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First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial

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A list of authors and their affiliations appears at the end of the paper

Preclinical evidence has suggested an interplay between the androgen receptor, which largely drives the growth of prostate cancer cells, and poly(ADP-ribose) polymerase. This association provides a rationale for their co-inhibition for the treatment of metastatic castration-resistant prostate cancer (mCRPC), an area of unmet medical need. The phase 3 TALAPRO-2 study investigated combining the poly(ADP-ribose) polymerase inhibitor talazoparib with enzalutamide versus enzalutamide alone as first-line treatment of mCRPC. Patients were prospectively assessed for tumor alterations in DNA damage response genes involved in homologous recombination repair (HRR). Two cohorts were enrolled sequentially: an all-comers cohort that was enrolled first (cohort 1; $N = 805$ (169 were HRR-deficient)), followed by an HRR-deficient-only cohort (cohort 2; $N = 230$). We present results from the alpha-controlled primary analysis for the combined HRR-deficient population ($N = 399$). Patients were randomized in a 1:1 ratio to talazoparib or placebo, plus enzalutamide. The primary endpoint, radiographic progression-free survival, was met (median not reached at the time of the analysis for the talazoparib group versus 13.8 months for the placebo group; hazard ratio, 0.45; 95% confidence interval, 0.33 to 0.61; $P < 0.0001$). Data for overall survival, a key secondary endpoint, are immature but favor talazoparib (hazard ratio, 0.69; 95% confidence interval, 0.46 to 1.03; $P = 0.07$). Common adverse events in the talazoparib group were anemia, fatigue and neutropenia. Combining talazoparib with enzalutamide significantly improved radiographic progression-free survival in patients with mCRPC harboring HRR gene alterations, supporting talazoparib plus enzalutamide as a potential first-line treatment for these patients. ClinicalTrials.gov Identifier: NCT03395197.

Recent approvals of new treatments have led to improved outcomes for patients with advanced prostate cancer[1,2]. However, metastatic disease remains aggressive and progression is inevitable, necessitating additional therapies for this population of often elderly men[1,3,4].

Around a quarter of advanced prostate cancers have alterations in DNA damage response genes involved directly or indirectly in homologous recombination repair (HRR), including *BRCA1/BRCA2* (refs. 5–8); these can sensitize tumors to treatment with poly(ADP-ribose) polymerase

e-mail: karim.fizazi@gustaveroussy.fr; neeraj.agarwal@hci.utah.edu

(PARP) inhibitors[9–14]. PARP inhibition as monotherapy is an established standard of care for those patients with late-stage prostate cancer.

Preclinical evidence suggests interplay between the androgen receptor, which largely drives the growth of prostate cancer cells, and PARP, providing a rationale for their co-inhibition[15,16]. Androgen receptor inhibition is associated with upregulated PARP activity and downregulated HRR gene expression[17,18], while PARP inhibition suppresses androgen receptor transcriptional activity[19–21].

Monotherapy with the PARP inhibitor talazoparib (1 mg per day) showed durable antitumor activity and a favorable benefit–risk profile in patients with heavily pretreated mCRPC with HRR gene alterations in the phase 2, TALAPRO-1 study[22]. TALAPRO-2 is a multinational phase 3 study evaluating talazoparib in combination with the androgen receptor inhibitor enzalutamide as a first-line treatment in patients with mCRPC[23]. An initial, non-randomized, open-label run-in study (part 1; $N = 19$) showed that when combined with enzalutamide at 160 mg per day, similar talazoparib exposure levels to the recommended monotherapy dose were achieved at 0.5 mg per day, establishing this as the starting dose for the combination[23,24]. Patients were then enrolled sequentially in two cohorts: unselected (cohort 1, all-comers cohort, recruited first) for alterations in DNA damage response genes directly or indirectly involved in HRR and selected (cohort 2) to ensure exclusive enrollment of patients with HRR-deficient disease. The first 805 patients with ($N = 169$) and without ($N = 636$) HRR gene alterations were enrolled as all-comers in cohort 1. Subsequently, an additional 230 patients selected for HRR gene alterations were recruited to complete the predefined enrollment for a combined HRR-deficient population ($N = 399$; Extended Data Fig. 1). All patients were prospectively tested for HRR gene alterations[23].

A recent analysis of the all-comers population of TALAPRO-2 revealed significant improvement in radiographic progression-free survival (rPFS) for talazoparib plus enzalutamide compared with enzalutamide as standard of care (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.51 to 0.78; $P < 0.0001$)[25]. Here, we report results of the prespecified alpha-powered independent analysis for the combined HRR-deficient population from both cohorts of TALAPRO-2.

Results

Patients

Between 18 December 2018 and 20 January 2022, 399 patients with HRR gene alterations were enrolled (169 enrolled during the accrual of the all-comers cohort; 230 additional patients to complete the planned accrual target of the combined HRR-deficient population; Fig. 1). Of the 399 enrolled patients, 397 had available prospective tumor tissue test results. Of these, 236 patients with central laboratory, nonhistorical tissue records also had blood samples that underwent concurrent prospective circulating tumor DNA testing after a protocol amendment (26 February 2020). The remaining 2 of 399 patients were enrolled based on circulating tumor DNA testing alone ($n = 1$) or had unspecified tissue source ($n = 1$).

The data cutoff date for the HRR-deficient cohort was 3 October 2022. Baseline characteristics were well balanced (Table 1 and Extended Data Table 1); representativeness of the patients is addressed in Extended Data Table 2. The most commonly altered HRR genes were *BRCA2, ATM* and *CDK12*.

Efficacy

Median follow-up for rPFS was 17.5 and 16.8 months for the talazoparib and placebo groups, respectively. Talazoparib plus enzalutamide significantly improved rPFS by blinded independent central review compared with placebo plus enzalutamide (HR, 0.45; 95% CI, 0.33 to 0.61; $P < 0.0001$; median not reached at the time of the analysis versus 13.8 months; Fig. 2).

A consistent treatment effect for rPFS was observed across prespecified clinical subgroups (Fig. 3a) and by investigator assessment (Extended Data Fig. 2). Among 149 patients who had received prior abiraterone or orteronel (a CYP17 inhibitor) or docetaxel for castration-sensitive disease, the HR was 0.43 (95% CI, 0.26 to

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

Characteristic	Talazoparib +enzalutamide (*N*=200)	Placebo +enzalutamide (*N*=199)
Median age (range)—years	70 (41–90)	71 (44–90)
Race		
White	137 (68)	136 (68)
Black or African American	6 (3)	5 (3)
Asian	45 (22)	39 (20)
Multiracial	0	1 (<1)
Other[a]	1 (<1)	1 (<1)
Not reported or unknown	11 (6)	17 (9)
Median baseline serum PSA (range)—μg l^{-1}	19.6 (0.2–3412.0)	18.0 (0.0–1055.0)
Gleason score[b]		
<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)
Prior treatment with a second-generation androgen receptor pathway inhibitor	17 (9)	17 (9)
Abiraterone	16 (8)	16 (8)
Orteronel	1 (<1)	1 (<1)
Prior taxane-based chemotherapy[c]	57 (28)	60 (30)
Patients with at least one alteration in corresponding HRR gene[d]	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* (%), unless otherwise indicated. [a]American Indian, Alaska Native, Native Hawaiian or Other Pacific Islander. [b]Not reported for the remaining patients. [c]All received docetaxel; HRR-deficient safety population. [d]$N = 3$ patients (1, talazoparib plus enzalutamide; 2, placebo plus enzalutamide) did not have HRR gene alterations and 1 patient in the talazoparib group was of unknown HRR gene alteration status. ECOG, Eastern Cooperative Oncology Group.

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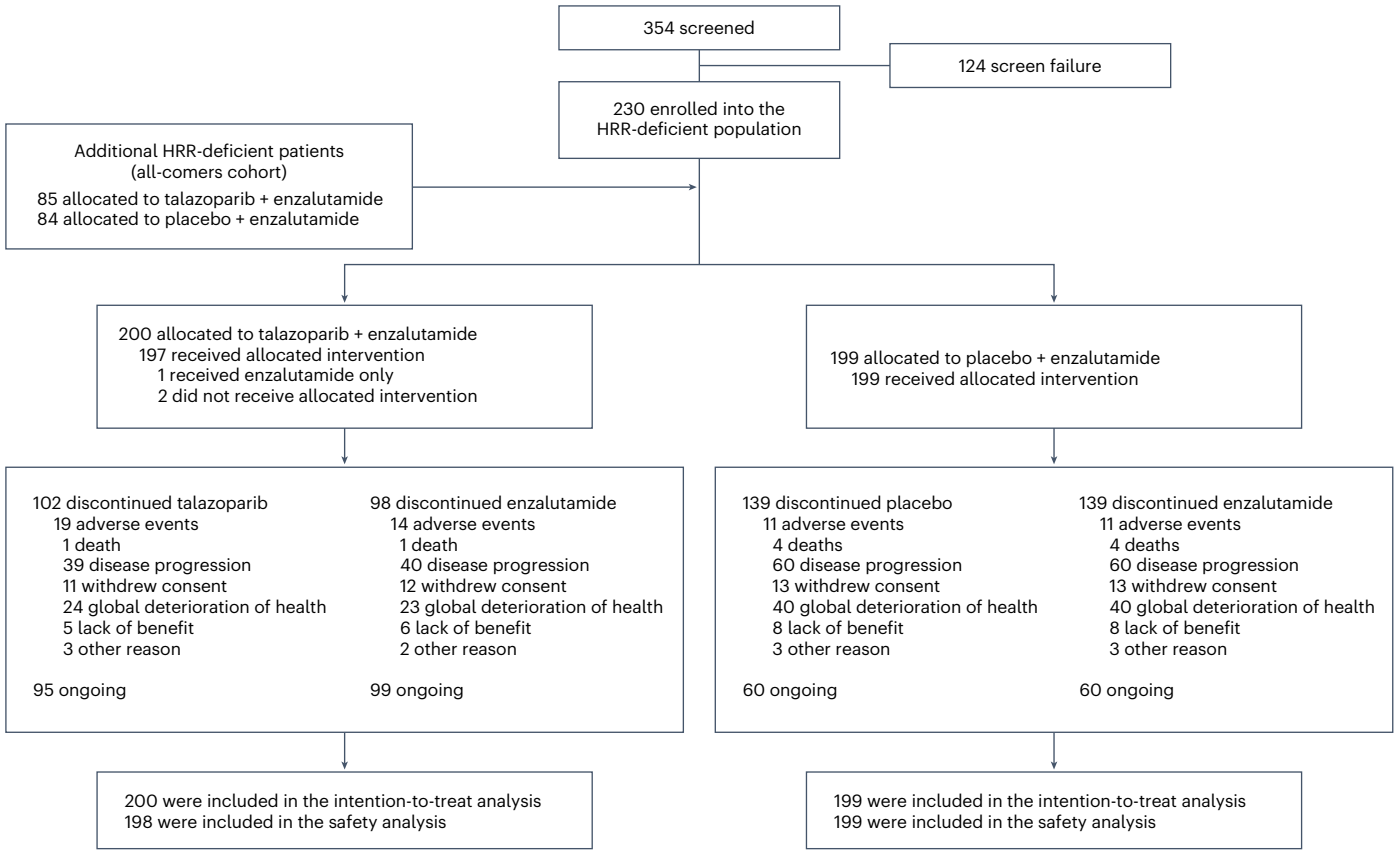

Fig. 1 | Trial profile. Flow diagram showing participant recruitment into the HRR-deficient population, randomization, follow-up and analysis populations.

