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The Efficacy of PARP Inhibitors According to Prior Taxanes Chemotherapy in Prostate Cancer Patients: A Meta-Analysis of Randomized Clinical Trials

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mCRPC; Prostate cancer; PARPi; Taxanes

1. Abstract

1.1. Background: No prospective data are available about the best treatment algorithm in mCRPC patients that had received intensified regimens in the castration-sensitive setting. We analyzed the efficacy of a PARPi for mCRPC patients according to prior taxanes treatment.

1.2. Methods: Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts. Data extraction was conducted according to the PRISMA statement. Combined relative risks (RRs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects methods, depending on studies heterogeneity. The statistical analyses were performed with RevMan software for meta-analysis (v.5.2.3).

1.3. Results: Five articles were selected for this meta-analysis, including a total of 2798 patients. Treatment with a PARPi significantly improved rPFS compared to control (HR=0.57; $p < 0.0001$) in the subgroup of patients treated with prior taxanes chemotherapy. Similarly, in the subgroup of patients that did not receive taxanes, rPFS was significantly improved with the PARPi compared to control (HR=0.71; $p < 0.0001$). No significant difference in rPFS was observed between the two subgroups ($p = 0.14$).

1.4. Conclusions: Treatment with a PARPi significantly prolongs rPFS of mCRPC patients, regardless from prior use of taxanes. Final OS data and prospective studies focused on the efficacy of PARPi in the specific subgroups of patients progressed after an "intensified" approach (a triplet of ADT plus docetaxel plus an ARTA) for de-novo mCSPC disease are highly expected.

2. Introduction

Defining the best sequence of treatments for metastatic castration-resistant prostate cancer (mCRPC) is a hot debate topic, particularly due to the increasing variety of active drugs available in clinical practice that include chemotherapy with taxanes (docetaxel and cabazitaxel), androgen receptor signaling inhibitors (ARSI - abiraterone and enzalutamide) and radiocompounds (Radium-223 and, more recently, 177Lu-PSMA) [1,2]. The growth of prostate cancer cells is highly dependent on androgens; hence the cornerstone of treatment of advanced disease has been androgen-deprivation therapy (ADT) for decades. However, a growing number of trials have recently shown that anticipating treatments (i.e. docetaxel, abiraterone, apalutamide, enzalutamide) in the metastatic castration-sensitive prostate cancer (mCSPC) setting significantly improves patients' outcomes when combined to ADT compared to ADT alone [3–6]. Notably, the PEACE-1 and ARASENS

trials demonstrated that a triplet of ADT, an ARSI (abiraterone and darolutamide, respectively) and docetaxel achieves even better results than the doublet of ADT plus docetaxel in the castration-sensitive phase of the disease [7,8]. These evidences bring to the surface a crucial problem: the treatment options left in the castration-resistant setting for those patients with an aggressive disease progressed after an intensified approach in the castration-sensitive phase of the disease.

