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EUO Collaborative Review – Priority Article

Combining PARP Inhibitors and Androgen Receptor Signalling Inhibitors in Metastatic Prostate Cancer: A Quantitative Synthesis and Meta-analysis

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Abstract

Context: PARP inhibitors (PARPi) are established treatments for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) deficiency after androgen receptor signalling inhibitor (ARSI) failure. New PARPi + ARSI combinations have been tested in all comers, although their clinical relevance in HRR-proficient tumours remains uncertain.

Objective: To quantitatively synthesise evidence from randomised trials assessing the efficacy and safety of PARPi + ARSI combinations for first-line treatment of mCRPC.

Evidence acquisition: We searched the PubMed, EMBASE, SCOPUS, and Cochrane Library databases up to February 28, 2023. Randomised controlled trials (RCTs) comparing PARPi + ARSI versus placebo + ARSI for first-line treatment of mCRPC were eligible. Two reviewers independently performed screening and data extraction and assessed the risk of bias, while a third reviewer evaluated the eligibility criteria.

Evidence synthesis: Overall, three phase 3 RCTs were included in the systematic review: PROPEL, MAGNITUDE, and TALAPRO-2. A total of 2601 patients with mCRPC were enrolled. Two of these trials (PROPEL and TALAPRO-2) assessed the radiographic progression-free survival benefit of PARPi + ARSI for first-line treatment of mCRPC, independent of HRR status. The pooled hazard ratio was 0.62 (95% confidence interval 0.53–

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Prostate cancer
Olaparib
Niraparib
Talazoparib

0.72). The pooled hazard ratio for overall survival was 0.84 (95% confidence interval 0.72–0.98), indicating a 16% reduction in the risk of death among patients who received the combination.

Conclusions: Results from this meta-analysis support the use of ARSI + PARPi combinations in biomarker-unselected mCRPC. However, such combinations might be less clinically relevant in HRR-proficient cancers, especially considering the change in treatment landscape for mCRPC.

Patient summary: We looked at outcomes from trials testing combinations of two classes of drugs (PARP inhibitors and ARSI) in advanced prostate cancer. We found that these combinations seem to work regardless of gene mutations identified as biomarkers of response to PARP inhibitors when used on their own.

1. Introduction

Prostate cancer is a highly heterogeneous disease, with different clinical and molecular subtypes [1]. Nearly one-third of patients with metastatic castration-resistant prostate cancer (mCRPC) harbour aberrations of homologous recombination repair (HRR) genes, and these cancers are generally sensitive to treatment with PARP inhibitors (PARPi) [2]. Olaparib and rucaparib were the first PARPi agents to be approved for the treatment of mCRPC: olaparib is licensed by the US American Food and Drug Association (FDA) for use in mCRPC with deleterious germline or somatic HRR gene mutations (including *BRCA1, BRCA2*, and *ATM*) and by the European Medicines Agency for *BRCA1/2*-mutated mCRPC [2]. Rucaparib was granted accelerated FDA approval for mCRPC with deleterious germline or somatic *BRCA1* or *BRCA2* gene mutations [2,3].

Therefore, PARPi represent a new therapeutic strategy as monotherapy in HRR/*BRCA*-altered mCRPC on the basis of their distinctive mechanism of action [4,5]. In particular, PARP-1 is a nuclear enzyme responsible for PARylation of target proteins using the cofactor NAD^+ [5]. On DNA damage, activated PARP-1 recruits proteins that promote repair of DNA single-strand breaks (SSBs), facilitating assembly of the base excision repair (BER) machinery [6]. Moreover, PARP-1 acts as a transcriptional regulator [7]. It has been shown that PARP-1 is a potent modulator of androgen receptor (AR) function, regulating its association with chromatin [7]. Inhibition of PARP-1 leads to trapping of PARP1 at SSB sites, resulting in replication-associated double-strand breaks, which are the most dangerous DNA lesions for cellular integrity. PARPi sensitises prostate cancer cells to both genotoxic insults and androgen deprivation [7]. Interestingly, castration-resistant prostate cancer (CRPC) models show significant upregulation of PARP-1 activity, suggesting that PARP-1 may be enhanced on tumour progression subsequent to AR-directed antiandrogenic therapy [7].