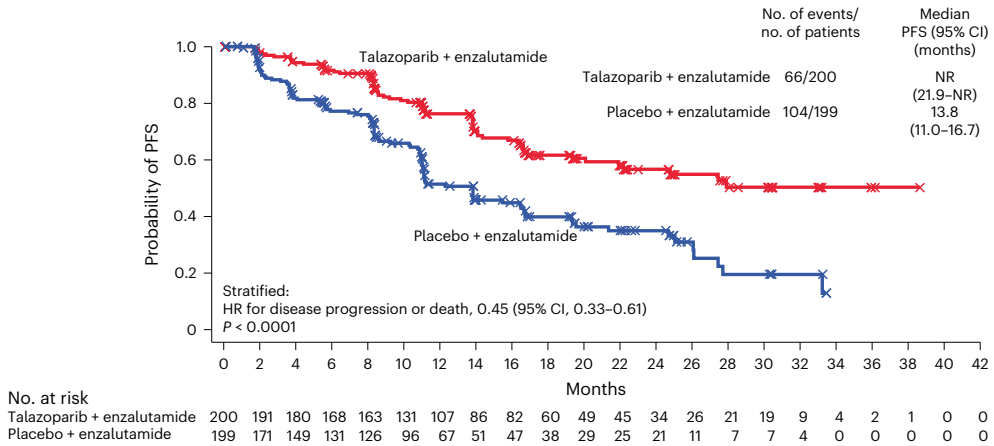

Fig. 2 | rPFS in patients with any HRR gene alteration (assessed by blinded independent central review; HRR-deficient intention-to-treat population). rPFS was compared between treatment groups using stratified log-rank test. HRs and associated 95% two-sided CIs were estimated by a Cox proportional hazards model. Median time to event was estimated by the Kaplan–Meier method, and 95% CIs were based on the Brookmeyer–Crowley method. The *P* value is two-sided. NR, not reached at the time of the analysis.

0.70; $P = 0.0006$) in favor of talazoparib plus enzalutamide. Among patients who had received abiraterone or orteronel ($n = 34$), the HR was 0.53 (95% CI, 0.20 to 1.42; $P = 0.20$), and among those who had received docetaxel ($n = 117$), the HR was 0.39 (95% CI, 0.22 to 0.69; $P = 0.0008$).

In a post hoc analysis, patients with *BRCA1/BRCA2* alterations had an 80% lower risk of radiographic progression or death (HR, 0.20; 95% CI, 0.11 to 0.36; $P < 0.0001$; Fig. 3a); those with non-*BRCA1/BRCA2* alterations had a 32% lower risk (HR, 0.68; 95% CI, 0.46 to 1.02; $P = 0.06$) with talazoparib plus enzalutamide. Further, notable improvements in rPFS were observed with talazoparib plus enzalutamide in the *BRCA2* single-gene subgroup, and in *BRCA* and *CDK12* clusters (Fig. 3b).

Overall survival data remain immature, with the majority of patients being alive: 43 (22%) patients in the talazoparib group and 53 (27%) in the placebo group had died at data cutoff. Three patients in the talazoparib group and 18 in the placebo group subsequently received a PARP inhibitor (all received olaparib) per the treating physician's judgment and local approval and availability of a PARP inhibitor.

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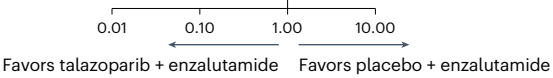
a By baseline characteristics

Subgroup		Talazoparib + enzalutamide	Placebo + enzalutamide	Hazard ratio (95% CI)	Two-sided *P* value
		No. of events/no. of patients			
Overall		66/200	104/199	0.45 (0.33–0.61)	<0.0001
Age—years	≥70	41/105	56/111	0.57 (0.38–0.86)	0.006
	<70	25/95	48/88	0.34 (0.21–0.55)	<0.0001
ECOG PS	0	47/128	63/118	0.50 (0.34–0.74)	0.0003
	1	19/72	41/81	0.39 (0.23–0.68)	0.0005
Gleason score	<8	13/42	20/52	0.71 (0.35–1.42)	0.33
	≥8	52/152	81/143	0.40 (0.28–0.57)	<0.0001
Stage at diagnosis	M0	24/84	43/84	0.42 (0.26–0.70)	0.0005
	M1	42/115	59/112	0.48 (0.32–0.72)	0.0002
Site of metastasis	Bone only	17/79	36/78	0.34 (0.19–0.60)	0.0001
	Soft tissue only	7/20	25/40	0.47 (0.20–1.10)	0.07
	Bone and soft tissue	41/96	43/80	0.50 (0.32–0.77)	0.001
Prior abiraterone* or docetaxel	Yes	26/75	39/74	0.43 (0.26–0.70)	0.0006
	No	40/125	65/125	0.46 (0.31–0.69)	<0.0001
BRCA1/2 alterations	Yes	15/71	54/84	0.20 (0.11–0.36)	<0.0001
	No†	50/127	50/113	0.68 (0.46–1.02)	0.06



b By selected gene subgroups‡

Subgroup	Talazoparib + enzalutamide	Placebo + enzalutamide	Talazoparib + enzalutamide	Placebo + enzalutamide	Hazard ratio (95% CI)	Two-sided *P* value
	No. of events/no. of patients		Median (months)			
All HRR-deficient	65/198	104/197	NR	13.8	0.44 (0.32–0.60)	<0.0001
Only *BRCA1*	2/8	5/9	20.0	11.7	0.17 (0.02–1.51)	0.07
Only *BRCA2*	11/55	40/60	NR	11.0	0.19 (0.10–0.38)	<0.0001
Only *PALB2*	3/6	4/5	NR	8.6	0.56 (0.12–2.51)	0.44
Only *CDK12*	12/28	18/30	21.9	13.8	0.49 (0.23–1.02)	0.05
Only *ATM*	12/35	7/22	NR	27.7	0.76 (0.30–1.94)	0.58
Only *CHEK2*	8/24	8/24	22.1	NR	0.90 (0.34–2.39)	0.83
BRCA cluster	15/71	54/84	NR	11.0	0.20 (0.11–0.36)	<0.0001
PALB2 cluster	3/7	6/8	NR	8.3	0.46 (0.12–1.87)	0.27
CDK12 cluster	13/35	23/36	21.9	13.8	0.38 (0.19–0.76)	0.004
ATM cluster	16/43	9/29	27.9	27.7	0.90 (0.39–2.04)	0.80
Other gene cluster	18/42	12/40	22.1	NR	1.51 (0.73–3.15)	0.26

Hierarchy

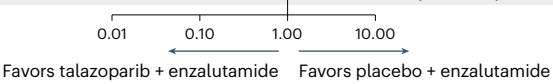


Fig. 3 | Subgroup analysis of rPFS. a,**b**, Subgroup analysis of rPFS by baseline characteristics (**a**) and by gene subgroups (**b**) (assessed by blinded independent central review; HRR-deficient intention-to-treat population). The overall HR for all patients, and by *BRCA1/BRCA2* alteration status, was based on a Cox proportional hazards model stratified by the randomization stratification factors. For all other subgroups, the HR was based on an unstratified Cox model with treatment as the only covariate. Data are presented as HRs with two-sided 95% CIs. *P* values are two sided. The asterisk indicates the inclusion of one patient in each treatment arm who received prior orteronel. †Excludes four patients who did not have HRR gene alterations but were incorrectly randomized to the HRR-deficient population; including these patients resulted in an HR of 0.72 (95% CI, 0.49 to 1.07) for the non-*BRCA* alterations subgroup. ‡Post hoc exploratory analysis; as this analysis was underpowered, the data are hypothesis-generating and should be interpreted with caution. Gene clustering alteration dominance hierarchy is any *BRCA1/BRCA2* alteration (*BRCA* cluster), then any *PALB2* (*PALB2* cluster), next any *CDK12* (*CDK12* cluster), then any *ATM* (*ATM* cluster), and finally, any of all other genes (with each patient counted only once). For the single-gene subgroups, only patients bearing alteration(s) in the designated HRR gene and none of the other HRR genes tested are shown, with a prevalence cutoff for display of ≥10 across arms. PS, performance status.

The HR for death was 0.69 (95% CI, 0.46 to 1.03; $P = 0.07$; Fig. 4a). In the *BRCA1/BRCA2* and non-*BRCA1/BRCA2* altered subgroups, the HRs for death were 0.61 (95% CI, 0.31 to 1.23; $P = 0.16$) and 0.66 (95% CI, 0.40 to 1.10; $P = 0.11$), respectively.

Confirmed objective response rate in patients with measurable disease at baseline was 67% (49/73; 95% CI, 55.1% to 77.7%) for the talazoparib group and 40% (26/65; 95% CI, 28.0% to 52.9%) for the placebo group (Fig. 4b). Time to prostate-specific antigen (PSA) progression, time to initiation of cytotoxic chemotherapy and investigator-assessed time to progression or death on first subsequent antineoplastic therapy were significantly prolonged in the talazoparib group (Fig. 4c–e; see Extended Data Table 3 for results of other secondary efficacy endpoints).

Safety

Median duration of treatment was 14.6 months for talazoparib and 14.7 months for enzalutamide in the talazoparib group, and 12.0 months for placebo and 12.1 months for enzalutamide in the placebo group. Median relative dose intensities in the talazoparib group were 81% for talazoparib and 100% for enzalutamide; 10% of the talazoparib group

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had moderate renal impairment at baseline requiring a starting dose of talazoparib of 0.35 mg per day.

The most common adverse events in the talazoparib group were anemia, fatigue, neutropenia, thrombocytopenia, nausea and decreased appetite. In the placebo group, fatigue, back pain and arthralgia were the most common adverse events (Table 2). The most common grade ≥3 adverse event in the talazoparib group was anemia (41%; Table 2), with a median time to onset of 3.3 months, and requiring dose modification of talazoparib according to the protocol. Thirty-six percent of patients in the talazoparib group received a packed red blood cell transfusion. At baseline, 56% of patients in the talazoparib group had grade 1–2 anemia. Only 4% of patients in the talazoparib group discontinued talazoparib due to anemia.

There were more dose interruptions and reductions due to adverse events in the talazoparib group than in the placebo group, but permanent discontinuation rates were similar (discontinuation of talazoparib in 10% versus placebo in 7% of patients; discontinuation of enzalutamide in 8% versus 7%; Table 2).

After a median follow-up for safety of 15.4 and 12.9 months for the talazoparib and placebo groups, respectively, no cases of myelodysplastic syndrome or acute myeloid leukemia were reported. Venous embolic and thrombotic events were reported in seven patients in the talazoparib group and two patients in the placebo group. There were four cases of pulmonary embolism (one grade 2, three grade 3) in the talazoparib group and two cases (both grade 3) in the placebo group. There were no treatment-related deaths.

