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Patient-reported Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Harboring DNA Damage Response Alterations Treated with Talazoparib: Results from TALAPRO-1

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Abstract

Background: Talazoparib has shown antitumor activity with a manageable safety profile in men with metastatic castration-resistant prostate cancer (mCRPC) and DNA damage response (DDR)/homologous recombination repair (HRR) alterations.
Objective: To evaluate patient-reported health-related quality of life (HRQoL) and pain in patients who received talazoparib in the TALAPRO-1 study, with a special interest in patients harboring breast cancer susceptibility gene 1 or 2 (*BRCA1/2*) mutations.
Design, setting, and participants: TALAPRO-1 is a single-arm, phase 2 study in men with mCRPC DDR alterations either directly or indirectly involved in HRR, who previously received one to two taxane-based chemotherapy regimens for advanced prostate cancer and whose mCRPC progressed on one or more novel hormonal agents.
Outcome measurements and statistical analysis: Men completed the European Quality-of-life Five-dimension Five-level scale (EQ-5D-5L), EQ-5D visual analog scale (VAS), and Brief Pain Inventory—Short Form at predefined time points during the study. The patient-reported outcome (PRO) population included men who completed a baseline and one or more postbaseline assessments before study end. Longitudinal mixed-

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Poly(ADP-ribose) polymerase inhibitor
Patient-reported outcomes
TALAPRO-1 trial
Talazoparib

effect models assuming an unstructured covariance matrix were used to estimate the mean (95% confidence interval [CI]) change from baseline for pain and general health status measurements among all patients and patients with *BRCA1/2* mutations.

Results and limitations: In the 97 men in the PRO population treated with talazoparib (*BRCA1/2*, *n* = 56), the mean (95% CI) EQ-5D-5L Index improved (all patients, 0.05 [0.01, 0.08]; *BRCA1/2* subset, 0.07 [0.03, 0.10]), as did the EQ-5D VAS scores (all patients, 5.42 [2.65, 8.18]; *BRCA1/2* subset, 4.74 [1.07, 8.41]). Improvements in the estimated overall change from baseline (95% CI) in the mean worst pain were observed in all patients (−1.08 [−1.52, −0.65]) and the *BRCA1/2* subset (−1.15 [−1.67, −0.62]). The probability of not having had experienced deterioration of worst pain by month 12 was 84% for all patients and 83% for the *BRCA1/2* subset.

Conclusions: In heavily pretreated men with mCRPC and DDR/HRR alterations, talazoparib was associated with improved HRQoL in all patients and the *BRCA1/2* subset. In both patient groups, worst pain improved from baseline and the probability of not experiencing a deterioration in worst pain with talazoparib was high.

Patient summary: We show that talazoparib was associated at least with no change or improvements in health-related quality of life (HRQoL) and pain burden in men with metastatic castration-resistant prostate cancer and DNA damage response/homologous recombination repair gene alterations in the TALAPRO-1 study. These findings in patient-reported HRQoL and pain complement the antitumor activity and tolerability profile of talazoparib.

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1. Introduction

Talazoparib is a small-molecule poly(ADP-ribose) polymerase inhibitor (PARPi) licensed for the treatment of germline breast cancer susceptibility gene 1 or 2 (*BRCA1/2*)–mutated advanced breast cancer [1]. TALAPRO-1 is a single-arm, phase 2 study evaluating the antitumor effects and tolerability of talazoparib in men with metastatic castration-resistant prostate cancer (mCRPC) harboring DNA damage response (DDR) alterations involved in homologous recombination repair (HRR). Men included were previously treated with one to two taxane-based chemotherapy regimens for advanced prostate cancer and had their mCRPC progress on one or more novel hormonal agents [2]. In the TALAPRO-1 study, talazoparib demonstrated durable antitumor activity with a manageable safety profile [2]. Across all gene alterations included in the panel, patients evaluable for antitumor activity exhibited an objective response rate of 30% (95% confidence interval [CI], 21–40), and 72% who had both baseline and postbaseline assessments experienced a decline in prostate-specific antigen (PSA) level [2]. In patients with a *BRCA1/2* mutation, the objective response rate was 46%. The safety profile in TALAPRO-1 was consistent with previous observations, with anemia, nausea, decreased appetite, and asthenia reported as the most common all-grade treatment-emergent adverse events (TEAEs) [2–5]. Hematological adverse events (AEs) were managed by supportive care and dose modifications, with 26% of patients experiencing dose reductions due to TEAEs and 12% permanently discontinuing talazoparib, but rarely discontinuing due to hematological TEAEs [2,6].

Overall, the objective response rates and decline in PSA in TALAPRO-1 suggested that talazoparib is an effective therapy for men with mCRPC harboring DDR/HRR alterations [2]. It is important to consider the impact of treatment on cancer-related symptoms, including cancer-related pain [7,8]: significant treatment goals include improvement of health-related quality of life (HRQoL) in patients who are symptomatic, and maintenance or improvement of HRQoL in those who are asymptomatic or minimally symptomatic [9–11]. Therefore, evaluating HRQoL and patient-reported pain is important in this population. Overall improvement or maintenance in HRQoL, pain intensity, and pain interference with niraparib has recently been reported in men with mCRPC and HRR gene alterations [12]. This is the first report of patient-reported outcomes (PROs) of HRQoL and pain with talazoparib treatment in men with mCRPC with DDR/HRR alterations, with additional data presented for the subset of patients with *BRCA1/2* mutations.