These preclinical data have been corroborated by clinical evidence. A phase 2 study investigating the efficacy of olaparib versus placebo in combination with abiraterone in patients with metastatic CRPC (mCRPC) whose disease progressed on docetaxel showed that investigator-assessed radiographic progression-free survival (rPFS) was significantly longer with olaparib + abiraterone than with abiraterone alone in a biomarker-unselected cohort (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.44–0.97; $p = 0.034$) [8]. Mutational status was assessed using tissue that was already available, with provision of an archival tumour sample or biopsy not mandated by the protocol. However, in a follow-up study by the same group, sequencing of germline and plasma samples increased the population with HRR-mutated status (HRR^+) from 27% to 68% of 142 randomised patients, and the benefit of the olaparib + abiraterone combination regardless of HRR^+ status was confirmed [9].

Taken together, these data represent a rationale for combining PARPi and AR signalling inhibitor (ARSI) agents in mCRPC. Here we present a quantitative synthesis of randomised trials assessing the efficacy and safety of PARPi + ARSI combinations in comparison to placebo + ARSI in first-line treatment of mCRPC.

2. Evidence acquisition

This work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10].

2.1. Study objective

The joint primary objectives of this study were assessment of rPFS and overall survival (OS) for PARPi + ARSI versus placebo + ARSI in patients with mCRPC. A prespecified subgroup analysis was performed to assess rPFS for patients with *BRCA1/2*-mutant, HRR biomarker-positive (HRR^+) or HRR biomarker-negative (HRR^-) mCRPC. The secondary objective was to assess safety by comparing the incidence of treatment-emergent adverse events (TEAEs) evaluated as grade $\geq$3 (G3–4) toxicities.

2.2. Search strategy

A literature search of the PubMed, EMBASE, Scopus, and Cochrane Library databases was carried out from database inception to February 2023. The search strategy included the keywords "metastatic castration resistant prostate cancer", "PARP inhibitors", "androgen receptor signalling inhibitors", and "randomised clinical trials". A search of conference abstracts reported at the European Society of Medical Oncology OncologyPRO conference and in the

American Society of Clinical Oncology library was performed from 2000 to February 2023 to identify relevant unpublished data. Specific keywords for each database and free text terms were combined with Boolean operators. Two reviewers (C.M. and E.F.G.) screened all full-text articles and abstracts independently. A third author (P.R.) reviewed the search results to apply the eligibility criteria to both sets of search outcomes and acted as an arbiter in case of disagreement between the two reviewers (C.M. and E.F.G.). Finally, reference lists from review articles and relevant studies on the same topic were crosschecked to confirm retrieval of all possible pertinent trials.

2.3. Trial eligibility and article selection

Eligible studies had to fulfil the following criteria: (1) a prospective randomised phase 2 or 3 trial designed to evaluate the efficacy and safety of PARPi + ARSI versus placebo + ARSI in first-line treatment of mCRPC; and (2) the HR or risk ratio (RR) for PFS and OS for the intention to treat (ITT) population and *BRCA1/2*-mutant, HRR^+ and HRR^- mCRPC subgroups, as well as G3–4 adverse events (AEs), had to be reported or could be computed from data presented in the publications selected.

Studies were excluded from the analysis for the following reasons: (1) nonrandomised prospective studies; (2) retrospective studies; and (3) ongoing studies that had not been presented at the time of the literature search. No language restriction was applied. For each eligible study, we collected data on the study design; main eligibility criteria; number of patients enrolled overall and in each treatment arm; number of OS, rPFS, and RR events; and main G3–4 TEAEs. Risk of bias (RoB) in the randomised controlled trials was independently assessed by two reviewers (C.M. and E.F.G.) using the Cochrane RoB tool [11]. Additional quality domains, including imprecision, inconsistency, indirectness, and potential for publication bias, were also assessed [12].

2.4. Statistical analysis

For data analysis, descriptive statistics were used to summarise baseline characteristics. A quantitative synthesis was performed for eligible randomised clinical trials with available data. For time-to-event data, HRs and 95% CIs were used to compare the results. RRs based on events data were calculated to compare G3–4 TEAEs between PARPi + ARSI and placebo + ARSI groups.