Discussion

In one of the largest studies in patients with mCRPC with HRR gene alterations, the prospectively defined, alpha-controlled primary outcome in the combined HRR-deficient population showed that talazoparib plus enzalutamide resulted in a clinically meaningful and statistically significant 55% reduction in risk of progression or death versus placebo plus enzalutamide as first-line treatment. These results build on the previous subgroup analysis of the HRR-deficient patients in the all-comers cohort, which showed a 54% reduction in risk of progression or death for talazoparib plus enzalutamide versus placebo plus enzalutamide (HR, 0.46; 95% CI, 0.30 to 0.70; $P = 0.0003$)[25]. Although overall survival data are immature and statistical significance was not reached, interim data favor this combination. Other key secondary endpoints, including time to PSA progression, time to cytotoxic chemotherapy and time to progression or death on the first subsequent antineoplastic therapy, favored the talazoparib group.

Importantly, TALAPRO-2 was not enriched for patients with *BRCA1/BRCA2* alterations, which were well balanced between the treatment arms (talazoparib group, 36%; placebo group, 42%); the observed *BRCA1/BRCA2* prevalence in the prospectively determined HRR-deficient population was in line with previous reports[5,7,8]. This is notable since *BRCA* alterations are a strong predictive factor toward improved treatment outcomes for patients receiving PARP inhibitor monotherapy[26]. Talazoparib plus enzalutamide reduced risk of progression or death by 80% in the *BRCA1/BRCA2* subgroup and by 32% in the non-*BRCA1/BRCA2* subgroup. The *CDK12* results are striking given an alteration prevalence of 5% to 7% according to the literature and that limited clinical data indicate poor prognosis with minimal benefit from PARP inhibitor monotherapy in patients who have prostate cancer and *CDK12* alterations[27]. *CDK12* deficiency is associated with a

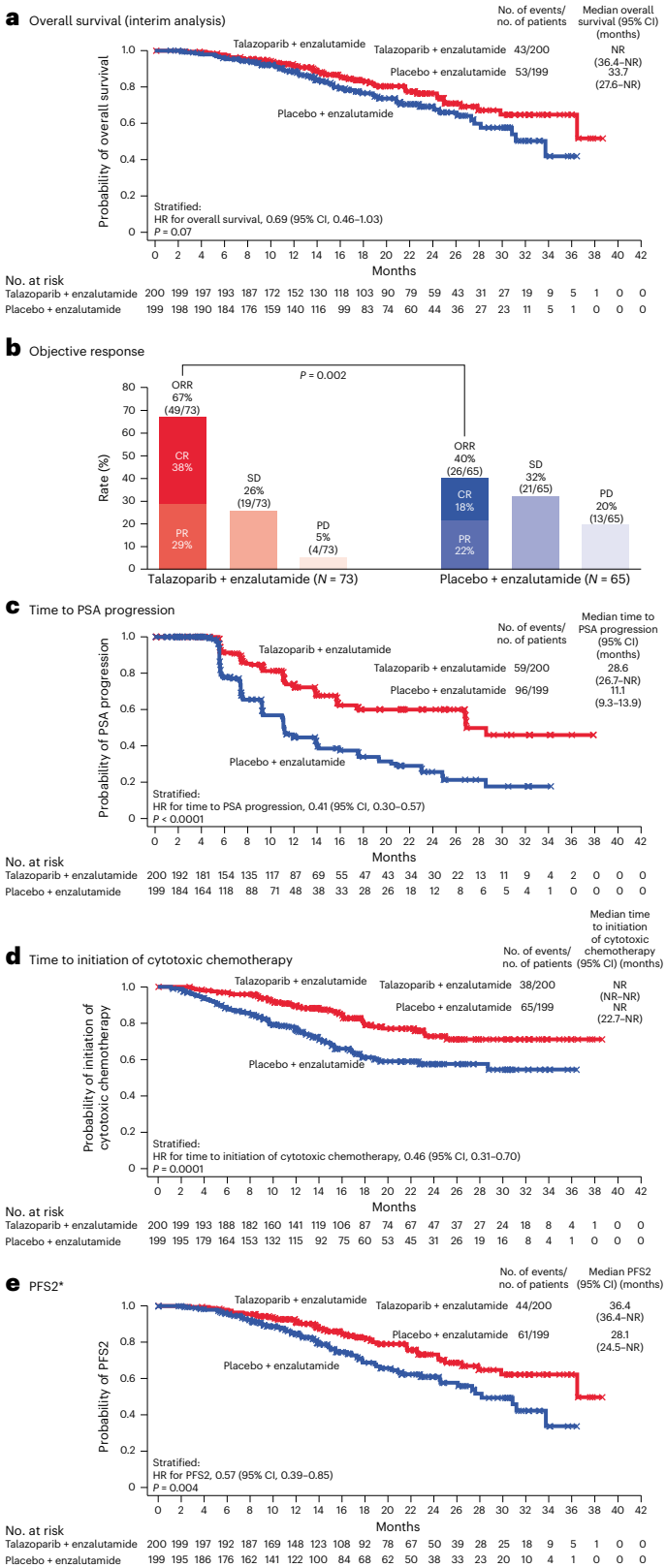

Fig. 4 | Secondary efficacy endpoints. a–e, Secondary efficacy endpoints: overall survival (**a**), objective response (**b**), time to PSA progression (**c**), time to initiation of cytotoxic chemotherapy (**d**) and PFS2 (**e**) (HRR-deficient intention-to-treat population). Time-to-event endpoints were compared between treatment groups using a stratified log-rank test. HRs and associated 95% two-sided CIs were estimated by a Cox proportional hazards model. Median time-to-event endpoints were estimated by the Kaplan–Meier method, and 95% CIs were based on the Brookmeyer–Crowley method. *P* values are two sided. The asterisk denotes that PFS2 was based on investigator assessment (time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurs first). CR, complete response; ORR, objective response rate; PD, progressive disease; PFS2, progression-free survival 2; PR, partial response; SD, stable disease.

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Table 2 | Summary of treatment-emergent adverse events (HRR-deficient safety population)[a]

	Talazoparib+ enzalutamide (*N*=198)		Placebo+ enzalutamide (*N*=199)	
Adverse event	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any adverse event	196 (99)	134 (68)	191 (96)	79 (40)
Treatment-related adverse event	180 (91)	105 (53)	144 (72)	28 (14)
Serious adverse event	60 (30)	54 (27)	40 (20)	32 (16)
Serious and treatment-related adverse event	27 (14)	23 (12)	0	0
Adverse event resulting in dose interruption of:				
Talazoparib/placebo[b]	114 (58)	·	34 (17)	·
Enzalutamide[c]	67 (34)	·	31 (16)	·
Adverse event resulting in dose reduction of:				
Talazoparib/placebo[b]	103 (52)	·	11 (6)	·
Enzalutamide[c]	28 (14)	·	12 (6)	·
Adverse event resulting in permanent drug discontinuation of:				
Talazoparib/placebo[b]	20 (10)	·	14 (7)	·
Enzalutamide[c]	15 (8)	·	14 (7)	·
Grade 5 adverse event	3 (2)[d]	·	5 (3)[d]	·
Most common adverse events (all grades in ≥10% of patients)[e]				
Anemia	128 (65)	81 (41)	31 (16)	9 (5)
Fatigue	66 (33)	3 (2)	53 (27)	2 (1)
Neutropenia	64 (32)	37 (19)	13 (7)	2 (1)
Thrombocytopenia	49 (25)	14 (7)	5 (3)	1 (<1)
Nausea	41 (21)	3 (2)	34 (17)	1 (<1)
Decreased appetite	40 (20)	2 (1)	28 (14)	2 (1)
Back pain	39 (20)	3 (2)	44 (22)	2 (1)
Leukopenia	37 (19)	11 (6)	15 (8)	0
Hypertension	36 (18)	16 (8)	38 (19)	16 (8)
Asthenia	31 (16)	4 (2)	29 (15)	0
Constipation	26 (13)	0	33 (17)	0
Fall	26 (13)	4 (2)	24 (12)	3 (2)
Arthralgia	25 (13)	0	44 (22)	0
Diarrhea	24 (12)	0	22 (11)	0
Hot flush	23 (12)	0	28 (14)	0
Dizziness	20 (10)	1 (<1)	15 (8)	2 (1)
Headache	12 (6)	0	22 (11)	1 (<1)

Data are *n* (%). [a]Shown are adverse events that occurred from the time of the first dose of study treatment through 28 d after permanent discontinuation of all study treatments or before initiation of a new antineoplastic or any investigational therapy, whichever occurs 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 randomized to talazoparib plus enzalutamide but received enzalutamide only (patients treated with both study treatments: *N*=197 for talazoparib plus enzalutamide; *N*=199 for placebo plus enzalutamide). [b]Includes permanent discontinuation/dose reduction/dose interruption of talazoparib/placebo only plus permanent discontinuation/dose reduction/dose interruption of both talazoparib/placebo and enzalutamide. [c]Includes permanent discontinuation/dose reduction/dose interruption of enzalutamide only plus permanent discontinuation/dose reduction/dose interruption of both talazoparib/placebo and enzalutamide. [d]None were considered treatment related. [e]None of these events were recorded as grade 5.

distinct chromosomal damage signature and disrupted replication and transcription[28,29], perhaps resulting in vulnerability to the combination of enzalutamide and talazoparib, a potent PARP trapper[30]. Although patient numbers were very small and the CIs wide, a similar benefit to that seen with *BRCA2* was also apparent in the *BRCA1* single-gene subgroup, with a smaller benefit apparent in the *PALB2* cluster. However, these post hoc analyses were underpowered and hypothesis generating, so the results should be interpreted with caution.

Two other recent phase 3 trials have explored the combination of PARP inhibitors and the androgen biosynthesis inhibitor abiraterone acetate/prednisone as first-line treatment for mCRPC. The PROpel (NCT03732820) trial, which enrolled all-comers without prospective assessment of *BRCA* or HRR status, demonstrated improved rPFS with the combination of olaparib plus abiraterone versus placebo plus abiraterone for patients with HRR gene alterations (HR, 0.50; 95% CI, 0.34 to 0.73)[31]. Exploratory analysis in the *BRCA1/BRCA2* subgroup showed an HR of 0.24 (95% CI, 0.12 to 0.45)[32]. The MAGNITUDE (NCT03748641) trial also showed improved rPFS with the combination of niraparib plus abiraterone versus placebo plus abiraterone for patients with HRR gene alterations (HR, 0.73; 95% CI, 0.56 to 0.96), with particular benefit in the *BRCA1/BRCA2* subgroup (HR, 0.53; 95% CI, 0.36 to 0.79)[33]. Exploratory single-gene analysis of the MAGNITUDE trial, although underpowered, showed potential benefit of combined PARP and androgen receptor inhibition in patients with a Fanconi anemia pathway gene alteration (*PALB2*, *BRIP1* and *FANCA*) beyond *BRCA1/BRCA2* (ref. 34), whereas a lack of differential benefit was seen in tumors with *CDK12* alterations[34]. Results from the PROfound (NCT02987543)[13] and TRITON-3 (NCT02975934)[14] phase 3 trials of PARP monotherapy (olaparib and rucaparib, respectively) in patients with pretreated mCRPC also indicated that patients with *BRCA2* alterations derived benefit. There was inconclusive evidence supporting *BRCA1* due to small patient numbers, preliminary positive evidence for *CDK12* in PROfound (HR below 1 but wide CIs) and lack of efficacy with *ATM*[13,14].

The main limitations of this study are due to the rapidly changing treatment landscape for patients with mCRPC. For example, the use of PARP inhibitors as a subsequent therapy was limited to a small number of patients (3 in the talazoparib group and 18 in the placebo group; all received olaparib). This small number most likely reflects the limited availability of PARP inhibitors for the treatment of mCRPC when the TALAPRO-2 study was carried out. Based on established phase 3 data[35], it is anticipated that survival in the placebo group in those who did not receive a subsequent PARP inhibitor may be shorter than in those who did. Also, the use of androgen receptor-targeted therapy has become more commonplace since patients were recruited to the TALAPRO-2 study[36–38]. Over one-third of the HRR-deficient population in TALAPRO-2 had received prior docetaxel or abiraterone for castration-sensitive disease[36], and these patients had a significant 57% reduction in risk of radiographic progression or death. However, only 8% of patients in either arm had received prior abiraterone; the benefit in these patients is hypothesis generating and warrants further studies.

The safety profile of talazoparib plus enzalutamide was closely aligned with that observed in the previously reported all-comers population[25]. The incidence of anemia, including grade 3 and 4 events, was higher than with talazoparib monotherapy[22,39]. Anemia was managed through close patient monitoring, protocol-mandated dose interruption to permit recovery followed by dose reduction for grade ≥3 anemia (once hemoglobin levels were <8 g dl^{-1}; to optimize individual treatment), and supportive measures, including packed red blood cell transfusions. To reflect the real-world patient population of mCRPC, often with bone metastases and bone marrow insufficiency, TALAPRO-2 could enroll patients with hemoglobin levels as low as 9 g dl^{-1}. Notably, more than half of the patients (56%) had grade 1 and 2 anemia at baseline. Although 41% developed grade 3 and 4 anemia after a median talazoparib treatment duration of 3.3 months, only 4% of patients discontinued talazoparib because of anemia. Importantly, no cases of myelodysplastic syndrome

or acute myeloid leukemia were reported. The incidence of permanent discontinuation was similar between the treatment groups, and the median relative dose intensity of talazoparib remained high at >80%.

In conclusion, these results support the use of talazoparib plus enzalutamide as a potential first-line treatment option for patients with mCRPC harboring tumor HRR gene alterations.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02704-x.

References

1. Sayegh, N., Swami, U. & Agarwal, N. Recent advances in the management of metastatic prostate cancer. *JCO Oncol. Pract.* **18**, 45–55 (2022).
2. Gillessen, S. et al. Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. *Eur. J. Cancer* **185**, 178–215 (2023).
3. Siegel, R. L., Miller, K. D., Wagle, N. S. & Jemal, A. Cancer statistics, 2023. *CA Cancer J. Clin.* **73**, 17–48 (2023).
4. Boyle, H. J. et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. *Eur. J. Cancer* **116**, 116–136 (2019).
5. Robinson, D. et al. Integrative clinical genomics of advanced prostate cancer. *Cell* **161**, 1215–1228 (2015).
6. Armenia, J. et al. The long tail of oncogenic drivers in prostate cancer. *Nat. Genet.* **50**, 645–651 (2018).
7. Chung, J. H. et al. Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. *JCO Precis. Oncol.* **3**, PO.18.00283 (2019).
8. Abida, W. et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. *JCO Precis. Oncol.* **1**, PO.17.00029 (2017).
9. Shen, Y. et al. BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. *Clin. Cancer Res.* **19**, 5003–5015 (2013).
10. Farmer, H. et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* **434**, 917–921 (2005).
11. Bryant, H. E. et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* **434**, 913–917 (2005).
12. Lord, C. J. & Ashworth, A. PARP inhibitors: synthetic lethality in the clinic. *Science* **355**, 1152–1158 (2017).
13. de Bono, J. et al. Olaparib for metastatic castration-resistant prostate cancer. *N. Engl. J. Med.* **382**, 2091–2102 (2020).
14. Fizazi, K. et al. Rucaparib or physician's choice in metastatic prostate cancer. *N. Engl. J. Med.* **388**, 719–732 (2023).
15. Rao, A., Moka, N., Hamstra, D. A. & Ryan, C. J. Co-inhibition of androgen receptor and PARP as a novel treatment paradigm in prostate cancer—where are we now? *Cancers* **14**, 801 (2022).
16. Agarwal, N. et al. The biology behind combining poly [ADP ribose] polymerase and androgen receptor inhibition for metastatic castration-resistant prostate cancer. *Eur. J. Cancer* **192**, 113249 (2023).
17. Asim, M. et al. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. *Nat. Commun.* **8**, 374 (2017).
18. Polkinghorn, W. R. et al. Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov.* **3**, 1245–1253 (2013).
19. Gui, B. et al. Selective targeting of PARP-2 inhibits androgen receptor signaling and prostate cancer growth through disruption of FOXA1 function. *Proc. Natl Acad. Sci. USA* **116**, 14573–14582 (2019).
20. Schiewer, M. J. et al. Dual roles of PARP-1 promote cancer growth and progression. *Cancer Discov.* **2**, 1134–1149 (2012).
21. Kounatidou, E. et al. A novel CRISPR-engineered prostate cancer cell line defines the AR-V transcriptome and identifies PARP inhibitor sensitivities. *Nucleic Acids Res.* **47**, 5634–5647 (2019).
22. de Bono, J. S. et al. Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial. *Lancet Oncol.* **22**, 1250–1264 (2021).
23. Agarwal, N. et al. Talazoparib plus enzalutamide in metastatic castration-resistant prostate cancer: TALAPRO-2 phase III study design. *Future Oncol.* **18**, 425–436 (2022).
24. Agarwal, N. et al. Clinical and safety outcomes of TALAPRO-2: a two-part phase III study of talazoparib (TALA) in combination with enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC). *J. Clin. Oncol.* **37**, 5076 (2019).
25. Agarwal, N. et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet* **402**, 291–303 (2023).
26. Pilié, P. G., Gay, C. M., Byers, L. A., O'Connor, M. J. & Yap, T. A. PARP inhibitors: extending benefit beyond *BRCA*-mutant cancers. *Clin. Cancer Res.* **25**, 3759–3771 (2019).
27. Antonarakis, E. S. et al. *CDK12*-altered prostate cancer: clinical features and therapeutic outcomes to standard systemic therapies, poly (ADP-ribose) polymerase inhibitors, and PD-1 inhibitors. *JCO Precis. Oncol.* **4**, 370–381 (2020).
28. Sokol, E. S. et al. Pan-cancer analysis of *CDK12* loss-of-function alterations and their association with the focal tandem-duplicator phenotype. *Oncologist* **24**, 1526–1533 (2019).
29. Wu, Y. M. et al. Inactivation of CDK12 delineates a distinct immunogenic class of advanced prostate cancer. *Cell* **173**, 1770–1782.e14 (2018).
30. Murai, J. et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. *Mol. Cancer Ther.* **13**, 433–443 (2014).
31. Clarke, N. W. et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid.* **1**, EVIDoa2200043 (2022).
32. US Food and Drug Administration. LYNPARZA (olaparib) prescribing information. 2023. https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/00997c3f-5912-486f-a7db-930b4639cd51/00997c3f-5912-486f-a7db-930b4639cd51_viewable_rendition__v.pdf. Accessed 22 Nov 2023.
33. Chi, K. N. et al. Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. *J. Clin. Oncol.* **41**, 3339–3351 (2023).
34. Chi, K. N. et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. *Ann. Oncol.* **34**, 772–782 (2023).
35. Hussain, M. et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N. Engl. J. Med.* **383**, 2345–2357 (2020).
36. Ciccarese, C. et al. Triplet therapy with androgen deprivation, docetaxel, and androgen receptor signalling inhibitors in metastatic castration-sensitive prostate cancer: a meta-analysis. *Eur. J. Cancer* **173**, 276–284 (2022).

37. Fizazi, K. et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2×2 factorial design. *Lancet* **399**, 1695–1707 (2022).
38. Smith, M. R. et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N. Engl. J. Med.* **386**, 1132–1142 (2022).
39. Mehra, N. et al. Talazoparib, a poly(ADP-ribose) polymerase inhibitor, for metastatic castration-resistant prostate cancer and DNA damage response alterations: TALAPRO-1 safety analyses. *Oncologist* **27**, e783–e795 (2022).

Karim Fizazi[1,22] ✉, Arun A. Azad[2], Nobuaki Matsubara[3], Joan Carles[4], Andre P. Fay[5], Ugo De Giorgi[6], Jae Young Joung[7], Peter C. C. Fong[8,9], Eric Voog[10], Robert J. Jones[11], Neal D. Shore[12], Curtis Dunshee[13], Stefanie Zschäbitz[14], Jan Oldenburg[15], Dingwei Ye[16], Xun Lin[17], Cynthia G. Healy[18], Nicola Di Santo[19], A. Douglas Laird[17], Fabian Zohren[20] & Neeraj Agarwal[21,22] ✉

[1]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France. [2]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia. [3]National Cancer Center Hospital East, Chiba, Japan. [4]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. [5]PUCRS School of Medicine, Porto Alegre, Brazil. [6]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy. [7]National Cancer Center, Goyang, Republic of Korea. [8]Auckland City Hospital, Auckland, New Zealand. [9]University of Auckland, Auckland, New Zealand. [10]Clinique Victor Hugo Centre Jean Bernard, Le Mans, France. [11]School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK. [12]Carolina Urologic Research Center, Myrtle Beach, SC, USA. [13]Arizona Urology Specialists, Tucson, AZ, USA. [14]National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany. [15]Akershus University Hospital (Ahus), Lørenskog, Norway. [16]Fudan University Shanghai Cancer Center, Shanghai, China. [17]Pfizer Inc., La Jolla, CA, USA. [18]Pfizer Inc., Collegeville, PA, USA. [19]Pfizer Inc., Durham, NC, USA. [20]Pfizer Inc., New York, NY, USA. [21]Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA. [22]These authors contributed equally: Karim Fizazi, Neeraj Agarwal. ✉e-mail: karim.fizazi@gustaveroussy.fr; neeraj.agarwal@hci.utah.edu

Methods

Trial design and patients

TALAPRO-2 (NCT03395197) is an ongoing double-blind, randomized, placebo-controlled trial. Details of the trial design have been published[23] and are in the protocol (Supplementary Protocol).

Eligibility criteria included ongoing androgen deprivation therapy; asymptomatic or mildly symptomatic mCRPC with HRR gene alterations; Eastern Cooperative Oncology Group performance status score of 0 or 1; progressive disease; adequate bone marrow function (hemoglobin ≥9 g dl^{-1}); and no prior life-prolonging systemic therapy for castration-resistant disease[23]. Prior docetaxel and abiraterone or orteronel in the castration-sensitive setting were allowed. Patients were randomized in a 1:1 ratio (using a centralized, interactive web response system and a permuted block size of 4) to receive 0.5 mg talazoparib (moderate renal impairment, 0.35 mg) or placebo (all received enzalutamide, 160 mg) once daily. Randomization was stratified by prior second-generation androgen receptor pathway inhibitor (abiraterone or orteronel) or docetaxel (yes/no). Formal crossover from the placebo group to the talazoparib group was not part of the study design.

Before randomization, patients consented to provide solid tumor tissue (de novo or archival) and/or blood-based samples, for prospective assessment of HRR gene alterations (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *FANCA*, *RAD51C*, *NBN*, *MLH1*, *MRE11A*, *CDK12*) using FoundationOne® CDx and/or FoundationOne Liquid® CDx (Foundation Medicine). Historical FoundationOne® test results could also be used. Patients were considered HRR-deficient if they had one or more alteration(s) in at least one of these 12 genes. For prospective HRR status determination, test records generated after the randomization date were excluded. Alterations were defined as truncating short variants, selected inactivating short variants identified as known/likely pathogenic per FoundationOne® pipeline, inactivating rearrangements or homozygous deletion of one or more exons. The definition of HRR alterations was the same for FoundationOne® Liquid CDx, except homozygous deletion of one or more exons was limited to *BRCA1/BRCA2* only. Notably, patients with heterozygous deletions of one or more exons alone were not enrolled in the HRR-deficient population.

Enrollment of patients with *ATM* and/or *CDK12* gene alterations was paused between January and November 2021 as their observed prevalence exceeded expectations[7] and was anticipated to suppress the representation of alterations in the remaining genes under study. The pause in enrollment of patients with *ATM* and/or *CDK12* gene alterations was driven by expected prevalence numbers based on the largest and most comprehensive prospective assessment of prostate cancer tumor samples using the FoundationOne® assay[7]. This pause occurred in a blinded fashion regarding distribution of HRR alterations to the two treatment arms and allowed a rebalancing of the distribution across the 12-gene panel in an effort to best reflect the prevalence in mCRPC[7].

Study treatment continued until radiographic progression, adverse event leading to permanent discontinuation, patient decision to discontinue or death. Treatment could continue after radiographic progression if the investigator determined benefit was still being derived.

The 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. The following independent ethics committees or Institutional Review Boards provided study approval: Comite de Revision Institucional - Hospital Britanico de Buenos Aires, CABA, Argentina; Comite de Etica 'Dr. Claude Bernard', Rosario, Argentina; Comite de Etica en Investigacion - Centro de Educacion Medica e Investigaciones Clinicas 'Norberto Quirno' – CEMIC, CABA, Argentina; Comite de Etica en Investigacion de la Fundacion OncoSalud (CEIFOS), Pergamino, Argentina; Comite Independiente De Etica Para Ensayos En Farmacologia Clinica, CABA, Argentina; Comite Institucional de Etica de la Investigacion en Salud (C.I.E.I.S) de la Clinica Universitaria Reina Fabiola, Cordoba, Argentina; Comite Institucional de Etica de Investigacion en Salud del Hospital Privado Centro Medico de Cordoba, Cordoba, Argentina; St Vincent's Hospital Human Research Ethics Committee, Darlinghurst, Australia; Bellberry Limited, Eastwood, Australia; Commissie Voor Medische Ethiek, Gent, Belgium; Comissao Nacional de Etica em Pesquisa/CONEP, Brasilia, Brazil; Comite de Etica em Pesquisa da Fundacao Pio XII - Hospital de Cancer de Barretos, Barretos, Brazil; Comite de Etica em Pesquisa da Universidade do Vale do Taquari – UNIVATES, Lajeado, Brazil; Comite de Etica em Pesquisa do Hospital Mae de Deus, Porto Alegre, Brazil; Comite de Etica em Pesquisa do Instituto D'Or de Pesquisa e Ensino, Rio de Janeiro, Brazil; Comite de Etica em Pesquisa-Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil; Comite de Etica em Pesquisa da Universidade Regional do Noroeste do Estado do Rio Grande do Sul, Ijui, Brazil; Comite de Etica em Pesquisa - CEP do Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo - HCFMUSP, Sao Paulo, Brazil; Comite de Etica em Pesquisa da Faculdade de Medicina do ABC, Santo Andre, Brazil; Comitê de Ética em Pesquisa do Instituto Nacional de Câncer Jose Alencar Gomes da Silva – INCA, Rio de Janeiro, Brazil; Comite de Etica em Pesquisa do Hospital Nossa Senhora da Conceicao - Grupo Hospitalar Conceicao, Porto Alegre, Brazil; Comite de Etica em Pesquisa da Sociedade Beneficente de Senhoras Hospital Sirio Libanes, Sao Paulo, Brazil; Comitê de Ética em Pesquisa do Hospital Alemão Oswaldo Cruz – SP, Sao Paulo, Brazil; Comite de Etica em Pesquisa da Pontificia Universidade Catolica do Rio Grande do Sul-PUC/RS, Porto Alegre, Brazil; Comite d'ethique de la recherche du CHUM, Montreal, Canada; Health Research Ethics Board of Alberta - Cancer Committee, Edmonton, Canada; Ontario Cancer Research Ethics Board, Toronto, Canada; Comite de Etica Cientifico Servicio de Salud Metropolitano Oriente, Santiago, Chile; Comite Etico Cientifico Hospital Gustavo Fricke Servicio de Salud Vina del Mar – Quillota, Vina del Mar, Chile; Comite de Etica Cientifica Servicio Salud Araucania Sur, Temuco, Chile; Ethics Committee of Zhongshan Hospital Fudan University, Shanghai, China; Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Ethics committee of Zhejiang Cancer Hospital, Hangzhou, China; Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Ethics Committee of Chongqing University Cancer Hospital, Chongqing, China; Ethics Committee of Beijing Cancer Hospital, Beijing, China; Ethics Committee of The First Affiliated Hospital of Anhui Medical University, Hefei, China; Medical Ethics Committee of First Affiliated Hospital of Xiamen University, Xiamen, China; Wuxi People's Hospital Ethics Committee, Wuxi, China; Ethics Committee of Nanjing Drum Tower Hospital, Nanjing, China; Ethics Committee of Shanghai Tenth People's Hospital, Shanghai, China; Clinical Trial Ethics Committee of Huazhong University of Science and Technology, Wuhan, China; Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China; Ethics Committee of Fudan University Cancer Hospital, Shanghai, China; Ethics Committee of Beijing Hospital, Beijing, China; Ethics Committee of Peking University First Hospital, Beijing, China; Peking University Third Hospital Medical Science Research Ethics Committee, Beijing, China; Ethics Committee for Clinical Trials of Drugs (Medical Apparatus) of Ningbo First Hospital, Ningbo, China; Ethics Committee of Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China; West China Hospital of Sichuan University Clinical Trial Ethics Committee, Chengdu, China; EC of Second Affiliated Hospital of Suzhou University, Suzhou, China; Shanghai General Hospital Medical Ethics Committee, Shanghai, China; Ethics Committee of Nanjing First Hospital, Nanjing, China; Clinical Trial Ethics Committee of Huazhong University of Science and Technology, Wuhan, China; Drug and Machinery Clinical trial Branch of EC of The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; Ethics Committee of

Yunnan Cancer Hospital, Kunming, China; The First Affiliated Hospital of Nanchang University Ethics Committee, Nanchang, China; Jilin Cancer Hospital Institutional Review Board, Changchun, China; Ethics Committee of The Second Hospital of Tianjin Medical University, Tianjin, China; Ethics Committee of Zhejiang Provincial People's Hospital, Hangzhou, China; Ethics Committee of The Fifth People's Hospital of Shanghai, Fudan University, Shanghai, China; Ethics Committee of Nantong Tumor Hospital, Nantong, China; Medical Ethics Committee of The First People's Hospital of Lianyungang, Lianyungang, China; The Clinical Trial Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; Eticka komise Krajska zdravotni a.s., Masarykova nemocnice v Usti nad Labem, Usti and Labem, Czech Republic; Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice Kralovske Vinohrady, Praha, Czech Republic; Eticka komise Fakultni Nemocnice Ostrava, Ostrava-Poruba, Czech Republic; Eticka komise Fakultni nemocnice Hradec Kralove, Hradec Kralove, Czech Republic; Helsingin ja Uudenmaan sairaanhoitopiiri, Helsinki, Finland; Comite De Protection Des Personnes (CPP) Sud-Ouest Et Outre-Mer III, Bordeaux, France; Ethikkommission der Aerztekammer Hamburg, Hamburg, Germany; Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága, Budapest, Hungary; Bnai Zion Medical Center Helsinki Committee, Haifa, Israel; Rambam Health Care Campus Helsinki Committee, Haifa, Israel; Tel Aviv Sourasky Medical Center Helsinki Committee, Tel Aviv, Israel; Rabin Medical Center Helsinki Committee, Petah Tikva, Israel; Shaare Zedek Medical Center Helsinki Committee, Jerusalem, Israel; Comitato Etico Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano, Italy; Comitato Etico Val Padana, Cremona, Italy; Comitato Etico Regionale (CER) dell'Umbria, Perugia, Italy; Comitato Etico Cardarelli-Santobono, Napoli, Italy; Comitato Etico Per Le Sperimentazioni Cliniche Dell'Azienda Provinciale Per I Servizi Sanitari, Trento, Italy; Comitato Etico della Romagna (CEROM), Meldola, Italy; Comitato Etico di Brescia, Brescia, Italy; Comitato Etico di Area Vasta Emilia Centro, Bologna, Italy; Comitato Etico IRCCS Pascale, Napoli, Italy; National Hospital Organization Central Review Board, Meguro-ku, Tokyo, Japan; National Cancer Center Institutional Review Board, Chuo-ku, Tokyo, Japan; Kindai University Hospital Institutional Review Board, Osakasayama, Japan; Yokohama City University Medical Center Institutional Review Board, Yokohama, Japan; Keio University Hospital Institutional Review Board, Shinjuku-ku, Tokyo, Japan; Nagoya University Hospital Institutional Review Board, Nagoya, Japan; Hokkaido University Hospital Institutional Review Board, Sapporo, Japan; Tokushima University Hospital Institutional Review Board, Tokushima, Japan; Chiba Cancer Center Institutional Review Board, Chiba, Japan; Hirosaki University School of Medicine & Hospital Institutional Review Board, Hirosaki, Japan; Yamagata Prefectural Central Hospital Institutional Review Board, Yamagata, Japan; Yokosuka Kyosai Hospital Institutional Review Board, Yokosuka, Japan; Hamamatsu University School of Medicine, University hospital Institutional Review Board, Hamamatsu, Japan; Osaka International Cancer Institute Institutional Review Board, Osaka-shi, Japan; Osaka University Hospital Institutional Review Board, Suita, Japan; Kanazawa University Hospital Institutional Review Board, Kanazawa, Japan; Kagoshima University Hospital Institutional Review Board, Kagoshima, Japan; Yamagata University Hospital Institutional Review Board, Yamagata, Japan; Kyungpook National University Chilgok Hospital Institutional Review Board, Daegu, Republic of Korea; Samsung Medical Center Institutional Review Board, Seoul, Republic of Korea; Asan Medical Center Institutional Review Board, Seoul, Republic of Korea; Severance Hospital, Yonsei University Health System Institutional Review Board, Seoul, Republic of Korea; Pusan National University Hospital Institutional Review Board, Busan, Republic of Korea; Seoul National University Hospital Institutional Review Board, Seoul, Republic of Korea; National Cancer Center Institutional Review Board, Goyang-si, Republic of Korea; The Catholic University of Korea Seoul St. Mary's Hospital Institutional Review Board, Seoul, Republic of Korea; Health and Disability Ethics Committee, Wellington, New Zealand; REK Sor-Ost, Oslo, Norway; Comite Institucional de Etica en Investigacion del INEN, Lima, Peru; Comite Institucional de Bioetica de Via Libre, Lima, Peru; Komisja Bioetyczna przy Okregowej Izbie Lekarskiej w Gdansku, Gdansk, Poland; Comissao de Etica para a Investigacao Clinica, Lisboa, Portugal; University of the Witwatersrand Human Research Ethics Committee (Medical), Johannesburg, South Africa; CEIm del Hospital Universitari Vall d'Hebron, Barcelona, Spain; Etikprovningsmyndigheten, Uppsala, Sweden; Health and Care Research Wales, Wales REC 3, Cardiff, United Kingdom; Advarra Institutional Review Board, Columbia, MD, United States; Vanderbilt Human Research Protection Program (VHRPP) Institutional Review Board, Nashville, TN, United States; 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Institutional Review Board, Lakeland, FL, United States; VA Med Ctr, Long Beach CA Institutional Review Board #1, Long Beach, CA, United States; Rush University Medical Center Institutional Review Board, Chicago, IL, United States; UCLA Office of the Human Research Protection Program, Los Angeles, CA, United States; VA Saint Louis Healthcare System Institutional Review Board, St. Louis, MO, United States; Baylor Scott and White Research Institute Institutional Review Board-Gold, Temple, TX, United States; Providence St. Joseph Health Institutional Review Board, Renton, WA, United States; IntegReview, Austin, TX, United States; Kaiser Permanente Northwest Institutional Review Board, Portland, OR, United States; Ochsner Institutional Review Board, New Orleans, LA, United States; Eisenhower Medical Center, Institutional Review Board, Rancho Mirage, CA, United States. All patients provided written informed consent.

Trial endpoints

The primary endpoint was rPFS by blinded independent central review per Response Evaluation Criteria in Solid Tumors (version 1.1; soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease)[23]. A full list of secondary endpoints is included in the Supplementary Methods, and these endpoints have been previously listed[23]. Planned secondary endpoints not reported in this article are: time to opiate use for prostate cancer pain, pharmacokinetics and patient-reported outcomes.

Exploratory subgroup analyses were conducted for rPFS by baseline characteristics (Supplementary Methods). A post hoc analysis of rPFS by *BRCA1/BRCA2* alteration status (yes/no) and by single genes and hierarchical gene clusters (*BRCA*, *PALB2*, *CDK12*, *ATM* and any of all other HRR genes) was also performed (Supplementary Methods).

Statistical analysis

Approximately 380 patients with HRR gene alterations were to be enrolled. To maintain overall type I error at or below a one-sided alpha level of 0.025, alpha was split equally between the all-comers cohort and HRR-deficient population.

For the primary comparison in the HRR-deficient population, 224 PFS 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. A prespecified interim analysis of PFS was planned after approximately 70% of the expected events (157 events). The HRR-deficient cohort would be stopped if the efficacy boundary was crossed and an interim efficacy analysis of overall survival would be performed. As the efficacy boundary ($P \leq 0.0038$) was crossed at this interim analysis, this became the final analysis. Other endpoints had no adjustment for multiplicity. Survival and safety follow-up continue.

Time-to-event endpoints 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 Cox proportional hazards model. Median time-to-event endpoints were estimated by the Kaplan–Meier method, and 95% CIs based on the Brookmeyer–Crowley method. For subgroup analysis of rPFS (except by *BRCA* status), the HR was based on an unstratified Cox model with treatment as the only covariate due to small patient numbers in some subgroups. Missing/partial dates were imputed as specified per protocol. Other missing data were not imputed. Reported *P* values are two sided.

Oracle Clinical Remote Data Capture was used for data collection, and SAS version 9.4 was used for data analysis.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

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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Author contributions

K.F., X.L., C.G.H., N.D.i.S., A.D.L., F.Z. and N.A. conceived and designed the study. X.L., C.G.H., N.D.i.S., A.D.L. and F.Z. acquired and analyzed the data. All authors contributed to data interpretation as well as development, writing and approval of the manuscript.

Competing interests

A.A.A. reports honoraria from Aculeus Therapeutics, Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Ipsen, Janssen, Merck Serono, Merck Sharp & Dohme, 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, Merck Sharp & Dohme, 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), MSD, Novartis, Pfizer, Sanofi and Synthorx; and travel, accommodations and/or expenses from Amgen, Astellas Pharma, Janssen, Merck Serono, Novartis, Pfizer and Tolmar; and receiving medical writing services 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. N.M. reports honoraria (personal) from Sanofi; research funding (institution) from Amgen, Astellas Pharma, AstraZeneca, Bayer, Chugai Pharma, Eisai, Janssen, Lilly, MSD, Pfizer, PRA Health Science, Roche, Seagen, Taiho and Takeda; and travel, accommodations and/or expenses (personal) from Pfizer. J.C. reports a consulting or advisory role for Advanced Accelerator Applications/Novartis, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Johnson & Johnson, MSD Oncology, Pfizer, Roche and Sanofi; participation in speakers' bureau for Astellas Pharma, Bayer and Johnson & Johnson; research funding (institution) from AB Science, Aragon Pharmaceuticals, AROG Pharmaceuticals, Astellas Pharma, AstraZeneca AB, AVEO Pharmaceuticals, Bayer AG, Blueprint Medicines, BN ImmunoTherapeutics, Boehringer Ingelheim España SA, Bristol Myers Squibb International Corporation, Clovis Oncology, Cougar Biotechnology, Deciphera, Exelixis, Genentech, GlaxoSmithKline, Incyte, Janssen-Cilag International NV, Karyopharm Therapeutics, Laboratoires Leurquin Mediolanum, Lilly, MedImmune, Millennium Pharmaceuticals, Nanobiotix, Novartis Farmacéutica SA, Pfizer, Puma Biotechnology, Roche, Sanofi Aventis GmbH, SFJ Pharmaceuticals Group and Teva; and travel, accommodations and/or expenses from AstraZeneca, BMS, Ipsen and Roche. 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Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-023-02704-x.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-023-02704-x.

Correspondence and requests for materials should be addressed to Karim Fizazi or Neeraj Agarwal.

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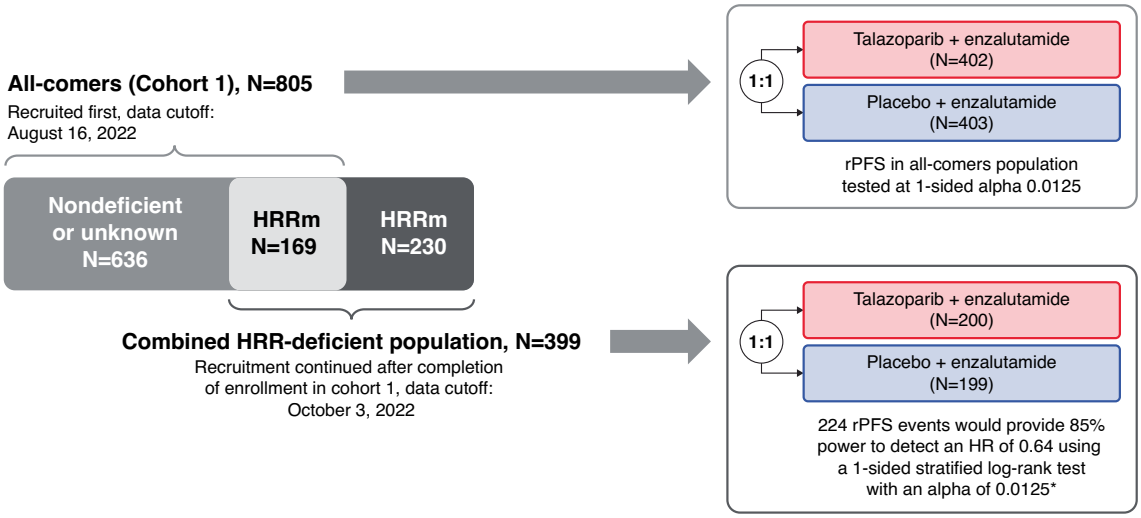

Extended Data Fig. 1 | Study Cohorts and Enrollment. *An interim analysis (IA) was planned with ~70% of the total required events. The HRRm cohort would be stopped for efficacy if the pre-specified efficacy boundary was crossed ($P \leq 0.003$). As the efficacy boundary was crossed at the IA rPFS, this became the final analysis. Survival and safety follow-up is continuing. All other endpoints are final. HRR denotes homologous recombination repair, HRRm HRR mutation-positive, and rPFS radiographic progression-free survival.

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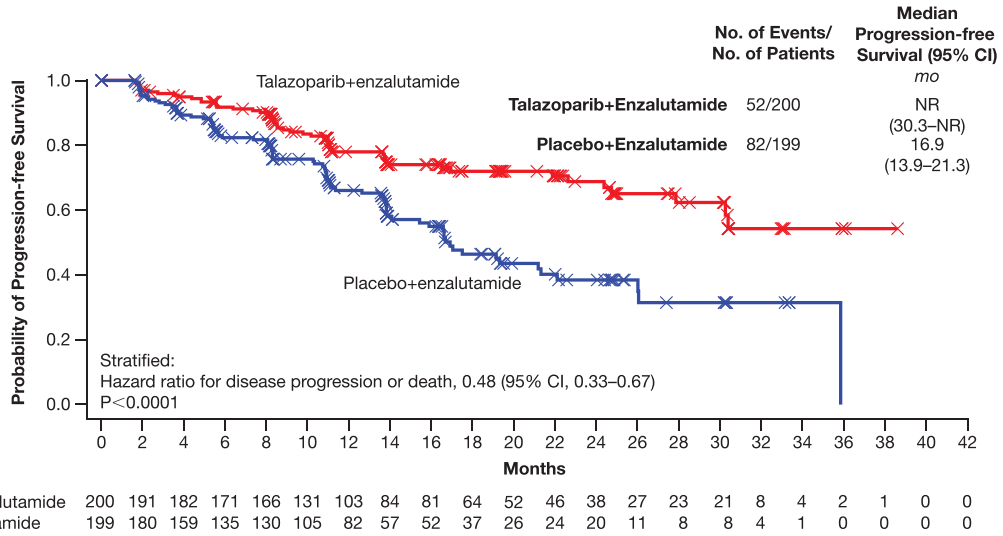

No. at Risk																					
Talazoparib+enzalutamide	200	191	182	171	166	131	103	84	81	64	52	46	38	27	23	21	8	4	2	1	0	0
Placebo+enzalutamide	199	180	159	135	130	105	82	57	52	37	26	24	20	11	8	8	4	1	0	0	0	0

Extended Data Fig. 2 | Investigator-Assessed rPFS (HRR-Deficient Intention-to-Treat Population). rPFS was compared between treatment groups using stratified log-rank test. HRs and associated 95% two-sided CIs were estimated by a Cox proportional hazards model. Median time to event was estimated by the Kaplan-Meier method, and 95% CIs based on the Brookmeyer-Crowley method. The P value is two-sided. CI denotes confidence interval, HR hazard ratio, HRR homologous recombination repair, NR not reached at the time of the analysis, and rPFS radiographic progression-free survival.

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Extended Data Table 1 | Additional Baseline Disease Characteristics (HRR-Deficient Intention-to-Treat Population)

Characteristic	Talazoparib + Enzalutamide (N=200)	Placebo + Enzalutamide (N=199)
Initial M stage at primary diagnosis*		
M0	84 (42)	84 (42)
M1	96 (48)	95 (48)
MX	19 (10)	17 (9)
Androgen deprivation therapy at baseline		
Bilateral orchiectomy	5 (2)	11 (6)
Androgen deprivation therapy	195 (98)	187 (94)†
Tissue source for prospective HRR gene alteration testing‡		
Tumor tissue only	75 (38)	80 (40)
Tumor tissue and blood (circulating tumor DNA)	123 (62)	119 (60)
Blood (circulating tumor DNA) only	1 (<1)	0

Data are no. (%). *Not reported for the remaining patients. †Prior androgen deprivation therapy was not available in the clinical database for one patient as of the data cutoff, although this patient received androgen deprivation therapy prior to enrollment and continued to receive this treatment. ‡The tissue source was not specified for one patient in the talazoparib arm. HRR denotes homologous recombination repair.

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Extended Data Table 2 | Representativeness of study participants

Category	
Disease under investigation	Metastatic castration-resistant prostate cancer
Special considerations related to:	
Age	Prevalence increases steeply with age, with the highest incidence in men >65 years of age
Race or ethnicity	African-American males have higher incidence and mortality rates for prostate cancer than White males
Geography	Throughout the world, prostate cancer incidence and mortality rates vary widely between countries, with mortality rates in 2020 between 7.8 and 13.7 per 100,000 in Europe, 8.3 in North America, and some of the lowest mortality rates in Asia (4.6 per 100,000 in East Asia)
Prior treatment	Many patients with metastatic castration-resistant prostate cancer will have received prior treatment for castration-sensitive disease with androgen deprivation therapy plus a hormonal therapy, such as abiraterone or enzalutamide, possibly in combination with docetaxel
Genetic alterations	Approximately one-quarter of advanced prostate cancers are reported to have alterations in DNA damage response genes involved either directly or indirectly in HRR, the most common being *BRCA2* (approximately 10%)
Overall representativeness of this trial	The age distribution of patients was consistent with that expected, with the majority of patients aged >65 years. The proportion of Black or African-American patients who underwent randomization was small (3%). Men were enrolled from diverse geographic locations including North America (12%), Europe/United Kingdom (48%), Asia (20% in China, Japan, and Republic of Korea), and the rest of the world (19%). More than half of the men received prior first-generation anti-androgen therapy* and approximately 30% received prior docetaxel. Only 8% of patients had received prior abiraterone. The patients were selected for HRR gene alterations; approximately 40% of these had *BRCA1/2* gene alterations

*Bicalutamide, flutamide, nilutamide, cyproterone acetate. HRR denotes homologous recombination repair.

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Extended Data Table 3 | Additional secondary efficacy outcomes (HRR-deficient intention-to-treat population)

	Talazoparib + Enzalutamide (N=200)	Placebo + Enzalutamide (N=199)	Hazard Ratio	P value (Two-Sided)
Median duration of response* (95% CI) — mo	20.3 (12.2–NR)	14.8 (6.6–25.8)		
PSA response ≥50%† — n/N (%)	171/198 (86)	125/199 (63)		<0.0001
(95% CI)	(81–91)	(56–70)		
Time to initiation of subsequent antineoplastic therapy				
Patients with use — no. (%)	44 (22)	85 (43)		
Median time to use (95% CI) — mo	NR (NR–NR)	18.8 (15.4–NR)	0.40	<0.0001
Time to first symptomatic skeletal event				
Patients with event — no. (%)	36 (18)	45 (23)		
Median time to first event (95% CI) — mo	NR (33.9–NR)	NR (32.9–NR)	0.69	0.09

Time-to-event endpoints were compared between treatment groups using stratified log-rank test. HRs and associated 95% two-sided CIs were estimated by a Cox proportional hazards model. Median time-to-event endpoints were estimated by the Kaplan–Meier method, and 95% CIs based on the Brookmeyer–Crowley method. P values are two-sided. *Only includes patients with confirmed complete response or partial response: talazoparib plus enzalutamide (*N*=49); placebo plus enzalutamide (*N*=26). †The number of patients with a baseline PSA value and at least one post-baseline PSA value: talazoparib plus enzalutamide (*N*=198); placebo plus enzalutamide (*N*=199). CI denotes confidence interval, HRR homologous recombination repair, NR not reached at the time of the analysis, and PSA prostate-specific antigen.

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Corresponding author(s): Karim Fizazi

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Oracle Clinical Remote Data Capture was used for data collection.
Data analysis	SAS version 9.4 was used for the data analysis.

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Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The study was in patients with metastatic castration-resistant prostate cancer; therefore, all participants were of male sex.
Reporting on race, ethnicity, or other socially relevant groupings	The baseline characteristics, including race, are reported in Table 1. As noted in Table S2 on the representativeness of the study participants, the proportion of Black or African-American patients who underwent randomization was small (3%). Men were enrolled from diverse geographic locations including North America (12%), Europe/United Kingdom (48%), Asia (20% in China, Japan, and Republic of Korea), and the rest of the world (19%).
Population characteristics	The baseline characteristics are reported in Table 1. The age distribution of patients was consistent with that expected, with the majority of patients aged >65 years. This manuscript reports the results in the HRR-deficient population selected for HRR gene alterations; approximately 40% of these had BRCA1/2 gene alterations. More than half of the men received prior first-generation anti-androgen therapy (bicalutamide, flutamide, nilutamide, cyproterone acetate) and approximately 30% received prior docetaxel. Only 8% of patients had received prior abiraterone.
Recruitment	Patients were enrolled in the TALAPRO-2 trial at 223 sites in 26 countries, including the USA, Europe, Israel, South America, South Africa, and the Asia-Pacific region. Part 2 of the TALAPRO-2 trial, including the HRR-deficient population reported in this manuscript, was randomized, double-blind, placebo-controlled, and an independent radiology facility was used to evaluate the primary endpoint (rPFS). Principal investigators selected patients based on their clinical judgment and their ability to ensure that the patients could meet the study requirements. In addition, there was scientific acknowledgement that the participants could benefit overall from the study intervention in alignment with randomized, double-blind, placebo-controlled trial principles. In protocol Amendment No. 6, the inclusion criteria were updated to reflect that HRR gene alteration status for participants randomized in Part 2 was determined by prospective testing using FoundationOne®CDx (tissue) and/or FoundationOne®Liquid CDx. Participants were considered HRR-deficient if the participant had one or more alteration(s) in at least one of the 12 HRR genes or if there was a discordant result between the tissue and liquid results.
Ethics oversight	The 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. The following independent ethics committees or Institutional Review Boards provided study approval: Comite de Revision Institucional - Hospital Britanico de Buenos Aires, CABA, Argentina; Comite de Etica "Dr. Claude Bernard", Rosario, Argentina; Comite de Etica en Investigacion - Centro de Educacion Medica e Investigaciones Clinicas "Norberto Quirno" – CEMIC, CABA, Argentina; Comite de Etica en Investigacion de la Fundacion OncoSalud (CEIFOS), Pergamino, Argentina; Comite Independiente De Etica Para Ensayos En Farmacologia Clinica, CABA, Argentina; Comite Institucional de Etica de la Investigacion en Salud (C.I.E.I.S) de la Clinica Universitaria Reina Fabiola, Cordoba, Argentina; Comite Institucional de Etica de Investigacion en Salud del Hospital Privado Centro Medico de Cordoba, Cordoba, Argentina; St Vincent's Hospital Human Research Ethics Committee, Darlinghurst, Australia; Bellberry Limited, Eastwood, Australia; Commissie Voor Medische Ethiek, Gent, Belgium; Comissao Nacional de Etica em Pesquisa/CONEP, Brasilia, Brazil; Comite de Etica em Pesquisa da Fundacao Pio XII - Hospital de Cancer de Barretos, Barretos, Brazil; Comite de Etica em Pesquisa da Universidade do Vale do Taquari – UNIVATES, Lajeado, Brazil; Comite de Etica em Pesquisa do Hospital Mae de Deus, Porto Alegre, Brazil; Comite de Etica em Pesquisa do Instituto D'Or de Pesquisa e Ensino, Rio de Janeiro, Brazil; Comite de Etica em Pesquisa-Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil; Comite de Etica em Pesquisa da Universidade Regional do Noroeste do estado do Rio Grande do Sul, Ijui, Brazil; Comite de Etica em Pesquisa - CEP do Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo - HCFMUSP, Sao Paulo, Brazil; Comite de Etica em Pesquisa da Faculdade de Medicina do ABC, Santo Andre, Brazil; Comitê de Ética em Pesquisa do Instituto Nacional de Câncer Jose Alencar Gomes da Silva – INCA, Rio de Janeiro, Brazil; Comite de Etica em Pesquisa do Hospital Nossa Senhora da Conceicao - Grupo Hospitalar Conceicao, Porto Alegre, Brazil; Comite de Etica em Pesquisa da Sociedade Beneficente de Senhoras Hospital Sirio Libanes, Sao Paulo, Brazil; Comitê de Ética em Pesquisa do Hospital Alemão Oswaldo Cruz – SP, Sao Paulo, Brazil; Comite de Etica em Pesquisa da Pontificia Universidade Catolica do Rio Grande do Sul-PUC/RS, Porto Alegre, Brazil; Comite d'ethique de la recherche du CHUM, Montreal, Canada; Health Research Ethics Board of Alberta - Cancer Committee, Edmonton, Canada; Ontario Cancer Research Ethics Board, Toronto, Canada; Comite de Etica Cientifico Servicio de Salud Metropolitano Oriente, Santiago, Chile; Comite Etico Cientifico Hospital Dr. Gustavo Fricke Servicio de Salud Vina del Mar – Quillota, Vina del Mar, Chile; Comite de Etica Cientifica Servicio Salud Araucania Sur, Temuco, Chile; Ethics Committee of Zhongshan Hospital Fudan University, Shanghai, China; Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Ethics committee of Zhejiang Cancer Hospital, Hangzhou, China; Ethics Committee of National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Ethics Committee of Chongqing University Cancer Hospital, Chongqing, China; Ethics Committee of Beijing Cancer Hospital, Beijing, China; Ethics Committee of The First Affiliated Hospital of Anhui Medical University, Hefei, China; Medical Ethics Committee of First Affiliated Hospital of Xiamen University, Xiamen, China; Wuxi People's Hospital Ethics Committee, Wuxi, China; Ethics Committee of Nanjing Drum Tower Hospital, Nanjing, China; Ethics Committee of Shanghai Tenth People's Hospital, Shanghai, China; Clinical Trial Ethics Committee of Huazhong University of Science and Technology, Wuhan, China; Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China; Ethics Committee of Fudan University Cancer Hospital, Shanghai, China; Ethics Committee of Beijing Hospital, Beijing, China; Ethics Committee of Peking University First Hospital, Beijing, China; Peking University Third Hospital Medical Science Research Ethics Committee, Beijing, China; Ethics Committee for Clinical Trials of Drugs (Medical Apparatus) of Ningbo First Hospital, Ningbo, China; Ethics Committee of Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China; West China Hospital of Sichuan University Clinical Trial Ethics Committee, Chengdu, China; EC of Second Affiliated Hospital of Suzhou University, Suzhou, China; Shanghai General Hospital Medical Ethics Committee, Shanghai, China; Ethics Committee of Nanjing First Hospital, Nanjing, China; Clinical Trial Ethics Committee of Huazhong University of Science and Technology, Wuhan, China; Drug and Machinery Clinical trial Branch of EC of The First Affil. Hosp. of Fujian Med. University, Fuzhou, China; Ethics Committee of Yunnan Cancer Hospital, Kunming, China; The First Affiliated Hospital of Nanchang

University Ethics Committee, Nanchang, China; Jilin Cancer Hospital Institutional Review Board, Changchun, China; Ethics committee of The Second Hospital of Tianjin Medical University, Tianjin, China; Ethics Committee of Zhejiang Provincial People's Hospital, Hangzhou, China; Ethics Committee of The Fifth People's Hospital of Shanghai, Fudan University, Shanghai, China; Ethics Committee of Nantong Tumor Hospital, Nantong, China; Medical Ethics Committee of The First People's Hospital of Lianyungang, Lianyungang, China; The Clinical Trial Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; Eticka komise Krajska zdravotni a.s., Masarykova nemocnice v Usti nad Labem, Usti and Labem, Czech Republic; Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice Kralovske Vinohrady, Praha, Czech Republic; Eticka komise Fakultni Nemocnice Ostrava, Ostrava-Poruba, Czech Republic; Eticka komise Fakultni nemocnice Hradec Kralove, Hradec Kralove, Czech Republic; Helsingin ja Uudenmaan sairaanhoitopiiri, Helsinki, Finland; Comite De Protection Des Personnes (CPP) Sud-Ouest Et Outre-Mer III, Bordeaux, France; Ethikkommission der Aerztekammer Hamburg, Hamburg, Germany; Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága, Budapest, Hungary; Bnai Zion Medical Center Helsinki Committee, Haifa, Israel; Rambam Health Care Campus Helsinki Committee, Haifa, Israel; Tel Aviv Sourasky Medical Center Helsinki Committee, Tel Aviv, Israel; Rabin Medical Center Helsinki Committee, Petah Tikva, Israel; Shaare Zedek Medical Center Helsinki Committee, Jerusalem, Israel; Comitato Etico Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano, Italy; Comitato Etico Val Padana, Cremona, Italy; Comitato Etico Regionale (CER) dell'Umbria, Perugia, Italy; Comitato Etico Cardarelli-Santobono, Napoli, Italy; Comitato Etico Per Le Sperimentazioni Cliniche Dell'Azienda Provinciale Per I Servizi Sanitari, Trento, Italy; Comitato Etico della Romagna (CEROM), Meldola, Italy; Comitato Etico di Brescia, Brescia, Italy; Comitato Etico di Area Vasta Emilia Centro, Bologna, Italy; Comitato Etico IRCCS Pascale, Napoli, Italy; National Hospital Organization Central Review Board, Meguro-ku, Tokyo, Japan; National Cancer Center IRB, Chuo-ku, Tokyo, Japan; Kindai University Hospital Institutional Review Board, Osakasayama, Japan; Yokohama City University Medical Center IRB, Yokohama, Japan; Keio University Hospital Institutional Review Board, Shinjuku-ku, Tokyo, Japan; Nagoya University Hospital IRB, Nagoya, Japan; Hokkaido University Hospital Institutional Review Board, Sapporo, Japan; Tokushima University Hospital Institutional Review Board, Tokushima, Japan; Chiba Cancer Center Institutional Review Board, Chiba, Japan; Hirosaki University School of Medicine & Hospital IRB, Hirosaki, Japan; Yamagata Prefectural Central Hospital Institutional Review Board, Yamagata, Japan; Yokosuka Kyosai Hospital Institutional Review Board, Yokosuka, Japan; Hamamatsu University School of Medicine, University hospital Institutional Review Board, Hamamatsu, Japan; Osaka International Cancer Institute Institutional Review Board, Osaka-shi, Japan; Osaka University Hospital Institutional Review Board, Suita, Japan; Kanazawa University Hospital IRB, Kanazawa, Japan; Kagoshima University Hospital Institutional Review Board, Kagoshima, Japan; Yamagata University Hospital Institutional Review Board, Yamagata, Japan; Kyungpook National University Chilgok Hospital Institutional Review Board, Daegu, Republic of Korea; Samsung Medical Center Institutional Review Board, Seoul, Republic of Korea; Asan Medical Center Institutional Review Board, Seoul, Republic of Korea; Severance Hospital, Yonsei University Health System Institutional Review Board, Seoul, Republic of Korea; Pusan National University Hospital Institutional Review Board, Busan, Republic of Korea; Seoul National University Hospital Institutional Review Board, Seoul, Republic of Korea; National Cancer Center Institutional Review Board, Goyang-si, Republic of Korea; The Catholic University of Korea Seoul St. Mary's Hospital Institutional Review Board, Seoul, Republic of Korea; Health and Disability Ethics Committee, Wellington, New Zealand; REK Sor-Ost, Oslo, Norway; Comite Institucional de Etica en Investigacion del INEN, Lima, Peru; Comite Institucional de Bioetica de Via Libre, Lima, Peru; Komisja Bioetyczna przy Okregowej Izbie Lekarskiej w Gdansku, Gdansk, Poland; Comissao de Etica para a Investigacao Clinica, Lisboa, Portugal; University of the Witwatersrand Human Research Ethics Committee (Medical), Johannesburg, South Africa; CEIm del Hospital Universitari Vall d'Hebron, Barcelona, Spain; Etikprovningsmyndigheten, Uppsala, Sweden; Health and Care Research Wales, Wales REC 3, Cardiff, United Kingdom; Advarra IRB, Columbia, MD, United States; Vanderbilt Human Research Protection Program (VHRPP) IRB, Nashville, TN, United States; University of Utah Institutional Review Board, Salt Lake City, UT, United States; Biomedical Research Alliance of New York, LLC / Institutional Review Board, Lake Success, NY, United States; Western Institutional Review Board, Puyallup, WA, United States; Sharp HealthCare Institutional Review Board, San Diego, CA, United States; Schulman Associates Institutional Review Board, Cincinnati, OH, United States; Loma Linda University Health - Institutional Review Board, Loma Linda, CA, United States; Administrative Panels on Human Subjects in Medical Research ("Stanford IRB"), Palo Alto, CA, United States; University of Maryland, Baltimore - Institutional Review Board, Baltimore, MD, United States; Cook County Health Office of Research and Regulatory Affairs, Chicago, IL, United States; Samaritan Health Services Regional Institutional Review Board, Corvallis, OR, United States; University of Iowa IRB-01, Human Subjects Office, Iowa City, IA, United States; Lakeland Regional Medical Center, Inc. IRB, Lakeland, FL, United States; VA Med Ctr, Long Beach CA IRB #1, Long Beach, CA, United States; Rush University Medical Center Institutional Review Board, Chicago, IL, United States; UCLA Office of the Human Research Protection Program, Los Angeles, CA, United States; VA Saint Louis Healthcare System Institutional Review Board, St. Louis, MO, United States; Baylor Scott and White Research Institute Institutional Review Board-Gold, Temple, TX, United States; Providence St. Joseph Health IRB, Renton, WA, United States; IntegReview, Austin, TX, United States; Kaiser Permanente Northwest Institutional Review Board, Portland, OR, United States; Ochsner Institutional Review Board, New Orleans, LA, United States; Eisenhower Medical Center, Institutional Review Board, Rancho Mirage, CA, United States. The full list of TALAPRO-2 investigators is included in the Supplementary Information table. All patients provided written informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size and power calculation were based on the log-rank test. For the primary comparison in the HRR-deficient population, 224

Sample size	progression-free survival events would provide 85% power to detect a hazard ratio of 0.64 using a one-sided stratified log-rank test at a significance level of 0.0125 with two pre-specified interim analyses based on Lan-DeMets α–spending and β-spending functions. Approximately 380 patients with HRR gene alterations were to be enrolled.
Data exclusions	Inclusion criteria for the TALAPRO-2 trial were pre-specified and previously published (Agarwal N et al. Future Oncol 2022;18(4):425-436).
Replication	Part 2 of TALAPRO-2 was a randomized, double-blind, placebo-controlled trial including a large number (N=399) of patients with HRR-deficient mCRPC. The FoundationOne®CDx and/or FoundationOne®Liquid CDx next-generation sequencing test was used for prospective assessment of HRR gene alterations. Enrollment of patients with ATM and/or CDK12 gene alterations was paused between January–November 2021 as their observed prevalence exceeded expectations and was anticipated to suppress representation of alterations in the remaining genes under study. The pause in enrollment of patients with ATM and/or CDK12 gene alterations was driven by expected prevalence numbers based on the largest and most comprehensive prospective assessment of prostate cancer tumor samples using the FoundationOne® Assay. This pause occurred in a blinded fashion regarding distribution of HRR alterations to the two treatment arms and allowed a rebalancing of the distribution across the 12 gene panel in an effort to best reflect the prevalence in mCRPC.
Randomization	Participants were randomized 1:1 by site personnel using a centralized Interactive Web Response System to talazoparib plus enzalutamide or matching placebo plus enzalutamide. Randomization was stratified by prior novel hormonal therapy or docetaxel for castration-sensitive prostate cancer.
Blinding	The sponsor, participants, and investigators were blinded to talazoparib or placebo during data collection, while enzalutamide was open-label (both treatment groups received enzalutamide). The blinding methodology in TALAPRO-2 prevented selection or ascertainment (i.e., information) biases and potentially improved the compliance and the retention of trial participants. In TALAPRO-2 the withholding of information about the assigned interventions from participants involved in the trial played a potentially major role in mitigating threats to the internal validity of the trial outcomes.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT03395197
Study protocol	A redacted version of the protocol will be available as part of the Supplementary Information.
Data collection	Data collection occurred at each study site (study start date: Dec 18, 2017; primary completion date: Oct 3, 2022 [NCT03395197; ClinicalTrials.gov]). Patients from 223 sites in 26 countries, including the USA, Europe, Israel, South America, South Africa, and the Asia-Pacific region were enrolled in the TALAPRO-2 trial (Agarwal N et al. Future Oncol 2022;18(4):425-436).
Outcomes	The primary endpoint was rPFS by blinded independent central review per RECIST 1.1 and PCWG3. Key secondary endpoints were overall survival, objective response rate, duration of soft tissue response, time to PSA progression, PSA response, PFS2 (investigator-assessed), safety, patient-reported outcomes, and pharmacokinetics.