About 20-30% of prostate cancers exhibit somatic or germline aberrations of homologous recombination repair (HRR) genes, with BRCA2 being the most frequently involved (~10%) [9]. Therefore, several trials investigated the activity of PARP-inhibitors (PARPi) in mCRPC, demonstrating better outcomes particularly in patients harboring HRR deficiency (HRD), and above all in BRCA1/2 mutated tumors [10–14]. In particular, the phase III PROfound study led to the approval of olaparib in pre-treated mCRPC patients progressed on an androgen receptor signaling pathway inhibitor (ARSI), given the remarkable OS advantage compared to another ARSI in the cohort of patients carrying BRCA1/2 mutations [12]. Furthermore, a recent novel therapeutic strategy of combining a PARPi plus an ARSi (androgen receptor signaling inhibitor) for first-line mCRPC showed promising results [15]. Indeed, combinations of abiraterone plus olaparib, abiraterone plus niraparib, and enzalutamide plus talazoparib demonstrated to significantly prolong radiographic PFS (rPFS) compared to abiraterone or enzalutamide monotherapy in PROpel, MAGNITUDE, and TALAPRO-2 phase 3 trials, respectively [16,17,18]. The PROpel study showed the superiority of olaparib plus abiraterone in terms of rPFS regardless of HRR status, even if the magnitude of the benefit was higher in the HRR and BRCA mutated subgroups compared to non-mutated tumors [16]. No significant overall survival (OS) advantage was observed in the overall population of the PROpel trial [19]. The rPFS advantage of niraparib plus abiraterone compared to abiraterone was restricted at the cohort of HRD+ patients in the MAGNITUDE study [17]. As concern the TALAPRO-2 trial, talazoparib+enzalutamide significantly improved rPFS regardless of HRR mutational status, with a greater benefit in the HRR-deficient population and especially in BRCA1/2 mutated patients [18]. Although preliminary, data about the combinations of abiraterone/enzalutamide and a PARPi could suggest their role as a promising first-line strategy for mCRPC patients. However, no prospective data are available about the efficacy of PARPi in mCRPC patients that had received intensified regimens in the castration-sensitive (mCSPC) setting (only 0.15%, 3.8%, and 8% of patients received prior ARSi in the PROpel, MAGNITUDE and TALAPRO-2 studies, respectively; around 20% received prior docetaxel at mCSPC stage in these trials). The aim of this analysis was to investigate the efficacy of PARPi in mCRPC patients based on the previous exposure to taxanes chemotherapy.

3. Patients and Methods

3.1. Definition of Outcomes

The primary endpoint of this analysis was to evaluate whether treatment with a PARPi compared to standard of care improved radiographic progression-free survival (rPFS) in the subgroup of mCRPC patients who had received prior taxanes chemotherapy.

3.2. Selection of Studies

We reviewed MEDLINE/PubMed, the Cochrane Library, and the ASCO University Meeting abstracts for citations up to 15 June 2023. The search criteria were limited to articles published in the English language and phase III or phase II RCTs in patients with prostate cancer. The MeSH terms used for the search of PubMed and the Cochrane Library were ‘prostate cancer’, ‘PARP inhibitor’, ‘mCRPC’, or the name of the drugs (i.e. niraparib, olaparib, talazoparib). For the search in the ASCO University abstracts, we used the name of the drugs and the terms ‘phase II’ or ‘phase III’. The summaries for the product characteristics were searched for at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. If more than one publication was found for the same trial, the most recent, complete and updated version was included in the final analysis.

Study quality was assessed using the Jadad 5-itemscale, taking into account randomisation, double blinding and withdrawals. The final score ranged from 0 to 5 [20].

3.3. Data Extraction

Two authors (CC and RI) conducted the data extraction independently. It was performed according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement [21], and any types of discrepancies were resolved by consensus. The data extracted for each trial were: first author’s name, year of publication, trial phase, number of enrolled patients, number of patients treated with prior taxane-based chemotherapy for mCSPC, treatment type used in the experimental and the control arms, and HRs for rPFS with the relative 95% CI for each treatment arm in the subgroup of patients treated with prior taxanes chemotherapy.

3.4. Statistical Methods

The HR for rPFS with the relative 95% confidence intervals (CIs) was extracted from each study. Summary HRs was calculated using random- or fixed-effects models, depending on the heterogeneity of the included studies. Statistical heterogeneity between the trials included in the meta-analysis was assessed using Cochrane’s Q statistic, and inconsistency was quantified with an I2 statistic (100% x [Q-df)/Q]) [22]. The assumption of homogeneity was considered invalid for p-values less than 0.1. When no substantial heterogeneity was observed, the pooled estimate, calculated based on the fixed-effects model, was reported using the inverse variance method. When substantial heterogeneity was observed, the pooled

estimate, calculated based on the random-effects model, was reported using the DerSimonian et al. method [23], which considers both within- and between-study variations [20]. A two-tailed p-value of less than 0.05 was considered statistically significant. All the data were collected using Microsoft Office Excel 2007. The statistical analyses were performed using the RevMan software for meta-analysis (v.5.2.3) [24]

4. Results

4.1. Search Results

The electronic search revealed 1002 citations, after screening 50 full text articles were reviewed for further assessment and 45 citations were excluded because did not meet the inclusion criteria. This reviewed process (Figure 1) led to the selection of five articles considered for final analysis based on their adequate quality and relevance for inclusion in the meta-analysis [12,15-18]. Four studies were randomized phase III trials, while the remaning one was a randomized phase II trial. Four studies evaluated the role of adding a PARPi (either olaparib, niraparib, or talazoparib) to abiraterone+prednisone or enzalutamide compared to the ARSi monotherapy. The other trial (PROfound study) randomized mCRPC patients with alterations in one of 15 selected HRR genes to olaparib monotherapy compared to an ARSI; we considered rPFS data about the overall population (including both cohort A of patients carrying alterations in BRCA1, BRCA2, or ATM, and cohort B of tumours with alterations in any of the other 12 genes) [12]. A total of 2798 patients were available for meta-analysis: 1502 in the experimental arms, and 1296 in the control arms. The characteristics of each trial analysed in this study are shown in Table 1.

Table 1: Selected studies for final analysis.

Trial	Phase	Trial Design				Disease setting	HRR mutation status		Median follow-up	rPFS (Exp/Ctr) (HR, 95%CI; p value)	mOS (Exp/ Ctr) (HR, 95%CI; p value)	Jadad
		Exp		Ctr			Exp	Ctr				
		Drug	Pts (N)	Drug	Pts (N)							
NCT01972217	2	ABI + OLAPARIB	71	ABI + pbo	71	mCRPC (previous treatment with docetaxel)	HRRm 11 (15%) HRR WT 15 (21%) HRR partially characterized 45 (63%)	HRRm 10 (14%) HRR WT 20 (28%) HRR partially characterized 41 (58%)	15.9 mo (Olaparib+abi) and 24.5 mo (ABI+pbo)	ITT 13.8 vs 8.2 mo HR 0.65 (0.44-0.97); p=0.034 HRRm 17.8 vs 6.5 mo HR 0.74 (0.26-2.12); p=0.58 HRR WT 15.0 vs 9.7 HR 0.52 (0.24-1.15); p=0.11 HRR partially characterized 13.1 vs 6.4 mo HR 0.67 (0.40-1.12); p=0.13	ITT 22.7 vs 20.9 mo HR 0.91 (0.60 – 1.38): p=0.66	5
PROfound	3	OLAPARIB	A: 162 A+B: 256	ABI or ENZA[##]	A: 83 A+B: 131	mCRPC progressed to prior therapy with ARSi, and/or taxanes	Cohort A: BRCA1 = 8 BRCA2 = 80 ATM = 60 Cohort A+B[@]: BRCA1 =8 BRCA2 = 81 ATM = 62 CDK12 = 61	Cohort A: BRCA1 = 5 BRCA2 = 47 ATM = 24 Cohort A+B[@]: BRCA1 =5 BRCA2 = 47 ATM = 24 CDK12 = 28	21.9 months	A: 7.4 vs. 3.6 mo (HR 0.34; 0.25 – 0.47); p<0.001 A+B: 5.8 vs. 3.5 mo (HR 0.49; 0.38 – 0.63); p<0.001	A: 19.1 vs. 14.7 mo (HR 0.69; 0.50 – 0.97); p=0.02 B: 14.1 vs. 11.5 mo (HR 0.96, 0.63 – 1.49)	3
MAGNITUDE	3	ABI + NIRAPARIB	212[#]	ABI + pbo	211[#]	1st line mCRPC	HRRm 212 BRCA1/2m 113	HRRm 211 BRCA1/2m 112	26.8 months	HRRm16.7 vs. 13.7 (HR 0.76, 0.60-0.97); p=0.0217** HRRm 19.0 vs. 13.9 (HR 0.64, 0.49-0.89); p=0.0022* BRCA1/2 mut= 19.5 vs. 10.9 (HR 0.55, 0.39-0.78); p=0.0007**	NE vs. NE (HR 0.767, 0.525-1.119), p=0.1682 BRCA1/2m 29.3 vs 28.6 (HR 0.88, 0.58-1.34); p=0.5505** Events: 43 vs 49	5

PROpel	3	ABI + OLAPARIB	399	ABI + pbo	397	1st line mCRPC	HRRm 111 (27.8%) HRR WT 279 (69.9%) HRR unknown 9 (2.3)	HRRm 115 (29.0%) HRR WT=273 (68.8%) HRR unknown 9 (2.3)	19.3 mo (olaparib+abi), 19.4 mo (abi+pbo)* 19.3 mo (ola+abi), 19.2 mo (abi+pbo) ** (Death events 381 [47.9%])	ITT 24.8 vs. 16.6 mo (HR 0.66, 0.54–0.81, p<0.0001)* ITT 27.6 vs. 16.4 mo (HR 0.61, 0.49–0.74, p<0.0001)** HRRm HR 0.50 (0.34-0.73) HRR WT HR 0.76 (0.60-0.97)	ITT 42.1 vs 34.7 (HR 0.81, 0.67-1.00); p=0.0544 HRRm NR vs 28.5 mo (HR 0.66, 0.45-0.95) HRR wt 42.1 vs 38.9 mo (HR 0.89-1.14)	5
TALAPRO-2	3	ENZA+ TALAZOPARIB	402	ENZA+pbo	403	1st line mCRPC	HRRm 85 (21.1%) HRR WT or unknown 317 (78.9%)	HRRm 84 (20.8%) HRR WT or unknown 319(79.2%)	24.9 mo (enza+tala), 24.6 mo (enza+pbo)	ITT NR vs 21.9 mo (HR 0.63, 0.51-0.78, p<0.001) HHRm 27.9 vs 16.4 mo (HR 0.46, 0.30-0.70, p<0.001) non-HRRm: NR vs 22.5 mo (HR 0.70, 0.54-0.89, p=0.004)	ITT HR 0.89, p=0.35 (31% of events)	5

ABI: abiraterone; CI: confidence interval; ENZA: enzalutamide; HR: hazard ratio; HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; mo: months; mOS: median overall survival; mPFS: median progression-free survival; m = mutation positive; mo = month; N: number of patients; NE: not evaluable; NR: not reached; pbo: placebo; vs: versus; WT: wild type.

*: investigator-assessment

**: central review

#: HRR mutation positive

##: at physician's choice

@: deleterious alterations in at least 1 of the 15 pre-specified genes: BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L

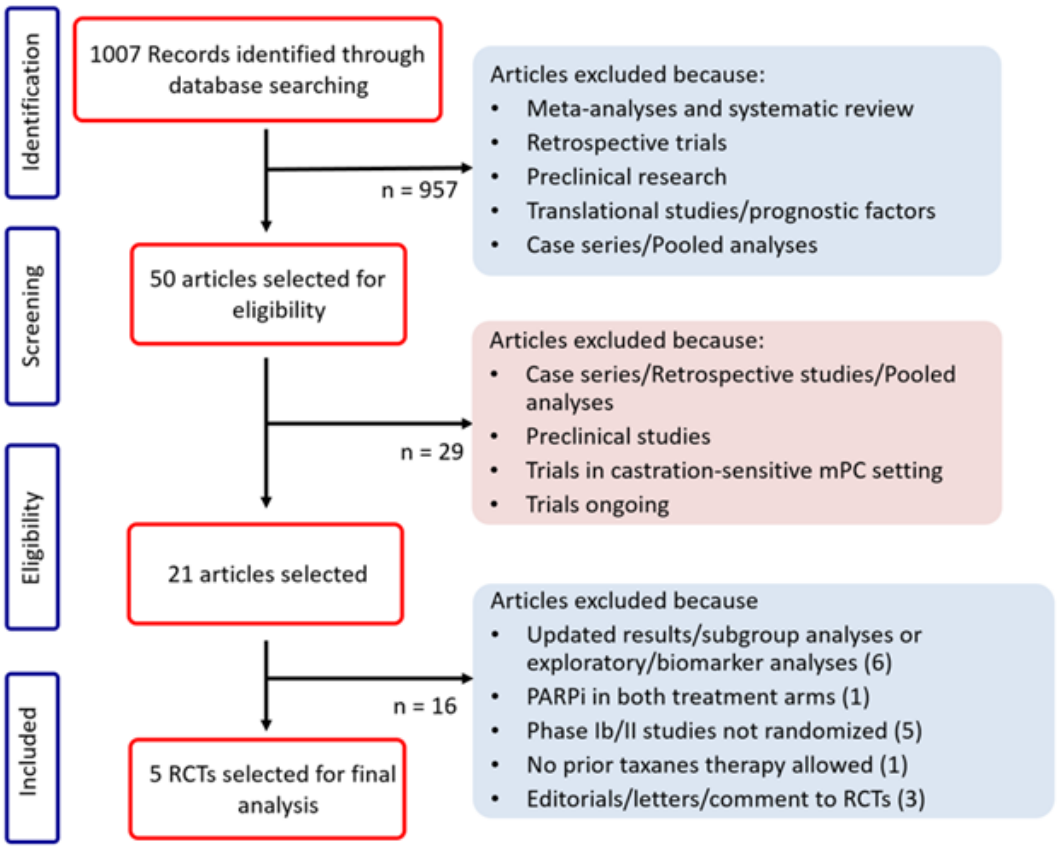

Figure 1: Selection of the included studies

4.2. PARPi versus standard of care for mCRPC patients according to prior use of taxanes chemotherapy

We assessed whether prior treatment with taxanes could impact the treatment efficacy of a PARPi compared to the standard of care for mCRPC patients in terms of rPFS. When considering patients treated with prior taxanes, treatment with a PARPi significantly improve rPFS compared to control (random-effect, HR=0.57; 95% CI 0.44–0.73; p<0.0001). Significant heterogeneity was observed in this analysis (Chi2 = 8.09, p = 0.09; I2 = 51%). Analogously, in the subgroup of patients that did not receive prior taxanes, rPFS was significantly improved with the PARPi compared to the control, with a reduction in the risk of radiographic progression of 29% (random-effect, HR=0.71; 95% CI 0.61–0.81; p < 0.0001). No significant heterogeneity was observed (Chi2 = 0.27, p = 0.97; I2 = 0%) (Figure 2). In the overall population, PARPi significantly prolonger PFS compare to control (random-effect; HR 0.64; 95%CI, 0.55–0.74; p <0.00001). No significant difference in rPFS was observed when comparing the efficacy of PARPi between the two sub-populations of patients previously treated with taxanes or not (p=0.14).

As concern OS, data were available for two out of the four studies (PROfound and PROpel), with a total of 1183 patients. Treatment with PARPi significantly prolonged OS in the overall population (fixed-effect; HR 0.80; 95%CI, 0.69–0.94; p =0.007). No significant heterogeneity was observed in this analysis (Chi2 = 3.48, p = 0.32; I2 = 14%). In the subgroup of patients previously treated with taxanes, a significant OS benefit was observed in favor of PARPi compared to control (fixed-effect; HR 0.70; 95%CI, 0.55–0.89; p =0.004). No significant heterogeneity was observed (Chi2 = 0.27, p = 0.61; I2 = 0%). On the contrary, no significant OS advantage was observed with PARPi in the subgroup of patients not pre-treated with taxanes (fixed-effect; HR 0.89; 95%CI, 0.72–1.10; p =0.29). No significant heterogeneity was observed (Chi2 = 1.07, p = 0.30; I2 = 7%). No significant interaction was shown between the two subgroups (p=0.14) (Figure 3).

4.4. Quality of the Studies

All the studies were randomized clinical trials, and all of them were of good quality according to the Jadad' scale (scores ≥3) (Table 1).

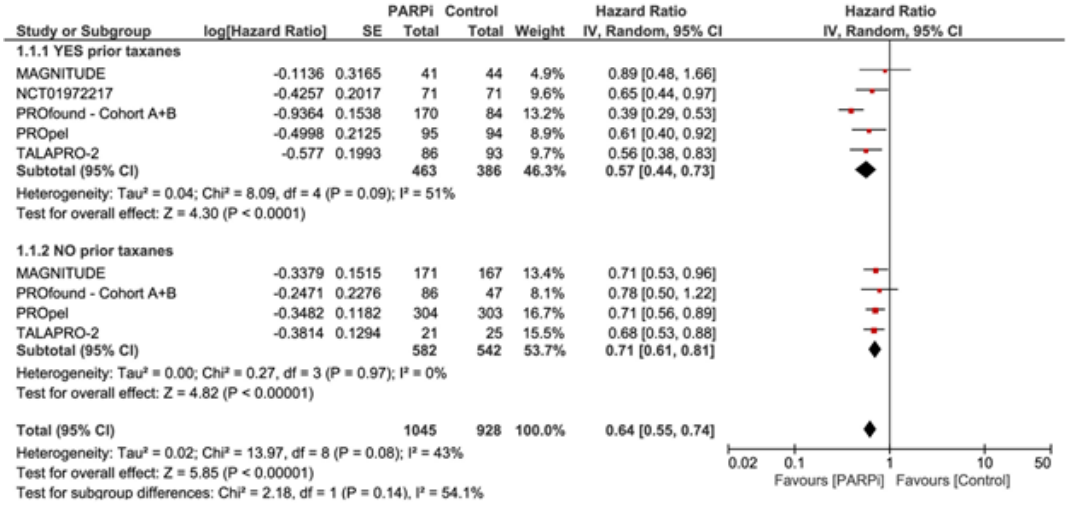

Figure 2: rPFS of PARPi compared to the standard of care (ARSi) according to prior docetaxel therapy

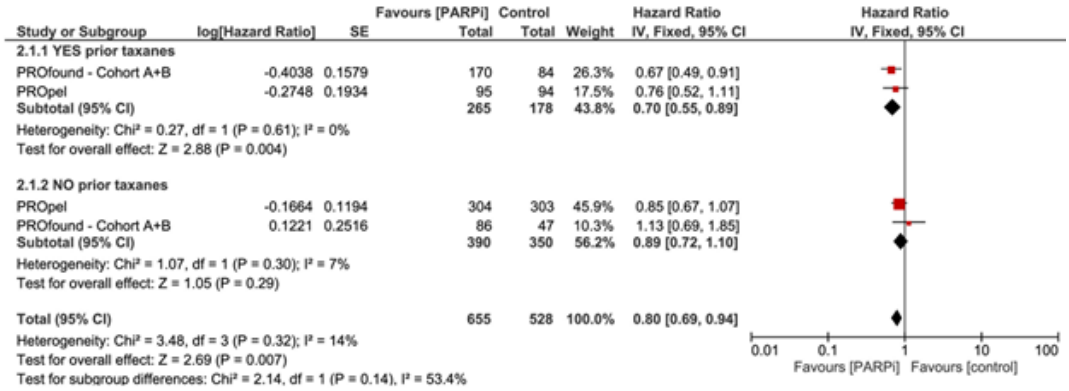

Figure 3: Overall survival of PARPi compared to the standard of care (ARSi) according to prior docetaxel therapy

5. Discussion

In the last years, the therapeutic scenario of metastatic prostate cancer patients has undergone profound changes. Actually, both castration-sensitive and castration-resistant phases of the disease have been enriched by a varied number of therapeutic agents (i.e. taxanes chemotherapy and/or ARSi) that, combined with ADT, significantly improved patients' outcomes. In particular, it has become evident that an early-intensified approach that includes both chemotherapy and an ARSi in association with ADT is responsible for a prolonged OS in a particular subgroup of high-volume mCSPC patients, with a more aggressive disease [7,8]. Defining the treatment algorithm for patients progressed after a triplet therapy in the castration-sensitive phase of the disease is one of the main challenging issues in the management of prostate cancer [25]. Indeed, the limited activity of an ARSi after progression to another ARSi has been questioned [1,26]. It is important to notice that, even if apalutamide used in non-metastatic CRPC patients significantly extended the PFS2 compared to placebo (with abiraterone as the most frequent second-line therapy administered, in more than 70% of cases), the completely different setting (and prognosis) of the disease does not allow translating these results in metastatic patients (especially if metastatic de-novo) [27]. Chemotherapy with cabazitaxel represents an effective option after progression to docetaxel and with a PFS inferior to 12 months with an ARSi, with the main limit of the tolerability profile (also considering the median advanced age of treated patients) [1]. The alpha emitter Radium-223 is restricted to patients with bone metastases, while 177Lu-PSMA requires PSMA-expressing tumor cells [28,29]. PARP inhibitors certainly represent a new therapeutic perspective in mCRPC patients harboring BRCA1 or BRCA2 mutations [11,12]. In the PROfound trial, olaparib led to significantly OS prolongation compared to an ARSi (either abiraterone or enzalutamide) in the cohort of patients (heavily pre-treated) carrying BRCA1, BRCA2, or ATM alteration, with a reduction of the risk of death of more than 30% (which was even greater when the analysis was adjusted for crossover to olaparib in the control group) [12]. Of note, the OS benefit was restricted to those patients with alterations in BRCA1 (HR for death 0.42) or BRCA2 (HR 0.59). Moreover, it is important to underline that the magnitude of OS advantage with olaparib was even greater in the subgroup of patients previously treated with taxanes (HR 0.56) compared to those that did not receive chemotherapy (HR 1.03), supporting the role of a PARPi in a subgroup of patients with a more aggressive disease. Finally, about 23% of patients with BRACA1/2 mutations in the PROfound trial were metastatic de-novo, but OS data in this specific subgroup at worse prognosis that progressed to an initial mCSPC phase of the disease are lacking. Recently, three international phase 3 studies, MAGNITUDE, PROpel and TALAPRO-2 have demonstrated the superiority in terms of rPFS of adding a PARPi (niraparib, olaparib, and talazoparib, respectively) to an ARSi (abiraterone in the first two trials, and enzalutamide in the last one) compared to ARSI plus placebo in mCRPC patients [16-18]. These three trials enrolled different populations of patients. The PROpel study included "all-comers" mCRPC patients; the status of HRD was determined post-hoc and could be assessed both on tissue and with liquid biopsy. Of note, the biomarker analysis recently presented at ESMO 2022 reinforced the role of HRR genes mutations (and in particular BRCA2 and 1) as predictors of PARPi efficacy [19]. The MAGNITUDE trial was prospectively designed to enroll patients in two separate cohorts, based on tissue analysis of a set of HRR genes: the biomarker-positive cohort (HRD+) and the biomarker-negative cohort (HRD-); the latter cohort interrupted prematurely the enrollment due to a pre-planned futility analysis that demonstrated the lack of benefit in HRR-proficient patients treated with niraparib [17]. The TALAPRO-2 trial randomized patients based on HRR status (assessed prospectively). Thus, unlike the PROpel trial, the HRD status was considered among stratification criteria [18]. Certainly, the lack of ARSi therapy (+/- docetaxel) in the mCSPC disease setting, which now represents the preferable treatment option for the vast majority of patients, makes the population included in these trials not current anymore. Furthermore, in molecularly selected patients (carrying BRCA1/2 mutations), whether the ARSi should be added to the PARPi or not remains an unsolved issue. As we have seen, all these trials compared experimental combination (ARSi+PARPi) with the ARSi as control arm and not with the PARPi monotherapy. Further studies are needed to state the best treatment sequence for BRCA1/2-mutated patients.

The aim of our analysis was to assess the efficacy of a PARPi in the particular cohort of patients with an aggressive disease to the point of justifying the use of prior taxanes therapy. We found that the rPFS benefit of a PARPi was significant regardless of the previous exposure to taxanes ($p = 0.14$). In particular, in the subgroup of patients who received taxanes, the PARPi significantly prolonged rPFS compared to placebo (HR=0.57; 95% CI 0.44–0.73; $p < 0.0001$).

Recently, the results of the TRITON 3 study were presented at 2023 American Society of Clinical Oncology (ASCO) Genitourinary Cancer Symposium. This trial evaluated the role of rucaparib monotherapy in mCRPC BRCA1, BRCA2 and ATM-mutated patients that had received one prior ARSi in any disease setting compared to physician's choice treatment (either docetaxel or another ARSi). In particular, rucaparib showed a significant rPFS benefit compared both to docetaxel (HR 0.64, p=0.0066) and to ARSi (HR 0.47, p<0.0001) as control arm [30]. These data provide fundamental information about the best therapeutic sequence to use in BRCA mutated mCRPC patients, confirming the advantage of an earlier use of the PARPi (prior of docetaxel) in this setting.

Therefore, PARPi seems to retain their activity regardless prior use of taxanes. Taken together results support, in BRCA1/2-mutated tumors an early use of PARPi (with persistent uncertainty

whether it is better alone or associated with an ARSi). As concern all-comer patients (unselected for HRR and BRCA1/2 alterations) with mCSPC treated with early docetaxel, the activity of PARPi [combined with ARSi] seems to be maintained, even if OS data are highly awaited to definitively state whether this strategy could be considered a standard of care.

Several limitations impair the results of our analysis. The lack of access to raw data, and the lack of available public data concerning outcomes of the PARPi therapy in specific subgroups (i.e. de novo mCSPC) represent an important limit. Moreover, the differences related to the HRD mutational status between the studies considered is also variables that could have limited our results. The main limit of our analysis certainly included the absence of mature OS data, which are needed to clearly state the impact of this strategy in mCRPC patients' management. Albeit with the limit of few patients included (and only 2 out of the 5 studies considered), the lack of a significant difference in term of OS with PARPi in mCRPC patients according to prior use of taxanes reinforces the idea of early PARPi treatment (especially in the BRCA mutated population). Certainly, the final OS results of MAGNITUDE and TALAPRO-2 study will probably add more information about the role of a PARPi (and its combination with an ARSI) in the treatment of mCRPC patients, BRCA1/2 mutated, progressed to chemotherapy.

In conclusion, our analysis demonstrated that treatment with a PARPi might represent an effective strategy for mCRPC patients, regardless of previous treatment with taxanes. For BRCA1/2-mutated mCRPC patients, available data support the early use of PARPi (whether alone or combined with an ARSi has to be clarified yet). In patients molecularly unselected with an aggressive disease (that have received an early "intensified" therapy in the castration-sensitive phase of disease), the activity of PARP inhibitors seems to be maintained. Final OS data and prospective studies focused on the efficacy of PARPi in the specific subgroups of patients progressed after an "intensified" approach (a triplet of ADT plus docetaxel plus an ARTA) for de-novo mCSPC disease are highly warranted to clearly state the first-line therapeutic algorithm of mCRPC patients.

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