Both a random-effect model with the Mantel-Haenszel method and a fixed-effect model were used to obtain pooled HR estimates [13]. Standard checks of the homogeneity assumption were carried out [14]. The Higgins I^2 index was computed as a quantitative measure of the percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error [15]. Owing to the small sample size of studies included, no further analyses were conducted to try to explain high heterogeneity among studies. All statistical analyses and the generation of forest plots were carried out using Stata version 16 (StataCorp, College Station, TX, USA).

3. Evidence synthesis

The search strategy returned 319 records (Fig. 1): after the exclusion of 90 duplicates and 178 irrelevant publications (wrong topic, abstract only, insufficient details), 51 publications were assessed for eligibility. Of these, 48 full-text records were excluded because they did not fulfil all the prespecified eligibility criteria (nonrandomised clinical trials, retrospective studies, protocol reports only). Thus, three articles on randomised phase 3 trials were eligible and were included in our systematic review [16–18]. A total of 2601 patients with mCRPC were enrolled in the three trials.

The main characteristics of the three trials are presented in Table 1, with outcome results provided for the ITT population and for the prespecified subgroups. The RoB assessment is summarised in Supplementary Table 1.

The details and key outcomes of the three studies are as follows (Table 1). The PROPEL study randomised 796 unselected patients with mCRPC to receive abiraterone acetate 1000 mg/prednisone 5 mg (AAP) twice daily plus either olaparib (300 mg twice daily) or placebo [4]. Biomarker analysis after randomisation revealed that both arms were balanced for underlying HRR alterations (29% in both study arms), including approximately 10% with *BRCA1/2* alterations [16]. Prior treatment with docetaxel in the hormone-sensitive setting was allowed, while previous AAP treatment was an exclusion criterion. Combination treatment prolonged rPFS irrespective of HRR status (median rPFS: 25 vs 16 mo; HR 0.67, 95% CI 0.56–0.81; $p < 0.001$). In the HRR^+ subgroup, median rPFS was not reached for the combination arm and was 14 mo for the AAP + placebo control arm (HR 0.50, 95% CI 0.34–0.73) [16].

The MAGNITUDE study assessed AAP plus either niraparib (200 mg once daily) or placebo in 423 patients with HHR gene mutations and 247 HRR-proficient patients [17]. Prior docetaxel for hormone-sensitive disease and up to 4 mo of AAP for mCRPC before randomisation were allowed [5]. In the HRR^+ cohort, rPFS was significantly better with the combination (median rPFS: 17 vs 14 mo; HR 0.73, 95% CI 0.56–0.96; $p = 0.022$) [17]. A prespecified futility analysis with a composite efficacy endpoint of prostate-specific antigen (PSA) progression and radiological progression showed no benefit for combination treatment in the HRR^- cohort (HR 1.09, 95% CI 0.75–1.57; $p = 0.66$) [17].

TALAPRO-2 evaluated the efficacy of enzalutamide (160 mg once daily) plus either talazoparib (0.5 mg once daily) or placebo. The study enrolled 805 patients irrespective of HRR mutational status (cohort 1). The HRR-mutant cohort was then prospectively extended, with a further 230 biomarker-positive patients recruited [18]. Median rPFS was not reached for the combination arm and was 22 mo for the control group of cohort 1 (HR 0.63, 95% CI 0.51–0.78; $p < 0.001$). In the HRR^+ subgroup analysis, median rPFS was 28 mo for the combination arm and 16 mo for the control arm (HR 0.46, 95% CI 0.30–0.70; $p < 0.001$) [18].

3.1. Clinical outcomes: rPFS and OS

Two of the three phase 3 trials (PROPEL and TALAPRO-2) included in our systematic review assessed the rPFS benefit

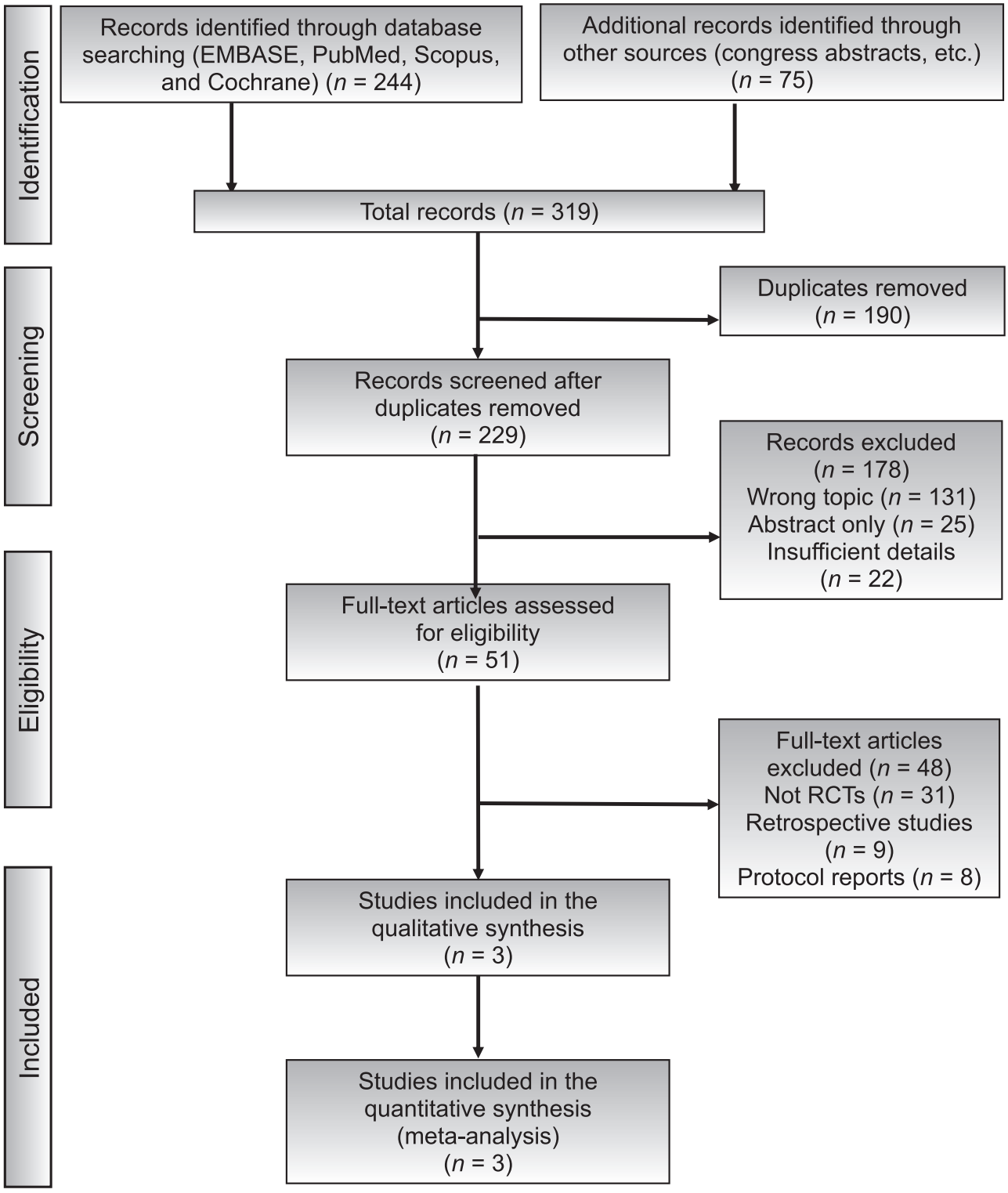


Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describing the study selection process. RCT = randomised controlled trial.

of PARPi + ARSI for first-line mCRPC treatment in the ITT population, with results suitable for meta-analysis (Fig. 2A). The pooled HR was 0.62 (95% CI 0.53–0.72), favouring PARPi + ARSI in comparison to placebo + ARSI. No significant heterogeneity between these studies was observed (I^2 = 0%).

Two of the three phase 3 trials (PROPEL and TALAPRO-2) assessed the OS benefit of PARPi + ARSI for first-line mCRPC treatment in the ITT population, with results suitable for meta-analysis (Fig. 2B). The pooled HR was 0.84 (95% CI 0.72–0.98), indicating a lower risk of death with PARPi + ARSI in comparison to placebo + ARSI. No significant

Table 1 – Main characteristics of the three randomised phase 3 studies included in the present meta-analysis

Trial	MAGNITUDE [5]		PROPEL [4]		TALAPRO-2[6]	
ARSI	Abiraterone		Abiraterone		Enzalutamide	
PARP inhibitor	Niraparib		Olaparib		Talazoparib	
Primary endpoint	rPFS by central review for HRR$^+$		rPFS by investigator for all comers		rPFS by central review for all comers	
Study start	January 2019		October 2018		December 2017	
Population	HRR$^+$ only HRR$^-$ stopped for futility		All comers		All comers	
	Exp arm	Control arm	Exp arm	Control arm	Exp arm	Control arm
Patients	212	211	399	397	402	403
HRR$^+$ status	100%	100%	28%	29%	21%	21%
Molecular testing	Prospective		After randomisation		After randomisation/ (prospective[a])	
Genes analysed	*ATM*, *BRCA1*, *BRCA2*, *BRP1*, *CDK12*, *CHECK2*, *FANCA*, *HDAC2*, *PALB2*		*ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRP1*, *CDK12*, *CHECK1*, *CHECK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*		*ATM*, *ATR*, *BRCA1*, *BRCA2*, *CHECK2*, *FANCL*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*	
Stratification factors	– Prior docetaxel for mHSPC – Prior ARSI for nmCRPC or mHSPC – Prior AA for 1st-line mCRPC – *BRCA1/2* vs non-*BRCA* HRR$^+$		– Prior docetaxel for mHSPC – Site of metastases		– HRR status – Prior AA or docetaxel for mHSPC	
rPFS						
All comers	–		25 vs. 16 mo HR 0.67 (95% CI 0.56–0.81) $p < 0.001$		NR vs 21.9 mo HR 0.63 (95% CI 0.51–0.78) $p < 0.001$	
HRR$^+$ status	16.5 vs 13.7 mo HR 0.73 (95% CI 0.56–0.96) $p = 0.022$		NR vs 13.9 mo HR 0.50 (95% CI 0.34–0.73)		27.9 vs 16.4 mo HR 0.46 (95% CI 0.30–0.70) $p < 0.001$	
BRCA2/1 mutation	19.5 vs 10.9 mo HR 0.55 (95% CI 0.39–0.78) $p = 0.0007$		NR vs 8.4 mo HR 0.23 (95% CI 0.12–0.43)		–	

AA = abiraterone acetate; ARSI = androgen receptor signalling inhibitor; CI = confidence interval; HR = hazard ratio; Exp = experimental; HRR$^+$ = homologous recombination repair mutation; HRR$^-$ = no HRR mutation; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; nmCRPC = nonmetastatic CRPC; NR = not reached; rPFS = radiological progression-free survival.
[a] Data not presented for prospective testing.

heterogeneity between the two studies was observed (I^2 = 0%). No OS data are available yet for the prespecified subgroups.

3.2. PFS subgroup analysis

All three phase 3 trials assessed the rPFS benefit of PARPi + ARSI versus placebo+ ARSI in HRR$^+$ and HRR$^-$ mCRPC subgroups [4–6]. The pooled HR for rPFS was 0.76 (95% CI 0.65–0.90) for HRR$^-$ mCRPC (Fig. 3A) and 0.57 (95% CI 0.42–0.78) for HRR$^+$ mCRPC (Fig. 3B), indicating a significant rPFS improvement for patients treated with PARPi + ARSI, irrespective of HRR status.

Two of the three trials (MAGNITUDE and PROPEL) included in our systematic review assessed the rPFS benefit of PARPi + ARSI in first-line treatment of *BRCA*-mutant mCRPC, with results suitable for meta-analysis (Fig. 3C). The PARPi + ARSI combination significantly improved rPFS in comparison to placebo + ARSI (HR 0.36, 95% CI 0.16–0.82). