 2020 was 1·4 million cases globally, and projections indicate that this incidence will roughly double to 2·9 million cases in 2040.¹ About 10–20% of patients with prostate cancer develop castration-resistant disease within about 5 years of follow-up.² Metastatic castration-resistant prostate

cancer, comprising 1–2% of all prostate cancer cases,³ is the most lethal stage of the disease, and survival outcomes remain poor despite the standard use of androgen receptor pathway inhibitors (ARPIs) in addition to androgen deprivation therapy.^{1,4} In the roughly 25% of patients with advanced prostate cancer who harbour alterations in DNA damage response genes

directly or indirectly involved with homologous recombination repair (HRR),^{5,6} the disease course is more aggressive and patients have a worse prognosis compared with those without HRR gene alterations.^{7–9} Median survival times following ARPIs as initial treatment for metastatic castration-resistant prostate cancer were shown to range from 25 months to 29 months in patients with metastatic castration-resistant prostate cancer harbouring HRR gene alterations,^{7,10} compared with 33 months to 36 months in unselected patients.^{11–14} *BRCA1/2* alterations, found in 10–12% of patients with metastatic castration-resistant prostate cancer,^{5,6} were found to be associated with even shorter survival times with ARPI treatment (median 18–23 months).^{7,9,10} Together, these data reinforce the need for additional therapies in patients with metastatic castration-resistant prostate cancer harbouring HRR gene alterations.

Tumours with HRR gene alterations are sensitive to treatment with poly(ADP) ribose polymerase (PARP) inhibitors, and in phase 2/3 clinical trials, antitumour responses have been observed in patients with metastatic castration-resistant prostate cancer harbouring tumour HRR gene alterations who have previously received at least one systemic therapy for castration-resistant disease.^{15–17} However, evidence suggests that effective treatments administered earlier in the disease course are likely to have the greatest impact on long-term outcomes in such patients.⁷ As shown in the phase 3 trials of MAGNITUDE (niraparib plus abiraterone acetate plus prednisone [AAP] vs AAP alone) and TALAPRO-2 (talazoparib plus enzalutamide vs enzalutamide alone), initial treatment of HRR-altered metastatic castration-resistant prostate cancer with PARP inhibitor and ARPI combinations has resulted in significant improvement in radiographic progression-free survival (rPFS) versus the ARPI backbone alone.^{18,19} In exploratory subgroup analyses of HRR-deficient patients in the phase 3 PROpel study (olaparib plus abiraterone acetate plus prednisone or prednisolone [AAP] vs AAP alone), there was also a trend in favour of the combination for rPFS.²⁰ However, an overall survival benefit was not found with niraparib plus AAP compared with AAP in patients harbouring HRR gene alterations in either the primary or subsequent analyses of MAGNITUDE.^{19,21,22} Although the final overall survival analysis of PROpel in the HRR-deficient population reported an overall survival benefit for olaparib plus AAP versus AAP, these post-hoc exploratory subgroup analyses were not powered for statistical significance.²³

TALAPRO-2 is a phase 3 trial evaluating the potent PARP inhibitor and PARP trapper talazoparib,²⁴ in combination with the ARPI enzalutamide,²⁵ versus enzalutamide with placebo as initial treatment for metastatic castration-resistant prostate cancer in patients receiving ongoing androgen deprivation therapy.^{18,26,27}

In the primary analysis of TALAPRO-2, treatment with talazoparib plus enzalutamide resulted in a significant

improvement in the alpha-independent primary endpoint, rPFS, versus enzalutamide plus placebo in the HRR-deficient population (hazard ratio [HR] 0.45 [95% CI 0.33–0.61]; $p < 0.0001$; median not reached vs 13.8 months).¹⁸ At the time of the primary analysis (data cutoff Oct 3, 2022), results from the alpha-protected key secondary endpoint of overall survival were immature and favoured talazoparib plus enzalutamide.¹⁸ Here we report the results from the final prespecified alpha-controlled analysis for overall survival (data cutoff Sept 3, 2024), which also includes a descriptive update of rPFS, extended safety follow-up, and updated global health status (GHS)/quality of life (QoL) for the HRR-deficient population (cohort 2) from TALAPRO-2. Results from the unselected cohort 1 population are reported elsewhere.²⁸