2. Patients and methods

2.1. Study design

TALAPRO-1 is an open-label, international, single-arm, phase 2 study of talazoparib in men with mCRPC harboring DDR gene alterations involved either directly or indirectly in HRR. Study design details were published previously [2]. Briefly, men with measurable soft-tissue disease were enrolled if they met the following criteria: (1) had mCRPC and harbored gene alterations in one or more of 11 DDR/HRR genes (*ATM*, *ATR*, *BRCA1*, *BRCA2*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, or *RAD51C*) likely to sensitize to PARPi; (2) were previously treated with one to two taxane-based chemotherapy regimens for advanced prostate cancer; and (3) progressed on one or more novel hormonal therapies in mCRPC. Talazoparib was administered orally at 1 mg/d or, in those with moderate renal impairment, 0.75 mg/d. Patients with grade 3 or 4 AEs were treated with dose modifications or appropriate supportive care, or both.

Evaluating talazoparib's effects on HRQoL and patient-reported pain was the secondary objective of the TALAPRO-1 trial. The PRO population included men in the efficacy population who completed a baseline and one or more postbaseline assessments before the end of study treatment.

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This study followed Good Clinical Practice standards, the Declaration of Helsinki, and the International Council on Harmonisation. The institutional review board or ethics committee at each study site approved the protocol. All patients provided signed informed consent.

2.2. Tumor response

Extent of disease was based on assessment at the end of the study by computed tomography or magnetic resonance imaging. Response status (complete or partial responses, stable disease, or progressive disease) was evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 and assessed by a blinded independent central review and investigator assessment.

2.3. Adverse events

The incidence of AEs was evaluated, coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities, version 23.0, and classified by severity using the Common Terminology Criteria for Adverse Events, version 4.03.

2.4. Patient-reported outcomes

This study evaluated HRQoL and patient-reported pain using the European Quality-of-life Five-dimension Five-level scale (EQ-5D-5L) and Brief Pain Inventory—Short Form (BPI-SF) instruments, respectively, which were assessed at baseline, every 2 wk before week 9, every 4 wk before week 25, and every 12 wk thereafter until disease progression. The EQ-5D-5L assesses a patient's health status and is designed for self-completion [13]. It consists of a descriptive system that defines health in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with five response categories (no problems, slight problems, moderate problems, severe problems, and extreme problems) [13]. It includes a visual analog scale (VAS) for respondents to rate their current health status from 0 (worst health) to 100 (best imaginable health) [14]. A unique EQ-5D-5L health state (or profile) for each patient was generated by combining the results for the dimensions, consisting of a five-digit code [14]. The health states were then converted to a preference-weighted summary score (weights derived from the general population), or EQ-5D-5L health utility index, with scores ranging from –0.594 to 1, with higher scores indicating better outcomes [14].

Patient-reported pain was assessed using the BPI-SF, a nine-item self-administered questionnaire that assesses worst pain, pain severity, and pain interference [15]. The BPI-SF pain severity index comprises four averaged items (worst pain, least pain, average pain, and pain now), with each item scored on a numeric rating scale between 0 (no pain/no interference) and 10 (pain as bad as you can imagine/completely interferes) [16]. The BPI-SF pain interference index comprises seven averaged items (general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life) [15]. Pain symptoms were recorded for seven consecutive days before each study visit, and the BPI-SF was also completed during each visit. Pain score averages were calculated for each visit and used to analyze change from baseline.

An analgesic log was recorded for seven consecutive days before and during each study visit. The average analgesic usage score according to the World Health Organization (WHO) criteria for each visit period was calculated and used in analyses for time to deterioration (TTD) and time to improvement in patient-reported pain symptoms. The WHO criteria for analgesic usage scores are as follows: 0 = no use, 1 = use of nonopioid analgesics, 2 = use of weak opioids for moderate pain, and 3 = use of strong opioids for severe pain.

2.5. Statistical analysis

Longitudinal mixed-effect models assuming an unstructured covariance matrix were used to assess change from baseline in general health status (EQ-5D-5L), worst pain, pain severity, and pain interference (BPI-SF). The TTD in worst pain and pain severity was assessed using the scores from the BPI-SF and defined as ≥2-point increase from baseline on two consecutive visits ≥4 wk apart, without a decrease in the WHO analgesic usage score. The frequency (number and percentage of patients with an event or censored) is presented for all patients. Patients without observed pain progression at the time of analysis were censored at the date of the last BPI-SF assessment. Kaplan-Meier estimates were presented together with a summary of associated statistics including the median and quartiles with two-sided 95% CIs. AEs were summarized descriptively.

Table 1 – Patient demographics

Characteristic	All patients (*N* = 97)	*BRCA1/2* subset (*n* = 56)
Age (yr)		
Median (Q1, Q3)	69 (63, 73)	69 (63, 72)
Mean (SD)	68.1 (7.7)	67.3 (7.4)
Race, *n* (%)		
White	85 (88)	49 (88)
Black	3 (3.1)	3 (5.4)
Asian	2 (2.1)	0
Not reported	7 (7.2)	4 (7.1)
Renal impairment, *n* (%)		
Normal/mild	78 (80)	45 (80)
Moderate	19 (20)	11 (20)
Baseline serum PSA (μg/l)		
Median (Q1, Q3)	119 (26.9, 303.1)	98.3 (17.9, 299.6)
Mean (SD)	329 (576)	287 (518)
Baseline testosterone (ng/dl)		
Median (Q1, Q3)	10.1 (10.1, 17.9)	10.1 (10.1, 15.5)
Mean (SD)	14.8 (7.9)	13.8 (7.3)
Baseline CTC count (cells/7.5 ml of blood)		
Median (Q1, Q3)	4.5 (0.0, 39.5)	3.0 (0.0, 19.0)
Mean (SD)	77.0 (200)	60.6 (166)
Total Gleason score, *n* (%)		
≤6	9 (9.3)	4 (7.1)
7 (3 + 4) and (4 + 3)	31 (32)	17 (30)
8–10	56 (58)	34 (61)
Not reported	1 (1.0)	1 (1.8)
Initial M stage at primary diagnosis, *n* (%)		
M0	38 (39)	25 (45)
M1	43 (44)	23 (41)
Mx	12 (12)	6 (11)
Not reported	4 (4.1)	2 (3.6)
Disease site, *n* (%)		
Visceral	32 (33)	15 (27)
ECOG performance status, *n* (%)		
0	41 (42)	24 (43)
1	49 (51)	28 (50)
2	7 (7.2)	4 (7.1)
Prior taxane use, *n* (%)		
Docetaxel only	50 (52)	32 (57)
Docetaxel and cabazitaxel	46 (47)	24 (43)
Not reported	1 (1.0)	0
Prior NHT, *n* (%)		
Abiraterone only	32 (33)	24 (43)
Enzalutamide only	37 (38)	20 (36)
Abiraterone and enzalutamide	27 (28)	12 (21)
Not reported	1 (1.0)	0

BRCA1/2 = breast cancer susceptibility gene 1 or 2; CTC = circulating tumor cells; ECOG = Eastern Cooperative Oncology Group; Mx = cancer cannot be measured; NHT = novel hormonal therapy; PSA = prostate-specific antigen; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.

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Post hoc analyses included outcomes stratified by all patients and the *BRCA1/2* subset. BPI-SF outcomes were also stratified by baseline pain status (asymptomatic/mild [BPI-SF score 0–4] and moderate/severe [BPI-SF score 5–10]) and by tumor responses. A post hoc analysis of time to improvement in pain, TTD in pain severity and interference, TTD in the EQ-5D-5L Index and VAS scores, and time to first opioid use was also conducted. Deterioration for the EQ-5D-5L Index and VAS was defined as a decrease of ≥0.06 points and ≥10 points, respectively, for two consecutive visits ≥4 wk apart. The time to first opioid use among opioid-naive patients was defined as the time from baseline to the first visit at which opioid use was recorded. Time to improvement in pain was defined as a decrease of ≥2 points for two consecutive visits ≥4 wk apart without an increase in the WHO analgesic usage score.

This was a one-sample study using one-sample analysis methods. For analyses of the baseline pain status subgroups and clinical response status subgroups, we used the original one-sample methods for the evaluation of changes in HRQoL and pain outcomes within the individual subgroups, as this was a primary objective of the study. The results of the one-way longitudinal analyses are displayed as forest plots. However, we also carried out, for each of the two status categories, a two-way analysis with an interaction term for a direct comparison of the relevant subgroups for each of the endpoints—worst pain, pain severity, pain interference, EQ-5D-5L Index, and EQ-5D VAS. A significant interaction would require caution in making any statement directly comparing the relevant subgroups.

3. Results

3.1. Patients

In TALAPRO-1, of the 1425 men screened, 1297 did not have HRR gene alterations or meet eligibility criteria and were excluded. Participants were screened before March 11, 2020 and enrolled by March 20, 2020. A total of 128 men were enrolled, of whom 127 were in the safety population and 104 with measurable disease were in the efficacy population. The PRO population included 97 men (*BRCA1/2*, *n* = 56) in the efficacy population. Most were White (88%) with a median age of 69 yr. Demographic characteristics for the overall patient population and for the *BRCA1/2* subset are summarized in Table 1.

3.2. European Quality-of-life Five-dimension Five-level scale

Treatment with talazoparib was associated with significant overall improvement from baseline in the EQ-5D-5L Index and EQ-5D VAS in all patients and the *BRCA1/2* subset (Fig. 1A). For the EQ-5D-5L Index, the mean (95% CI) change from baseline was 0.05 (0.01, 0.08) in all patients and 0.07 (0.03, 0.10) in the *BRCA1/2* subset. For the EQ-5D VAS, the change from baseline was 5.42 (2.65, 8.18) in all patients

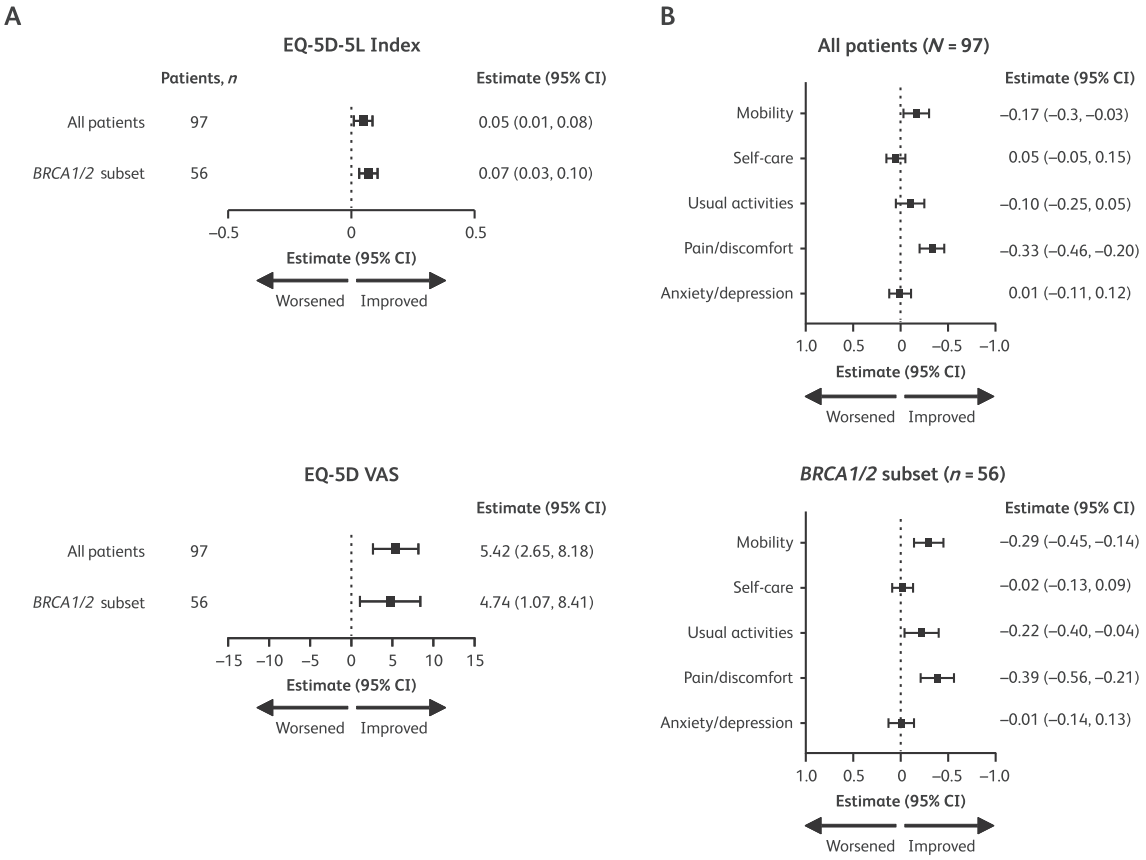

Fig. 1 – Change from baseline in EQ-5D-5L Index score, EQ-5D VAS scores, and EQ-5D-5L individual domain scores. The mean change from baseline by the overall patient population and the *BRCA1/2* subset of patients in the (A) EQ-5D-5L Index and EQ-5D VAS scores, and (B) EQ-5D-5L individual dimension scores. For the EQ-5D individual domains, higher scores are associated with worse health states, whereas for the EQ-5D-5L Index and EQ-5D VAS, larger values are associated with better health status. *BRCA1/2* = breast cancer susceptibility gene 1 or 2; CI = confidence interval; EQ-5D-5L = European Quality-of-life Five-dimension Five-level scale; VAS = visual analog scale.

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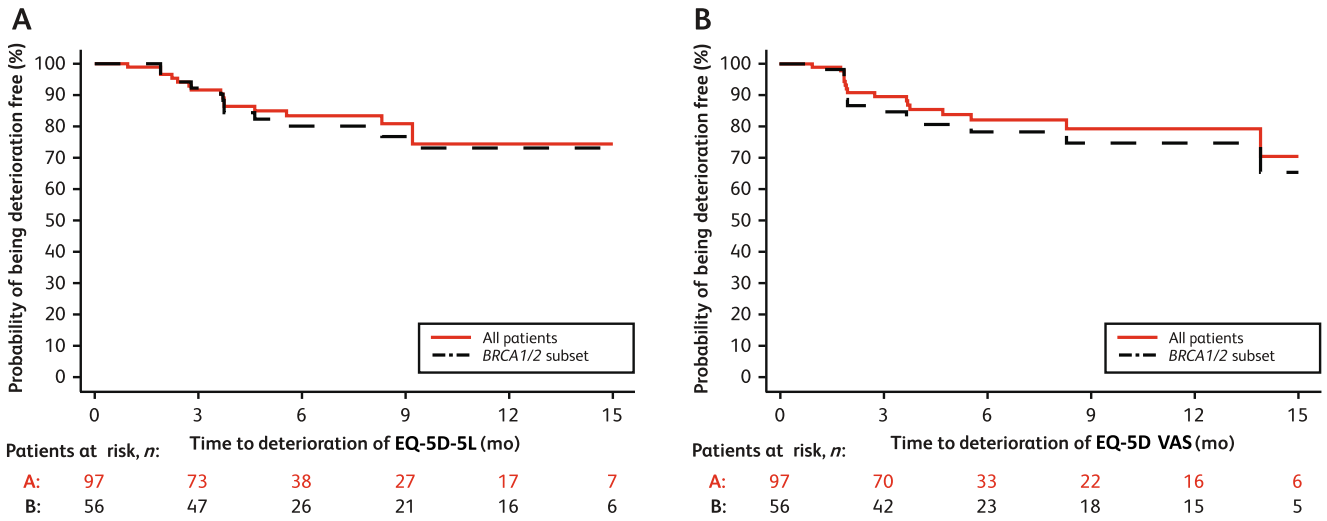

Fig. 2 – Time to deterioration analysis of the EQ-5D-5L Index and EQ-5D VAS score. Survival curves of time to deterioration in the (A) EQ-5D-5L Index and (B) EQ-5D VAS score in the overall population and the *BRCA1/2* subset. The minimally important differences for deterioration in the EQ-5D-5L Index and EQ-5D VAS score are ≥0.06 and ≥10 points, respectively, for two consecutive visits at least 4 wk apart. *BRCA1/2* = breast cancer susceptibility gene 1 or 2; EQ-5D-5L = European Quality-of-life Five-dimension Five-level scale; VAS = visual analog scale.

and 4.74 (1.07, 8.41) in the *BRCA1/2* subset. Based on changes from baseline in the individual EQ-5D-5L dimension scores, mobility and pain/discomfort improved in all patients and the *BRCA1/2* subset; usual activities improved in the *BRCA1/2* subset only (Fig. 1B). In the TTD analysis for the EQ-5D-5L, the probabilities of not having deteriorated by month 12 were 74% for the all-patient group and 73% for the *BRCA1/2* subset (Fig. 2A). The corresponding probabilities for the EQ-5D VAS were 79% and 75% (Fig. 2B).

3.3. *Brief Pain Inventory—Short Form*

3.3.1. *Change from baseline*

With talazoparib, improvements in the estimated overall change from baseline in mean pain burden (worst pain, pain severity, and pain interference) were observed in all patients and within the *BRCA1/2* subset. Additionally, improvements in the pain interference subscales were observed in all patients and within the *BRCA1/2* subset (general activity, mood, walking ability, normal work, relations, sleep, and enjoyment of life), except for interference with relations in all patients, which remained unchanged (Fig. 3A and 3B).

3.3.2. *By baseline pain*

In men with asymptomatic or mild baseline pain, BPI-SF scores (worst pain, pain severity, and pain interference) did not change with talazoparib (Fig. 4A). Among patients with moderate to severe baseline pain, talazoparib was associated with an improvement from baseline in worst pain, pain severity, and pain interference in all patients and within the *BRCA1/2* subset (Fig. 4B). In the direct comparison of the two baseline pain subgroups, there was a highly significant interaction (ie, interaction $p < 0.01$) for all three endpoints, that is, worst pain, pain severity, and pain interference, rendering direct comparison between subgroups inadvisable.

3.3.3. *By clinical response*

In the post hoc BPI-SF analysis by clinical response, an improvement in worst pain and pain severity was observed in patients with complete or partial response, stable disease, and progressive disease (Supplementary Fig. 1A). For pain interference, an improvement was observed in patients with complete or partial response and stable disease. Improvements were also observed for patients with complete or partial responses and stable disease in all the subscales of pain interference (except for relations in the stable disease group; Supplementary Fig. 1B). Among patients with progressive disease, individual pain interference scales remained unchanged (Supplementary Fig. 1B). In direct comparisons of the clinical outcome categories, no significant interaction (ie, $p > 0.05$) was seen for any of the pain endpoints.

3.3.4. *TTD and time to improvement*

In the TTD analysis for worst pain, the probabilities of not having deteriorated by month 12 were 84% for all patients and 83% for patients in the *BRCA1/2* subset (Supplementary Fig. 2A). The corresponding probabilities for all patients and the *BRCA1/2* subset were 89% for pain severity, and 88% and 90%, respectively, for pain interference (Supplementary Fig. 2B and 2C). In patients treated with talazoparib, pain deterioration in individual interference indices was generally similar across all patients and in the *BRCA1/2* subset (Supplementary Fig. 3). In the time to improvement analysis for worst pain, the probabilities of not having improved by month 12 were 64% for all patients and 62% for patients in the *BRCA1/2* subset (Supplementary Table 1). The corresponding probabilities for all patients and the *BRCA1/2* subset were 78% for pain severity, and 78% and 68%, respectively, for pain interference (Supplementary Table 2). Swimmer plots of clinically meaningful improvement or deterioration in worst pain by baseline pain status in the overall cohort excluding patients in the *BRCA1/2* subset

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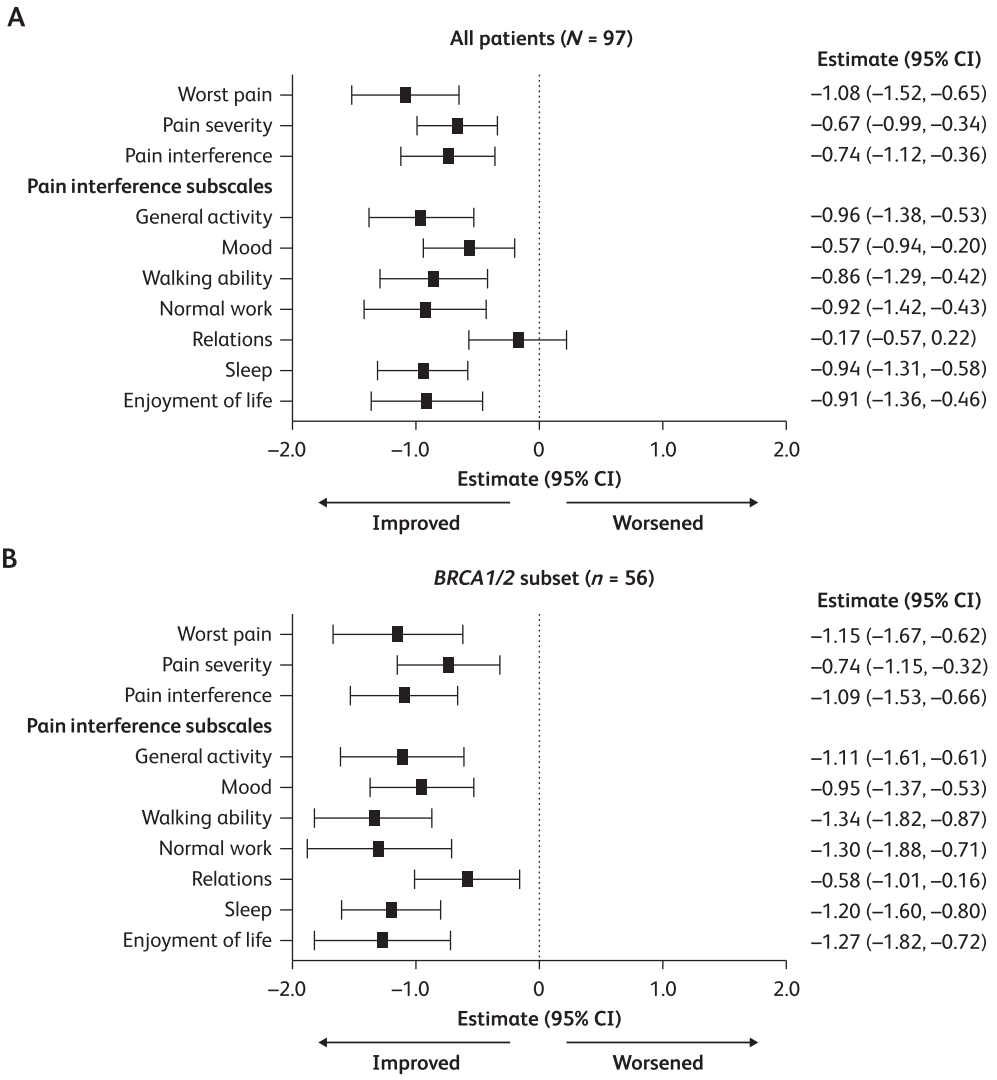

Fig. 3 – Estimated overall change from baseline in BPI-SF pain burden. The mean change from baseline by the (A) overall cohort and (B) *BRCA1/2* subset of patients in the self-reported worst pain, pain severity, and pain interference, and in the seven pain interference items. BPI-SF = Brief Pain Inventory—Short Form; *BRCA1/2* = breast cancer susceptibility gene 1 or 2; CI = confidence interval.

(rather than all patients, for simplicity) and in the *BCRA1/2* subset are presented in Supplementary Figure 4.

3.3.5. *Time to first opioid use*

Among opioid-naive patients at baseline, the probability of remaining opioid free at 12 mo was 62% in all patients and the *BRCA1/2* subset (Fig. 5).

3.4. *Safety*

In this PRO-evaluable population, 95% of all patients and 96% of patients in the *BRCA1/2* subset reported any all-cause TEAE (Supplementary Table 2). Anemia, nausea, and decreased appetite were the most commonly reported TEAEs. Anemia was the most common grade 3/4 TEAE in all patients (31%) and the *BRCA1/2* subset (36%).

When patients were stratified by the presence or absence of anemia, among those with anemia, the EQ-5D-5L Index score did not change in all patients but improved in the *BRCA1/2* subset (Supplementary Fig. 5). In addition, the EQ-5D VAS score improved among all patients. Among patients without anemia, the EQ-5D-5L Index score improved in all patients and the *BRCA1/2* subset, while the EQ-5D VAS score improved among all patients and remained unchanged in the *BRCA1/2* subset.

4. Discussion

In patients with metastatic cancer, delaying cancer progression while maintaining HRQoL is a major goal when developing new therapeutics [14,17]. The US Food and Drug Administration encourages PRO-based data as evidence of drug effectiveness, and has outlined a guidance that reviews and evaluates the existing methodologies used to generate PRO-based study reports [18]. In TALAPRO-1, talazoparib monotherapy had antitumor activity in men with germline and/or somatic DDR alterations associated with HRR, who had exhausted most available treatment options for mCRPC [2]. The antitumor effects were most pronounced in

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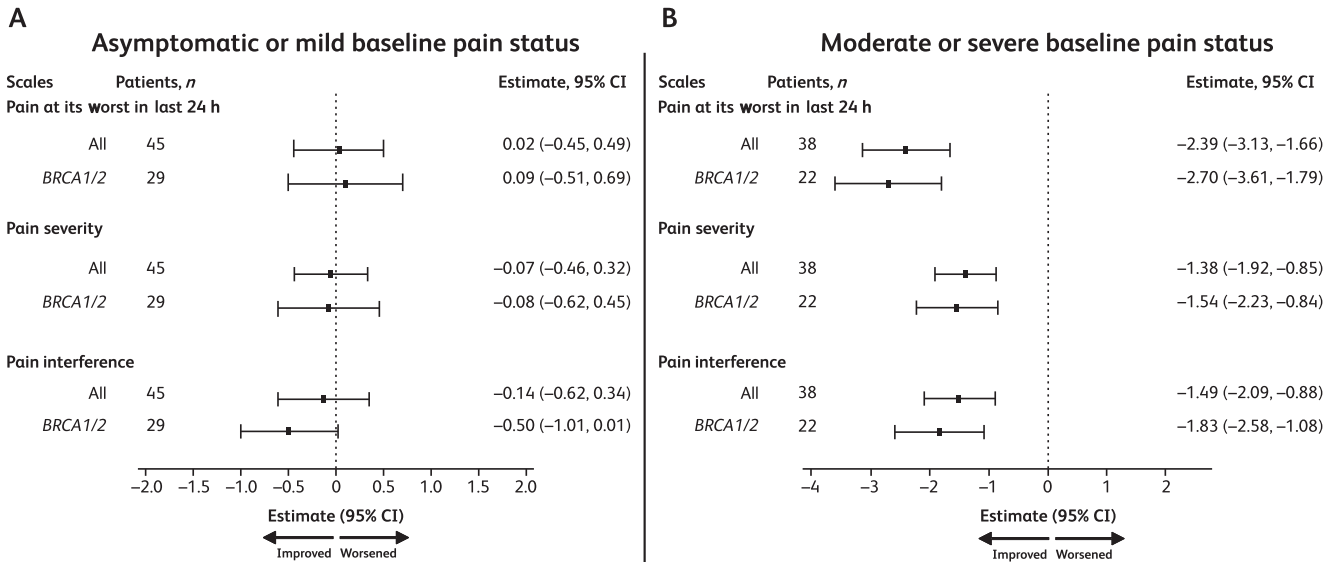

Fig. 4 – Forest plots of change from baseline in pain burden. Mean changes from baseline in self-reported worst pain, pain severity, and pain interference in the overall cohort and the *BRCA1/2* subset for patients whose baseline pain status was (A) asymptomatic or mild (BPI-SF score 0–4) and (B) moderate or severe (BPI-SF score 5–10). BPI-SF = Brief Pain Inventory—Short Form; *BRCA1/2* = breast cancer susceptibility gene 1 or 2; CI = confidence interval.

patients harboring *BRCA1/2* gene alterations among all other DDR/HRR tumor core genes. In cancer patients, PROs have been shown to be associated with clinical outcomes, particularly improvements in tumor response to therapy [19]. This suggested that TALAPRO-1 patients harboring *BRCA1/2* gene alterations would receive the most benefit in HRQoL and pain burden. Here, we show that HRQoL and patient-reported pain burden either improved or did not change after treatment with talazoparib, with more pronounced benefits in patients harboring *BRCA1/2* gene alterations.

Men with metastatic prostate cancer can experience significant pain, mostly related to bone metastases, and pain palliation through better cancer control is an important goal in the development of new therapeutics [20,21]. The phase 3 PROfound study (NCT02987543) of men with mCRPC and HRR gene alterations who progressed on prior novel hormonal agents reported that, compared with patients receiving enzalutamide or abiraterone, patients receiving olaparib reported better HRQoL functioning over time, delayed deterioration in HRQoL scores, and reduced pain burden [22]. In the phase 2 GALAHAD study (NCT02854436) of men with mCRPC and HRR gene alterations, niraparib treatment improved or maintained overall HRQoL, pain intensity, and pain interference, and those with *BRCA1/2* alterations had greater benefits [12]. In this study, among all patients and patients in the *BRCA1/2* subset, the EQ-5D-5L Index and EQ-5D VAS scores improved from baseline, and the probability of not having had experienced a deterioration in the EQ-5D-5L Index or EQ-5D VAS by month 12 with talazoparib was over 70%. Similarly, in all patients and in the *BRCA1/2* subset, the probability of not having had experienced a deterioration in worst pain by month 12 was >82%. Importantly, while patients who were asymptomatic at baseline would be unable to "improve" their pain status, it should be noted that the study patients were heavily pretreated and the finding that pain status in the asymptomatic/mild baseline pain subgroup did not deteriorate over time is clinically relevant. These findings add to available literature on PROs in PARPi therapies and demonstrate the beneficial effects of PARPi therapy on patient-reported pain.

For patients with metastatic prostate cancer, treatments are palliative; therefore, either no change and/or improvement in quality of life is an important goal. Here, in addition to the aforementioned benefits on pain burden, we show that talazoparib either maintained or improved HRQoL, as measured by both the EQ-5D-5L Index and the EQ-5D VAS. The way that overall health is described on the EQ-5D VAS can be influenced by any aspect of HRQoL that matters to the patient. It is not uncommon to see variation

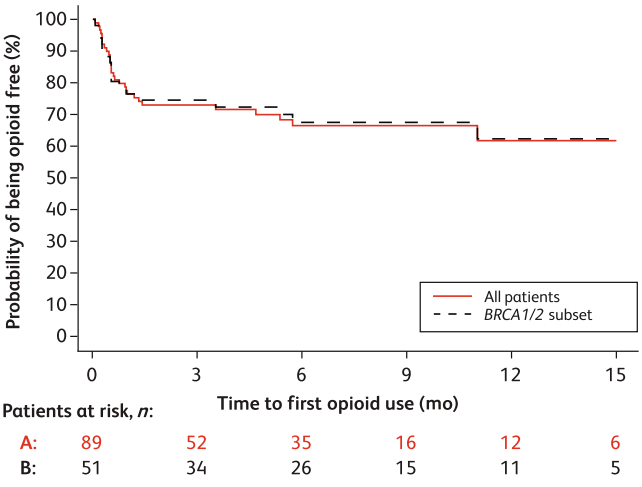

Fig. 5 – Time to first opioid use. Survival curves of time to first opioid use among patients who were opioid naive at baseline in the overall population and the *BRCA1/2* subset. *BRCA1/2* = breast cancer susceptibility gene 1 or 2.

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between some PROs over time as some patients can improve, some can deteriorate, and some improve and then deteriorate (or vice versa). All patients and patients in the *BRCA1/2* cohort reported improvements in HRQoL, as measured by the EQ-5D-5L Index and EQ-5D VAS scores, with greater improvements reported in the *BRCA1/2* subset, suggesting that talazoparib has a greater HRQoL benefit in patients with *BRCA1/2* alterations.

The tolerability profile of talazoparib observed in this study was consistent with that in previous studies, including the most common TEAEs observed with talazoparib treatment: anemia, nausea, and decreased appetite [3–5]. When patients were stratified by the presence or absence of anemia, the EQ-5D-5L Index and EQ-5D VAS scores were generally similar.

This study is limited by its small sample size, the heterogeneity of the different disease molecular subtypes, and the lack of a control arm, making it challenging to differentiate regression to the mean from a benefit from talazoparib (and from other parallel antisymptom interventions). However, phase 3 studies of talazoparib plus novel hormonal therapy with a comparator arm are ongoing (ClinicalTrials.gov NCT03395197 and NCT04821622).

5. Conclusions

In this population of men with mCRPC harboring DDR/HRR alterations from the TALAPRO-1 trial, talazoparib was associated with an overall improvement in patient-reported HRQoL EQ-5D-5L Index, EQ-5D VAS, and worst pain burden, in all patients and within the *BRCA1/2* subset. These findings complement the antitumor activity and tolerability profile of talazoparib reported previously.

***Author contributions*:** Fred Saad had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Healy, Bhattacharyya, Arondekar, Niyazov.
Acquisition of data: Healy, Bhattacharyya, Arondekar, Niyazov.
Analysis and interpretation of data: Saad, de Bono, Barthélémy, Dorff, Mehra, Scagliotti, Stirling, Machiels, Renard, Maruzzo, Higano, Gurney, Healy, Bhattacharyya, Arondekar, Niyazov, Fizazi.
Drafting of the manuscript: Saad, de Bono, Barthélémy, Dorff, Mehra, Scagliotti, Stirling, Machiels, Renard, Maruzzo, Higano, Gurney, Healy, Bhattacharyya, Arondekar, Niyazov, Fizazi.
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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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Peer Review Summary

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References

[1] Rugo HS, Ettl J, Woodward NE, et al. EMBRACA: efficacy outcomes in clinically relevant subgroups comparing talazoparib (TALA), an oral poly ADP ribose polymerase (PARP) inhibitor, to physician's choice of therapy (PCT) in patients with advanced breast cancer and a germline *BRCA* mutation. Chicago, IL: ASCO Annual Meeting; 2018.

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

[3] de Bono J, Ramanathan RK, Mina L, et al. Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline *BRCA1/2* mutations and selected sporadic cancers. Cancer Discov 2017;7:620–9.

[4] Hurvitz SA, Goncalves A, Rugo HS, et al. Talazoparib in patients with a germline *BRCA*-mutated advanced breast cancer: detailed safety analyses from the phase III EMBRACA trial. Oncologist 2020;25:e439–50.

[5] Turner NC, Telli ML, Rugo HS, et al. A phase II study of talazoparib after platinum or cytotoxic nonplatinum regimens in patients with advanced breast cancer and germline *BRCA1/2* mutations (ABRAZO). Clin Cancer Res 2019;25:2717–24.

[6] Mehra H, Fizazi K, de Bono JS, et al. Talazoparib (TALA), an oral poly (ADP-ribose) polymerase (PARP) inhibitor for men with metastatic castration-resistant prostate cancer (mCRPC) and DNA damage response (DDR) alterations: detailed safety analyses from TALAPRO-1 trial. J Clin Oncol 2021;39:5047.

[7] Kaya E, Feuer D. Prostate cancer: palliative care and pain relief. Prostate Cancer Prostatic Dis 2004;7:311–5.

[8] Holm M, Doveson S, Lindqvist O, Wennman-Larsen A, Fransson P. Quality of life in men with metastatic prostate cancer in their final years before death—a retrospective analysis of prospective data. BMC Palliat Care 2018;17:126.

[9] Chi KN, Protheroe A, Rodriguez-Antolin A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol 2018;19:194–206.

[10] Fizazi K, Kramer G, Eymard JC, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. Lancet Oncol 2020;21:1513–25.

[11] Feyerabend S, Saad F, Li T, et al. Survival benefit, disease progression and quality-of-life outcomes of abiraterone acetate plus prednisone versus docetaxel in metastatic hormone-sensitive prostate cancer: a network meta-analysis. Eur J Cancer 2018;103:78–87.

[12] Smith MR, Sandhu SK, George DJ, et al. Health-related quality of life (HRQoL) at final analysis of the GALAHAD study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and DNA repair defects (DRD). Ann Oncol 2021;32(suppl_5):S626–77.

[13] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

[14] Devlin N, Herdman M, Pavesi M, et al. Health-related quality of life effects of enzalutamide in patients with metastatic castration-resistant prostate cancer: an in-depth post hoc analysis of EQ-5D data from the PREVAIL trial. Health Qual Life Outcomes 2017;15:130.

[15] Im DD, Jambaulikar GD, Kikut A, Gale J, Weiner SG. Brief Pain Inventory-Short Form: a new method for assessing pain in the emergency department. Pain Med 2020;21:3263–9.

[16] Atkinson TM, Rosenfeld BD, Sit L, et al. Using confirmatory factor analysis to evaluate construct validity of the Brief Pain Inventory (BPI). J Pain Symptom Manage 2011;41:558–65.

[17] Cherny NI, Dafni U, Bogaerts J, et al. ESMO—magnitude of clinical benefit scale version 1.1. Ann Oncol 2017;28:2340–66.

[18] US Food and Drug Administration. Patient-reported outcome measures: use in medical product development to support labeling claims. Guidance for industry. Rockville, MD; 2009.

[19] Bouchard LC, Aaronson N, Gondek K, Cella D. Cancer symptom response as an oncology clinical trial end point. Expert Rev Qual Life Cancer Care 2018;3:35–46.

[20] Schaffer EM, Basch EM, Schwab GM, Bennett AV. Comparison of weekly and daily recall of pain as an endpoint in a randomized phase 3 trial of cabozantinib for metastatic castration-resistant prostate cancer. Clin Trials 2021;18:408–16.

[21] Fizazi K, Massard C, Smith M, et al. Bone-related parameters are the main prognostic factors for overall survival in men with bone metastases from castration-resistant prostate cancer. Eur Urol 2015;68:42–50.

[22] Thiery-Vuillemin A, de Bono J, Hussain M, et al. Pain and health-related quality of life with olaparib versus physician's choice of next-generation hormonal drug in patients with metastatic castration-resistant prostate cancer with homologous recombination repair gene alterations (PROfound): an open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:393–405.