Methods

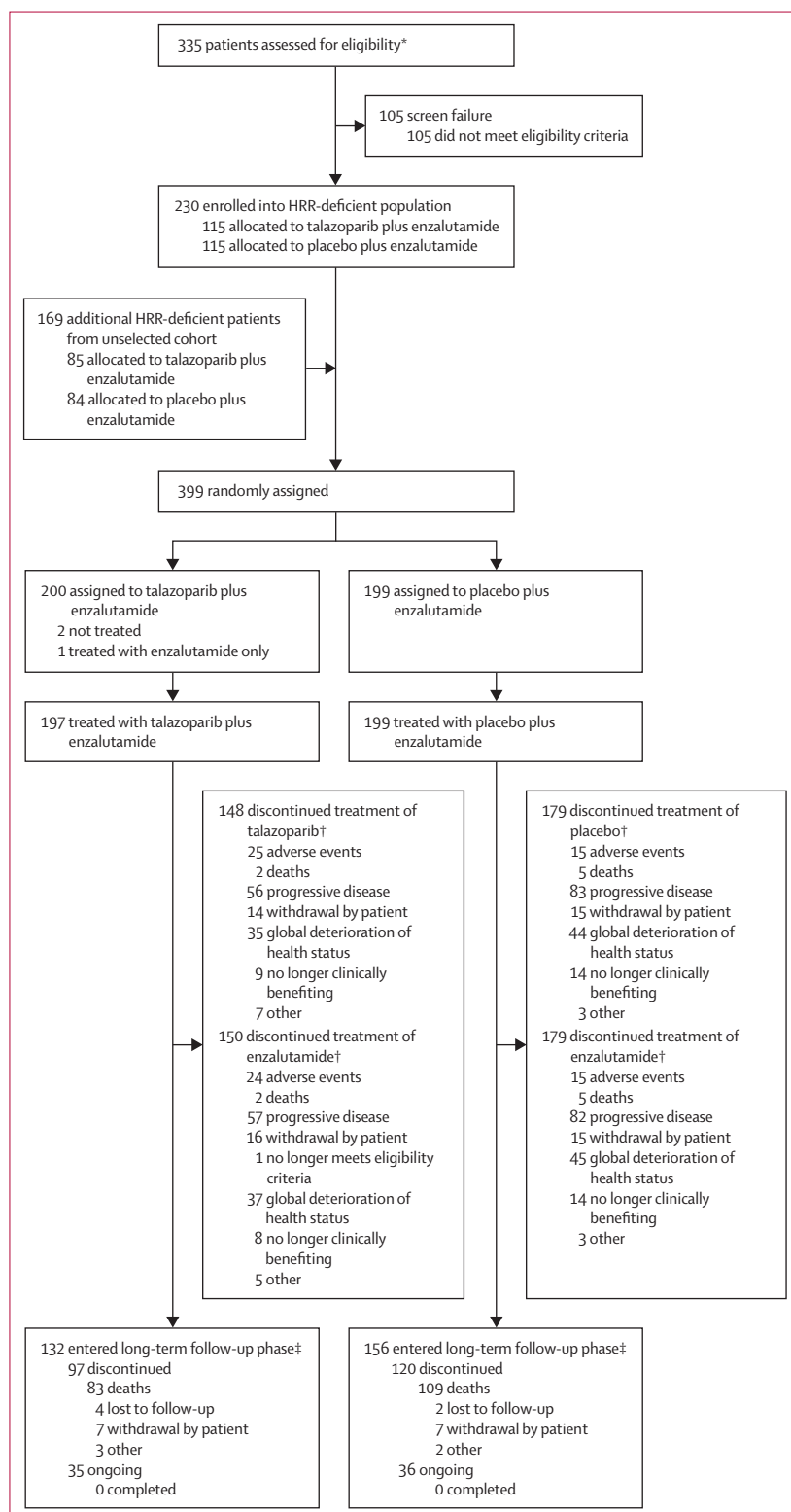
Study design and participants

The study design, eligibility criteria, and methods of TALAPRO-2 have been published previously.²⁶ TALAPRO-2 is an ongoing double-blind, randomised, placebo-controlled, multinational trial, which recruited patients in the HRR-deficient cohort from 142 hospitals, cancer centres, and medical centres in 26 countries in North America, Europe, Israel, South America, South Africa, and the Asia-Pacific region.²⁶ The protocol has been published previously and can be found in the appendix of the primary paper.¹⁸

Eligibility criteria included ongoing androgen deprivation therapy, asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer with HRR gene alterations, progressive disease, and no previous life-prolonging systemic therapy for castration-resistant prostate cancer (except for androgen deprivation therapy [required in patients who had not received bilateral orchiectomy] and first-generation antiandrogens).²⁶ Previous docetaxel and abiraterone or orteronel in the castration-sensitive setting were allowed. Patients who received previous enzalutamide, apalutamide, or darolutamide for prostate cancer were excluded. A full list of criteria is in the appendix of the primary paper.¹⁸

Before randomisation, all patients consented to have solid tumour tissue (de novo or archival [preserved by formalin fixation and paraffin embedding]) or blood-based samples, or both, prospectively assessed for HRR gene alterations (*ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, and *RAD51C*) using clinical trial assays based on FoundationOne CDx or FoundationOne Liquid CDx.²⁹ These tests are next-generation sequencing-based in vitro diagnostic tests that use targeted high-throughput hybridisation-based capture technology (Foundation Medicine, Cambridge, MA, USA).²⁹ Patients were considered HRR-deficient if they had at least one alteration in at least one of these 12 genes.¹⁸ Historical results of tumour tissue testing based on FoundationOne or FoundationOne CDx could also be

used. A protocol amendment (Feb 26, 2020) allowed concurrent prospective circulating tumour DNA (ctDNA) and tumour tissue testing.



All patients were prospectively assessed for HRR alterations in tumour tissue before randomisation and enrolled sequentially in two cohorts. The first 805 patients were enrolled (cohort 1) in an unselected cohort for HRR gene alterations (169 HRR gene alterations and 636 no HRR gene alterations or unknown; figure 1). The 169 patients with HRR gene alterations enrolled in the unselected cohort were combined with the subsequently enrolled 230 patients with HRR gene alterations to form cohort 2, the HRR-deficient population (n=399; figure 1).^{18,27}

The TALAPRO-2 trial was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local laws. The protocol and amendments were approved by the institutional review board and independent ethics committee for each site. This study was initially approved by the University of Utah Institutional Review Board (IRB 00105905) on Oct 3, 2018, with approval renewed yearly, including a most recent approval date of Aug 7, 2024). For a full list of independent ethics committees or institutional review boards that provided study approval, see the initial publication of the first interim analysis results for the HRR-deficient population of TALAPRO-2.¹⁸ All patients provided written informed consent.¹⁸

Sites were instructed that study participants should self-report both ethnicity and race, with ethnicity being asked before race. If the participant refused to provide either their ethnicity or race, or if local laws prohibited collection of these data, the sites were to record as “not reported”.

Randomisation and masking

Patients with HRR-deficient tumours were randomly assigned (1:1) to oral talazoparib 0.5 mg (0.35 mg if moderate renal impairment was present) plus oral enzalutamide 160 mg once daily (talazoparib group) or enzalutamide 160 mg once daily plus placebo (control group) by site personnel, using a centralised interactive web response system and a permuted block size of four for each stratum. Randomisation was stratified by previous second-generation ARPI (abiraterone or orteronel) or docetaxel, or both, for castration-sensitive prostate cancer (yes vs no). Formal crossover from the control group to the talazoparib group was not permitted.

Figure 1: Trial profile

HRR=homologous recombination repair. *The number of patients has been updated from the primary analysis to address a programming error in which 19 patients from the China extension cohort had been included in the clinical study report. †148 patients in the talazoparib plus enzalutamide group discontinued treatment of both talazoparib and enzalutamide. 179 patients in the placebo plus enzalutamide arm discontinued treatment of both placebo and enzalutamide. ‡Long-term follow-up began after safety follow-up and occurred every 8 weeks until week 25 and every 12 weeks thereafter until death, patient withdrawal of consent for follow-up, or study termination.

The sponsor, patients, and investigators were masked to talazoparib or placebo, and enzalutamide was open label (see appendix p 3 for additional details on study blinding procedures).

Procedures

Patients in the talazoparib group received talazoparib plus enzalutamide as previously described.^{18,27} Patients in the control group received matched placebo plus enzalutamide. Patients were to remain on blinded treatment until radiographic progression assessed by blinded independent central review (BICR), an adverse event leading to permanent discontinuation, patient decision to discontinue treatment, or death. Treatment beyond radiographic progression was permitted in patients who per the investigators' opinion were continuing to derive benefit from treatment.

The schedule and timing of radiographic, prostate-specific antigen (PSA), and safety assessments during the treatment period have been previously published.^{18,27} Briefly, study assessment visits were every 2 weeks up to week 17, every 4 weeks up to week 53, every 8 weeks thereafter while on study drug, then 28 days after discontinuation of all study treatments or before initiation of a new antineoplastic or investigational therapy, whichever occurred first. Imaging scans (CT of chest, CT or MRI of abdomen and pelvis, and whole-body bone scan) were done every 8 weeks until week 25 and every 12 weeks thereafter. Survival status was monitored through long-term follow-up, every 8 weeks until week 25 and every 12 weeks thereafter, until the patient died or withdrew consent, or was lost to follow-up, or the study was terminated. For overall survival, follow-up was planned to continue until the planned final overall survival analysis. Additional information regarding patient-reported outcome assessments is in the supplemental methods (appendix p 3).

Safety follow-up continued for 28 days after permanent treatment discontinuation of all study treatments or before initiation of a new antineoplastic or investigational therapy, whichever occurred first. Long-term follow-up began after safety follow-up and occurred every 8 weeks until week 25 and every 12 weeks thereafter until death, patient withdrawal of consent for follow-up, or study termination. See the previously published protocol for full details on the schedule of assessments during the reporting period and long-term follow-up.²⁷

Outcomes

The primary endpoint of rPFS by BICR per Response Evaluation Criteria in Solid Tumours (RECIST version 1.1; soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (PCWG3; bone disease) has previously been reported.¹⁸ A descriptive update of rPFS data is reported in this paper.

The key secondary alpha-protected prespecified endpoint of overall survival was defined as the time from

randomisation to death due to any cause. Patients last known to be alive were censored at the date of last contact. Prespecified exploratory subgroup analyses for overall survival were performed by baseline characteristics to test treatment effect within the subgroups: age (<70 years vs ≥70 years), geographical region (Asia, EU and UK, North America, or rest of the world), Eastern Cooperative Oncology Group performance status (0 vs 1), Gleason score (<8 vs ≥8), stage at diagnosis (M0 vs M1), type of progression (PSA only vs imaging-based with or without PSA progression), baseline PSA (<median vs ≥median), site of metastasis (bone only vs soft tissue only vs both bone and soft tissue), and previous taxane or ARPI for castration-sensitive prostate cancer (yes vs no). Post-hoc analyses of overall survival were also performed based on subgroups defined by prospective HRR gene test results: by *BRCA* alteration status (*BRCA1/2*-altered by either ctDNA or tissue vs non-*BRCA1/2*-altered). Post-hoc exploratory analyses of efficacy by gene are described in the appendix (p 3). Updated analyses from other secondary endpoints included objective response rate (in patients with measurable soft tissue disease at baseline per RECIST 1.1 and confirmed by follow-up radiographic assessment at least ≥4 weeks later with no evidence of confirmed bone disease progression on repeated bone scans ≥6 weeks apart per PCWG3 criteria) and duration of soft tissue response (both by BICR); proportion of patients with PSA response of 50% or greater (confirmed by a second consecutive value ≥21 days later); time to PSA progression (defined as a ≥25% increase in PSA with an absolute increase of ≥2 ng/mL above nadir and confirmed by a consecutive test ≥21 days later); time from randomisation to initiation of cytotoxic chemotherapy; time to initiation of subsequent antineoplastic therapy; time to first symptomatic skeletal event; time to opiate use for prostate cancer pain (to be reported separately); time to disease progression (investigator-assessed) on the first subsequent antineoplastic therapy for prostate cancer or death; extended follow-up safety assessments (incidence of adverse events characterised by type; severity [graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03]); and time to definitive deterioration in and estimated mean change from baseline in cancer-specific GHS/QoL, functioning, and symptom scores per the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). Additional secondary endpoints (patient-reported outcomes and pharmacokinetics) will be reported separately.

Statistical analysis

Efficacy was analysed in the HRR-deficient intention-to-treat population. Approximately 380 patients were to be enrolled in the HRR-deficient cohort. For the primary endpoint of rPFS and the key secondary endpoint of overall survival, alpha was split equally between the

See Online for appendix

unselected and HRR-deficient populations to maintain overall type I error at or below a one-sided alpha level of 0.025. The prespecified final analysis of alpha-protected overall survival in the HRR-deficient population occurred at the time of the final analysis of overall survival in the unselected population (data cutoff Sept 3, 2024).

Sample size and power calculations were based on a stratified log-rank test and were done using the software package East 6 (Cytel, Cambridge, MA, USA). For the primary comparison in the HRR-deficient population, 224 progression-free survival events based on a Lan DeMets α -spending function would provide 85% power to detect an HR of 0.64 using a one-sided stratified log-rank test at a significance level of 0.0125. The prespecified first interim analysis of rPFS occurred after 170 events in the HRR-deficient population. The HRR-deficient cohort would be stopped for efficacy if the efficacy boundary was crossed. Overall survival was tested only if the rPFS results showed statistically significant improvement in a hierarchical stepwise procedure to preserve the overall type I error. As the efficacy boundary ($p \leq 0.0038$) was crossed at this interim analysis, this analysis became the final analysis for rPFS and an interim analysis of overall survival was done.¹⁸ There was no second interim analysis of overall survival planned for the HRR-deficient population. A final analysis of overall survival in the HRR-deficient population was planned at the same time as the final analysis of overall survival in the unselected population, when approximately 438 deaths occurred in the unselected population. Other endpoints had no adjustment for multiplicity. For overall survival in the HRR-deficient population, 173 overall survival events would provide 36% power to detect an HR of 0.75 using a one-sided log-rank test at a significance level of 0.0125. To achieve statistical significance at the final overall survival analysis, the one-sided p value from the stratified log-rank test needed to be 0.012 or less (two-sided p value ≤ 0.024) based on a group sequential design with O'Brien–Fleming spending function. At the time of the final analysis of overall survival, a descriptive update of rPFS and other secondary endpoints was planned to be provided.

Time-to-event endpoints, including overall survival, were compared between treatment groups using a stratified log-rank test unless otherwise stated. HRs and associated 95% two-sided CIs were estimated by a stratified Cox proportional hazards model, which allowed separate baseline hazards to be fitted to each stratum of the randomisation stratification factors. Median time-to-event endpoints were estimated using the Kaplan–Meier method, and 95% CIs were based on the Brookmeyer–Crowley method. For subgroup analysis of overall survival (except by *BRCA* status), the HR was based on an unstratified Cox model with treatment as the only covariate because of the small patient numbers in some subgroups.

The safety analysis population included all patients who received at least one dose of the study drug. Adverse

events were coded to Preferred Term and System Organ Class using the Medical Dictionary for Regulatory Activities and classified by severity using NCI-CTCAE version 4.03.

Missing or partial dates were imputed as specified per the appendix of the primary paper.²⁷ Other missing data were not imputed. All reported p values are two-sided. For exploratory subgroup analyses and descriptive updates, p values were nominal and descriptive. SAS (version 9.4) statistical software was used for data analysis. The sponsor, Pfizer, commissioned an independent external data monitoring committee for ongoing monitoring of efficacy and safety. TALAPRO-2 is registered with ClinicalTrials.gov, NCT03395197.

Role of the funding source

The sponsor (Pfizer) was involved in the trial design (together with the academic steering committee), data analysis, and data interpretation, and funded medical writing support. Astellas Pharma provided enzalutamide.

Results

Between Dec 18, 2018, and Jan 20, 2022, 399 patients with HRR gene alterations were randomly assigned to the talazoparib group (200 [50%] patients) or the control group (199 [50%] patients; figure 1). Of these, 169 (42%) patients were included as part of the unselected cohort (cohort 1) and 230 (58%) additional patients were recruited to the HRR-deficient cohort after the unselected cohort had completed recruitment. Data cutoff for this analysis was Sept 3, 2024. At the time of the final analysis, 49 (25%) patients in the talazoparib group and 20 (10%) patients in the control group remained on study treatment. Important protocol deviations in at least 10% of patients are listed in the appendix (p 7). As previously reported, baseline demographics and disease characteristics were well balanced across treatment groups, except for minor differences in the number of patients with bone metastases (175 [88%] in the talazoparib group and 158 [79%] in the control group; table 1).¹⁸ The most commonly altered HRR genes were *BRCA2*, *ATM*, and *CDK12*.

At the time of the final analysis of overall survival in the HRR-deficient cohort, 93 (46%) patients in the talazoparib group and 126 (63%) in the control group had died, with a median follow-up of 44.2 months (IQR 36.0–50.8). Talazoparib plus enzalutamide significantly improved overall survival compared with enzalutamide plus placebo (HR 0.62 [95% CI 0.48–0.81]; two-sided $p=0.0005$; figure 2A) in patients with HRR-deficient metastatic castration-resistant prostate cancer. Median overall survival was 45.1 months (95% CI 35.4–not reached) in the talazoparib group versus 31.1 months (27.3–35.4) in the control group.

A consistent treatment effect for overall survival favouring talazoparib plus enzalutamide was observed

across prespecified clinical subgroups (appendix p 4). Among the 149 (37%) of 399 patients who had received previous treatment with docetaxel or an ARPI for castration-sensitive disease, the HR for overall survival was 0·66 (95% CI 0·43–1·01; two-sided $p=0\cdot056$) in favour of talazoparib plus enzalutamide.

In subgroup analyses, patients with *BRCA1/2* alterations by prospective testing of either ctDNA or tumour tissue who received talazoparib plus enzalutamide had a 50% lower risk of death (HR 0·50 [95% CI 0·32–0·78]; two-sided $p=0\cdot0017$) compared with enzalutamide plus placebo (figure 2B). Among patients with *BRCA1/2* alterations, the probability of survival at 4 years was 53% in the talazoparib plus enzalutamide group and 23% in the control group. Patients with non-*BRCA1/2* HRR alterations receiving talazoparib plus enzalutamide had a 27% lower risk of death (HR 0·73 [95% CI 0·52–1·02]; two-sided $p=0\cdot066$) compared with those receiving enzalutamide plus placebo (figure 2C). Among these patients, the probability of survival at 4 years was 46% in the talazoparib plus enzalutamide group and 33% in the control group.

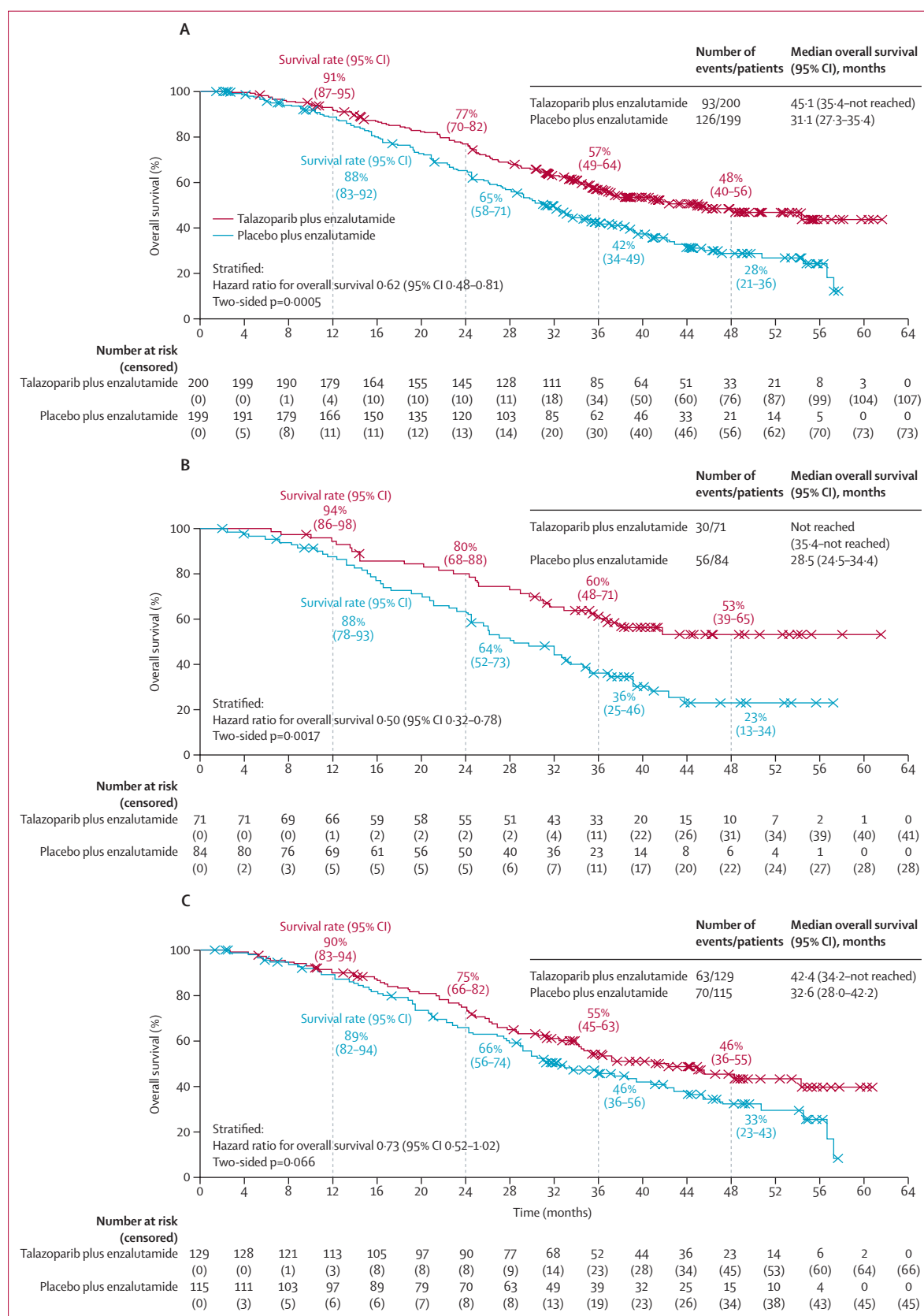
A lower percentage of patients in the talazoparib group ($n=73$ [37%]) received subsequent systemic antineoplastic therapy compared with the control group ($n=113$ [57%]; appendix p 8). The most common subsequent therapies ($\geq 10\%$ overall) with overall survival benefit in metastatic castration-resistant prostate cancer were docetaxel (42 [21%] patients in the talazoparib group and 63 [32%] in the control group), cabazitaxel (22 [11%] and 34 [17%]), and abiraterone (13 [7%] and 23 [12%]). Subsequent single-agent PARP inhibitor therapies (most commonly olaparib) were administered per investigator discretion according to their approval and limited availability in respective countries, and were received by seven (4%) patients in the talazoparib group and 31 (16%) patients in the control group.

Results of rPFS by BICR at the final analysis (HR 0·47 [95% CI 0·36–0·61]; two-sided $p<0\cdot0001$) were descriptive and consistent with that of the primary analysis. Talazoparib plus enzalutamide showed a median rPFS of 30·7 months (95% CI 24·3–38·5) versus 12·3 months (11·0–16·5) with enzalutamide alone (figure 3). At the final analysis, results for other secondary efficacy endpoints were consistent with the primary analysis (appendix p 9). Confirmed objective response rate in patients with measurable disease at baseline was 69% (50/72 [95% CI 58–80]; complete response in 32 [44%] of 72) for the talazoparib group and 38% (25/65 [95% CI 27–51]; complete response in 11 [17%] of 65) for the control group. Time to PSA progression, time to initiation of cytotoxic chemotherapy, and investigator-assessed time to progression or death on first subsequent antineoplastic therapy favoured the talazoparib plus enzalutamide group, consistent with the primary analysis. rPFS and overall survival by HRR gene alteration subgroups are shown in figure 4 (objective

	Talazoparib plus enzalutamide (n=200)	Placebo plus enzalutamide (n=199)
Age, years	70 (65–76)	71 (64–76)
Race		
White	137 (68%)	136 (68%)
Black or African American	6 (3%)	5 (3%)
Asian	45 (22%)	39 (20%)
Multiracial	0	1 (<1%)
Other*	1 (<1%)	1 (<1%)
Not reported or unknown	11 (6%)	17 (9%)
Baseline serum PSA, µg/L	19·6 (6·7–62·8)	18·0 (7·1–57·4)
Gleason score†		
<8	42 (21%)	52 (26%)
≥8	152 (76%)	143 (72%)
Disease site		
Bone (including with soft tissue component)	175 (88%)	158 (79%)
Lymph node	82 (41%)	94 (47%)
Visceral (lung)	23 (12%)	26 (13%)
Visceral (liver)	9 (4%)	6 (3%)
Other soft tissue	23 (12%)	20 (10%)
ECOG performance status		
0	128 (64%)	118 (59%)
1	72 (36%)	81 (41%)
Previous treatment with a second-generation androgen receptor pathway inhibitor	17 (9%)	17 (9%)
Abiraterone	16 (8%)	16 (8%)
Orteronel	1 (<1%)	1 (<1%)
Previous taxane-based chemotherapy‡	57 (28%)	60 (30%)
Patients with at least one alteration in corresponding HRR genes§	198 (99%)	197 (99%)
ATM	47 (24%)	39 (20%)
ATR	3 (2%)	12 (6%)
BRCA1	11 (6%)	12 (6%)
BRCA2	62 (31%)	73 (37%)
CDK12	36 (18%)	39 (20%)
CHEK2	34 (17%)	37 (19%)
FANCA	4 (2%)	5 (3%)
MLH1	9 (4%)	1 (<1%)
MRE11A	1 (<1%)	2 (1%)
NBN	8 (4%)	3 (2%)
PALB2	9 (4%)	8 (4%)
RAD51C	2 (1%)	2 (1%)

Data are n (%) or median (IQR). Reprinted from Fizazi K, Azad AA, Matsubara N, et al.¹⁸ ARPI=androgen receptor pathway inhibitor, ECOG=Eastern Cooperative Oncology Group. HRR=homologous recombination repair. PSA=prostate-specific antigen. *American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander. †Not reported for the remaining patients. ‡All received docetaxel; HRR-deficient safety population. §Three patients (one in the talazoparib plus enzalutamide group and two in the placebo plus enzalutamide group) did not have HRR gene alterations, and one patient in the talazoparib group was of unknown HRR gene alteration status.

Table 1: Summary of baseline characteristics (HRR-deficient intention-to-treat population)



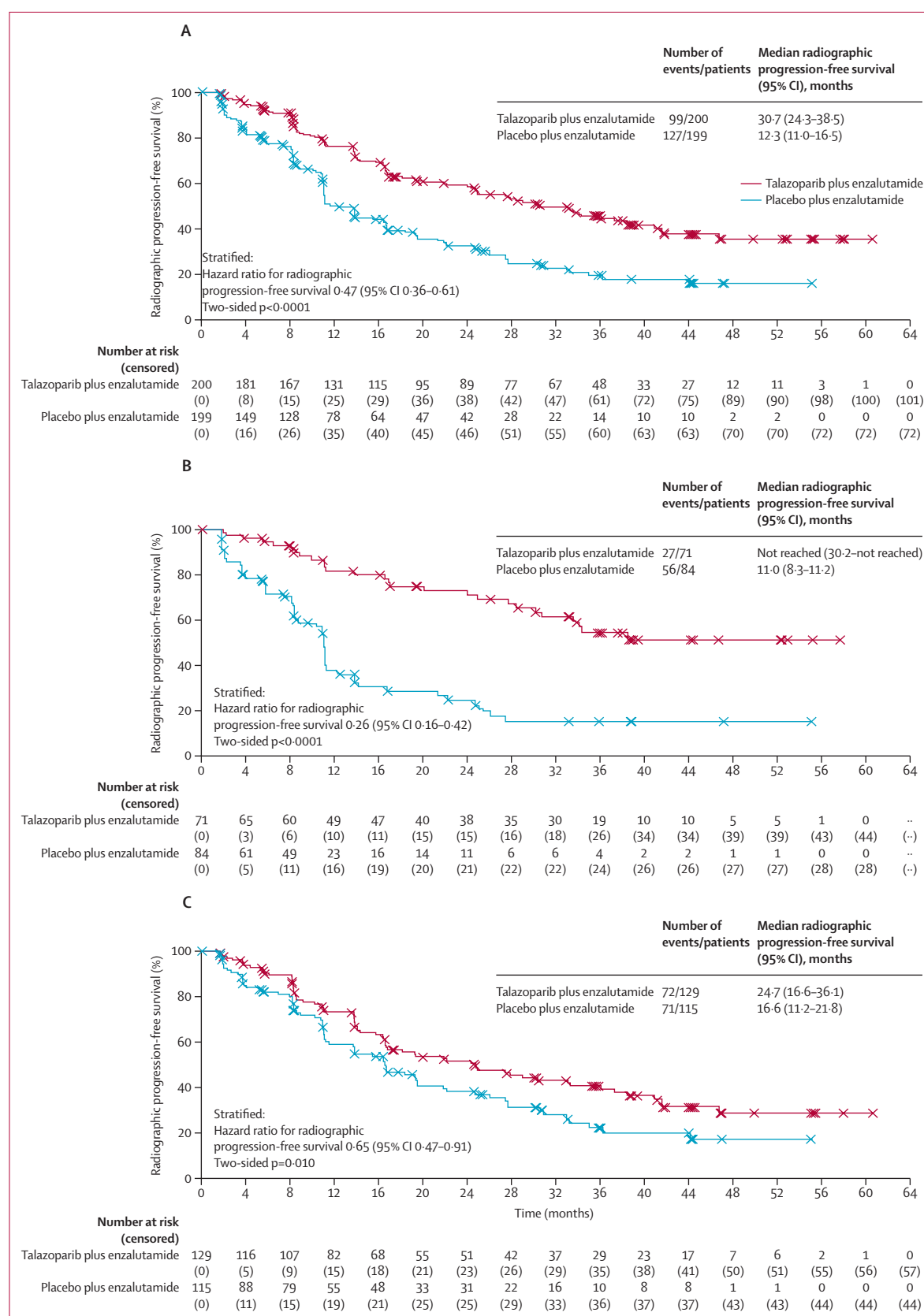


Figure 3: Radiographic progression-free survival
Radiographic progression-free survival in patients with (A) any HRR gene alteration; (B) BRCA1/2 gene alterations; and (C) non-BRCA1/2 HRR gene alterations (assessed by BICR; HRR-deficient intention-to-treat population). BICR=blinded-independent central review. HRR=homologous recombination repair.

response rates by BICR and by HRR gene alteration subgroups are shown in the appendix [p 5]) and showed broad overall benefit across genes with talazoparib plus enzalutamide.

Median duration of treatment was 20·3 months (IQR 9·6–38·4) for talazoparib and 13·8 months (5·8–24·2) for placebo. Median duration of treatment for enzalutamide was 20·8 months (10·1–37·9) in

the talazoparib group and 13·8 months (5·8–24·8) in the control group. Median relative dose intensities in the talazoparib group were 78·3% (60·1–100·0) for talazoparib and 99·8% (94·9–100·0) for enzalutamide.

Consistent with the findings of the primary analysis,¹⁸ the most common all-cause adverse events (in ≥25% of patients) in the talazoparib group were anaemia (132 [67%] patients), neutropenia (69 [35%]), fatigue (69 [35%]), and thrombocytopenia (51 [26%]), and in the control group were fatigue (56 [28%]) and arthralgia (49 [25%]; table 2). The most common grade 3–4 adverse events (in ≥10% of patients) in the talazoparib group were anaemia (86 [43%] patients), neutropenia (39 [20%]), and hypertension (22 [11%]; table 2). The median time to onset of grade 3–4 anaemia was 3·4 months (IQR 2·3–5·3), requiring dose modification of talazoparib according to the protocol.

A packed red blood cell transfusion was received by 78 (39%) patients in the talazoparib plus enzalutamide group; among these 78 patients, the median number of transfusions was two (IQR 1–3). There were more dose interruptions and reductions due to adverse events in the talazoparib plus enzalutamide group than in the control group (table 2). The most common adverse events (≥10%) leading to a dose interruption of talazoparib were anaemia in 85 (43%) patients, neutropenia in 30 (15%), and thrombocytopenia in 18 (9%). The most common adverse events (≥10%) leading to a dose reduction of talazoparib were anaemia in 89 (45%) patients and neutropenia in 31 (16%). Talazoparib was permanently discontinued in 26 (13%) patients and 19 (10%) patients discontinued placebo because of adverse events; discontinuation rates of enzalutamide due to adverse events were similar in each group. Only nine (5%) patients discontinued talazoparib due to anaemia.

Venous embolic and thrombotic events were observed in 11 (6%) patients in the talazoparib group (equating to 2·6 events per 100 patient-years of reporting), including six patients with pulmonary embolism, two patients with deep vein thrombosis, and one patient with venous embolism. Two (1%) patients in the placebo group experienced venous embolic or thrombotic events (both pulmonary embolism), equating to 0·7 events per 100 patients-years of reporting. One case of pneumonitis each was observed in the talazoparib and control groups. No cases of acute myeloid leukaemia or myelodysplastic syndrome were noted in either treatment group with longer follow-up.

In analyses of patient-reported outcomes at the final data cutoff, median time to definitive deterioration in patient-reported GHS/QoL was 34·2 months (95% CI 25·6–44·1) with talazoparib plus enzalutamide and 22·1 months (17·6–33·0) with placebo plus enzalutamide (HR 0·77 [95% CI 0·56–1·06]; $p=0\cdot11$; appendix p 6). QoL was maintained in patients treated with talazoparib plus enzalutamide compared with patients treated with placebo plus enzalutamide as no clinically meaningful

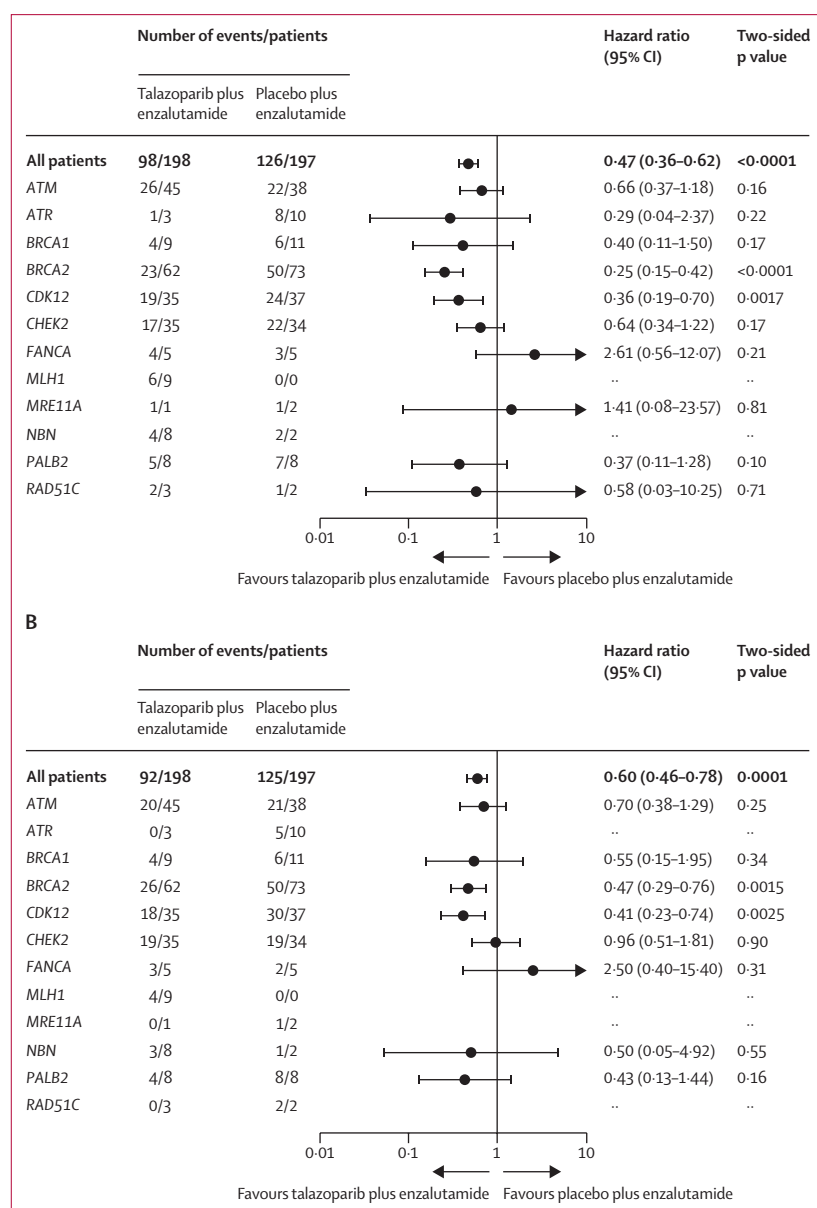


Figure 4: Radiographic progression-free survival assessed by BICR (A) and overall survival by HRR gene alteration subgroups (B)

Figure shows results in the HRR-deficient intention-to-treat population and uses all available tumour and pre-screening or screening circulating tumour DNA records, including records generated after randomisation date. For the subgroups of patients with non-BRCA alterations, patients with co-occurring BRCA1 or BRCA2 alterations are excluded. For the subgroup of patients with BRCA1 alterations, patients with co-occurring BRCA2 alterations are excluded. Patients with co-alterations in multiple genes not including BRCA1/2 are counted under each individual corresponding gene subgroup. All patients category is based on prospective test results. BICR=blinded independent central review. HRR=homologous recombination repair.

(ten-point change) between-group differences were observed in GHS/QoL, function, or symptom scores.

Discussion

In this prespecified, alpha-controlled final analysis of overall survival in the HRR-deficient cohort of the phase 3 TALAPRO-2 trial, talazoparib plus enzalutamide administered as initial treatment for metastatic castration-resistant prostate cancer resulted in both a statistically significant and clinically meaningful improvement (based on the magnitude of differences in medians) in overall survival versus standard-of-care enzalutamide in patients with metastatic castration-resistant prostate cancer harbouring HRR gene alterations. Median overall survival with talazoparib plus enzalutamide was 45·1 months, extending median survival by over a year compared with the enzalutamide control group (31·1 months). These data are striking in this population of patients for whom historical outcomes have remained particularly poor.⁷⁻⁹ To our knowledge, and to date, talazoparib plus enzalutamide is the only PARP inhibitor plus ARPI combination to show a statistically significant improvement in overall survival versus ARPI alone in HRR-deficient metastatic castration-resistant prostate cancer, with a longer median overall survival than those reported in trials for existing standard-of-care treatments (including docetaxel, ARPIs, and PARP inhibitor plus ARPI combinations) in patients with HRR-deficient metastatic castration-resistant prostate cancer or unselected patients with metastatic castration-resistant prostate cancer.^{11-14,21,23,30} Results from the unselected cohort of TALAPRO-2 (reported separately)²⁸ also showed a statistically significant improvement in overall survival with talazoparib plus enzalutamide versus enzalutamide plus placebo; median overall survival with talazoparib plus enzalutamide was 45·8 months in the unselected population.²⁸ The extended overall survival in TALAPRO-2 might reflect, in part, the availability of newer life-prolonging agents not available during earlier trials of initial treatment for metastatic castration-resistant prostate cancer.

BRCA alterations are, in addition to being a prognostic factor,⁷ a strong predictive factor for response to PARP inhibition. As expected, striking clinical benefit was noted in the subgroup of TALAPRO-2 patients with *BRCA1/2*-altered metastatic castration-resistant prostate cancer, a population for whom median survival is typically less than 25 months.^{7,8,10} Talazoparib plus enzalutamide resulted in a 50% reduction in risk of death versus enzalutamide alone in patients with *BRCA1/2* gene alterations. Although median overall survival was not reached, 53% of patients with *BRCA1/2* alterations were alive in the talazoparib plus enzalutamide group at 4 years versus 23% in the control group, thus reinforcing the efficacy of this combination in these patients with a high unmet need. In post-hoc exploratory analyses of PROpel, overall survival favoured olaparib

	Talazoparib plus enzalutamide (n=198)		Placebo plus enzalutamide (n=199)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any adverse event	197 (99%)	149 (75%)	194 (97%)	88 (44%)
Treatment-related adverse event	182 (92%)	116 (59%)	150 (75%)	28 (14%)
Serious adverse event	79 (40%)	71 (36%)	47 (24%)	39 (20%)
Serious and treatment-related adverse event	32 (16%)	..	1 (<1%)	..
Adverse event resulting in dose interruption of				
Talazoparib or placebo*	123 (62%)	..	42 (21%)	..
Enzalutamide†	80 (40%)	..	38 (19%)	..
Adverse event resulting in dose reduction of				
Talazoparib or placebo*	109 (55%)	..	10 (5%)	..
Enzalutamide†	33 (17%)	..	12 (6%)	..
Adverse event resulting in permanent drug discontinuation of				
Talazoparib or placebo*	26 (13%)	..	19 (10%)	..
Enzalutamide†	25 (13%)	..	19 (10%)	..
Grade 5 adverse event‡	5 (3%)‡	..	6 (3%)‡	..
Most common adverse events (all grades in ≥10% of patients)§				
Anaemia	132 (67%)	86 (43%)	37 (19%)	9 (5%)
Fatigue	69 (35%)	3 (2%)	56 (28%)	2 (1%)
Neutropenia	69 (35%)	39 (20%)	14 (7%)	2 (1%)
Thrombocytopenia	51 (26%)	15 (8%)	5 (3%)	1 (<1%)
Back pain	48 (24%)	3 (2%)	46 (23%)	3 (2%)
Decreased appetite	46 (23%)	2 (1%)	31 (16%)	2 (1%)
Hypertension	44 (22%)	22 (11%)	39 (20%)	16 (8%)
Nausea	43 (22%)	3 (2%)	36 (18%)	1 (<1%)
Leukopenia	43 (22%)	14 (7%)	15 (8%)	0
Fall	39 (20%)	5 (3%)	28 (14%)	3 (2%)
Asthenia	34 (17%)	5 (3%)	33 (17%)	0
Arthralgia	33 (17%)	1 (<1%)	49 (25%)	0
Constipation	32 (16%)	0	41 (21%)	0
Diarrhoea	27 (14%)	0	24 (12%)	0
Hot flush	24 (12%)	0	33 (17%)	0
Pyrexia	22 (11%)	1 (<1%)	4 (2%)	0
Dizziness	21 (11%)	1 (<1%)	16 (8%)	2 (1%)
Weight decreased	21 (11%)	4 (2%)	18 (9%)	1 (<1%)
Dyspnoea	20 (10%)	1 (<1%)	11 (6%)	0
Headache	14 (7%)	0	24 (12%)	1 (<1%)

Data are n (%). HRR=homologous recombination repair. Shown are adverse events that occurred from the time of the first dose of study treatment until 28 days after permanent discontinuation of all study treatments or before initiation of a new antineoplastic or any investigational therapy, whichever occurred first. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. All data are reported per the safety population defined as all patients who were treated with at least one dose of study treatment, including one patient who was randomly assigned to talazoparib plus enzalutamide but received enzalutamide only (197 patients in the talazoparib plus enzalutamide group and 199 patients in the placebo plus enzalutamide group treated with both study treatments). *Includes permanent discontinuation, dose reduction, or dose interruption of talazoparib or placebo only plus permanent discontinuation, dose reduction, or dose interruption of both talazoparib or placebo and enzalutamide. †Includes permanent discontinuation, dose reduction, or dose interruption of enzalutamide only plus permanent discontinuation, dose reduction, or dose interruption of both talazoparib or placebo and enzalutamide. ‡One death occurred in the talazoparib group due to disease progression and was reported by the investigator as having a reasonable possibility that the event was treatment-related, with study medications contributing to the immediate cause of death, which was reported as septic shock. No events in the placebo group were considered treatment related. §None of these events were recorded as grade 5.

Table 2: Summary of adverse events (HRR-deficient safety population)

plus AAP (HR 0·29 [95% CI 0·14–0·56]) in the *BRCA1/2*-altered population; whereas, a more modest trend favouring niraparib plus AAP (HR 0·79 [0·55–1·12];

nominal $p=0.18$) was noted in MAGNITUDE for this population.^{22,23}

Importantly, the prospectively determined HRR-deficient population from TALAPRO-2 was not enriched for patients with *BRCA1/BRCA2* alterations, aligned with previous *BRCA1/2* prevalence reports.^{5,6,31} In patients with non-*BRCA* HRR alterations in TALAPRO-2, a trend towards a lower risk of death was observed with talazoparib plus enzalutamide versus the enzalutamide control (HR 0.73 [95% CI 0.52–1.02]), with median overall survival being nearly 10 months longer in the talazoparib plus enzalutamide group. Additionally, based on post-hoc exploratory analyses of efficacy by gene, overall survival benefit was evident across multiple individual HRR gene subgroups, including individual non-*BRCA* HRR genes. These data show that the overall survival improvement observed in the HRR-deficient population was not solely driven by benefit derived in patients with *BRCA1/2* alterations.

At the final analysis of the HRR-deficient population in TALAPRO-2, significant improvement in rPFS¹⁸ was also associated with significant improvement in overall survival. In the updated analysis of rPFS, the risk of progression or death was reduced by 53%; the median rPFS was reached for the experimental group (30.7 months), extended by 18.4 months over the control group. As expected, the median rPFS in the enzalutamide group in TALAPRO-2 (12.3 months [95% CI 11.0–16.5]) was substantially lower than the rPFS observed with this agent in a genomically unselected metastatic castration-resistant prostate cancer population (20.0 months [95% CI 18.9–22.1] in PREVAIL³²), highlighting the worse prognosis associated with HRR gene alterations in metastatic castration-resistant prostate cancer.

The safety profile of talazoparib plus enzalutamide in the HRR-deficient population of TALAPRO-2 after extended follow-up was consistent with the primary analysis.^{18,27,33} Anaemia, an on-target effect of PARP inhibition and trapping impacting erythropoiesis,³⁴ was the most common adverse event in the talazoparib group. However, anaemia was not a cumulative treatment-related toxicity; mean change in haemoglobin from baseline in all patients receiving talazoparib plus enzalutamide was less than 2 g/dL and reached a nadir after 15 weeks of treatment and recovered thereafter.³³ Anaemia was managed with regular patient monitoring, dose modifications, red blood cell transfusions, and haematologic supportive measures; the percentage of patients discontinuing talazoparib because of anaemia remained low at 5%. Dosing modifications, particularly dose reductions of talazoparib for managing adverse events, did not result in clinically meaningful changes in efficacy of talazoparib plus enzalutamide.³⁵ Exposure-adjusted analyses suggest no increased risk of embolic and thrombotic events with longer follow-up compared with the primary analysis.¹⁸ No cases of myelodysplastic syndrome or acute myeloid leukaemia were reported.

The rate of permanent discontinuations due to treatment-emergent adverse events was similar between the two arms (13% with talazoparib plus enzalutamide vs 10% with control). Finally, patient-reported QoL was maintained with talazoparib plus enzalutamide treatment with extended follow-up.

This analysis of TALAPRO-2 had some limitations. While ARPIs are increasingly being used to treat metastatic castration-sensitive prostate cancer,¹ the number of patients with prior ARPI treatment was small in the HRR-deficient population of TALAPRO-2. In exploratory subgroup analyses of patients who received a previous ARPI ($n=34$ [9%]), the HRs for rPFS and overall survival favoured the combination (rPFS HR 0.35 [95% CI 0.13–0.96], $p=0.034$; overall survival HR 0.94 [0.41–2.13], $p=0.87$). This finding was also true for patients who received previous taxane chemotherapy ($n=117$ [29%]; rPFS HR 0.37 [95% CI 0.23–0.62], $p<0.0001$; overall survival HR 0.58 [0.35–0.97], $p=0.035$). This exploratory analysis suggests the potential for benefit in these populations, and future efforts should focus on confirming the efficacy of the combination in this pretreated population.

In addition, TALAPRO-2 was not designed to assess sequential treatment and only a small proportion of patients in the control group (16%) received PARP inhibitors as subsequent therapy. Although subsequent PARP inhibitor exposure (as monotherapy or as combination therapy with ARPI) was lower than would be expected for patients with HRR gene alterations or *BRCA* alterations given the current clinical landscape, this finding could be attributed to the timing of PARP inhibitor approvals, availability, and reimbursement during the follow-up period of this study.¹⁸

Therefore, the comparative benefit of early versus late treatment with a PARP inhibitor in combination with an ARPI for metastatic castration-resistant prostate cancer could not be assessed. However, evidence from other trials, including the phase 2 BRCAAway trial,³⁶ indicates that up-front PARP inhibitor plus ARPI combinations in newly diagnosed metastatic castration-resistant prostate cancer might be more effective than sequential treatment. In BRCAAway, treatment with olaparib combined with AAP more than doubled median progression-free survival compared with either olaparib alone or AAP alone, or with AAP followed sequentially with olaparib, in patients with newly diagnosed metastatic castration-resistant prostate cancer and *BRCA1/2* and/or *ATM* alterations.³⁶

In conclusion, the combination of talazoparib and enzalutamide resulted in a clinically meaningful improvement in overall survival versus enzalutamide alone in patients with HRR-deficient metastatic castration-resistant prostate cancer. To date, this is the only PARP inhibitor and ARPI combination to show statistically significant overall survival improvement over standard-of-care ARPI in metastatic castration-resistant

prostate cancer, showing a 38% reduction in the risk of death. These overall survival data complement the rPFS benefit previously noted with this combination in this population.¹⁸ There were no new safety signals identified with extended follow-up. These results provide robust support for the use of talazoparib plus enzalutamide as a standard of care for the initial treatment of metastatic castration-resistant prostate cancer with HRR gene alterations.

Contributors

All authors, including those employed by the sponsor, contributed to data interpretation, and development, writing, and approval of the final manuscript. KF and XL accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

KF reports honoraria (institution) for participation in advisory boards and talks from Advanced Accelerator Applications/Novartis, Amgen, Astellas Pharma, AstraZeneca, Bayer, Clovis Oncology, Daiichi Sankyo, Janssen, MSD, Novartis, Pfizer, and Sanofi; and honoraria (personal) for participation in advisory boards from Arvinas, CureVac, MacroGenics, and Orion. AAA reports honoraria from Aculeus Therapeutics, Amgen, Arvinas, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Ipsen, Janssen, Merck Serono, MSD, Novartis, Noxopharm, Pfizer, Sanofi, Telix Pharmaceuticals, and Tolmar; consulting fees from Aculeus Therapeutics, Astellas Pharma, Janssen, and Novartis; participation on advisory boards for Amgen, Arvinas, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Ipsen, Janssen, Merck Serono, MSD, Novartis, Noxopharm, Pfizer, Sanofi, Telix, and Tolmar; participation on a data safety monitoring board for OncoSec; research funding (institution unless stated otherwise) from Aptevo Therapeutics, Astellas Pharma (investigator), AstraZeneca (investigator), Bionomics, Bristol Myers Squibb, Exelixis, Gilead Sciences, GlaxoSmithKline, Hinova Pharmaceuticals, Ipsen, Janssen, Lilly, MedImmune, Merck Serono (investigator), Merck Serono (institutional), MSD, Novartis, Pfizer, Sanofi, and Synthorx; travel, accommodation, or expenses from Amgen, Astellas Pharma, Bayer, Hinova Pharmaceuticals, Janssen, Merck Serono, Novartis, Pfizer, and Tolmar; and medical writing services support from Astellas Pharma, Exelixis, and Pfizer; he is Chair of the Urologic Oncology Group for the Clinical Oncology Society of Australia, and Chair of the Translational Research Subcommittee and on the Scientific Advisory Committee for the ANZUP Cancer Trials Group. NM reports honoraria (personal) from Sanofi; research funding (institution) from Amgen, Astellas Pharma, AstraZeneca, Bayer, Chugai Pharma, Eisai, Janssen, Lilly, MSD, Pfizer, PRA Health Sciences, Roche, Seagen, Taiho, and Takeda; and travel, accommodations, or expenses (personal) from Pfizer. JC has received personal fees for serving as a consultant to Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, Johnson & Johnson, MSD Oncology, Novartis (AAA), Pfizer, Roche, and Sanofi; has participated in a speakers bureau for Astellas Pharma, Bayer, and Johnson & Johnson; has received research funding for their institution from AB Science, Aragon Pharmaceuticals, AROG Pharmaceuticals, Astellas Pharma, AstraZeneca AB, AVEO Pharmaceuticals, Bayer AG, Blueprint Medicines Corporation, BN Immunotherapeutics, Boehringer Ingelheim España, Bristol Myers Squibb, Clovis Oncology, Cougar Biotechnology, Deciphera Pharmaceuticals, Exelixis, F Hoffmann-La Roche, Genentech, GlaxoSmithKline, Incyte Corporation, Janssen-Cilag International NV, Karyopharm Therapeutics, Laboratoires Leurquin Mediolanum, Lilly, MedImmune, Millennium Pharmaceuticals, Nanobiotix, Novartis Farmacéutica, Pfizer, Puma Biotechnology, Sanofi-Aventis, SFJ Pharma, and Teva Pharma; and has received travel or accommodation expenses from AstraZeneca, Bristol Myers Squibb, Ipsen, and Roche. APF reports honoraria from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, and Roche; a consulting or advisory role for Bayer, Ipsen, Janssen, MSD, Novartis, Pfizer, and Roche; stock or stock options in Brazilian Information Oncology;

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Data sharing

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results/> for more information.

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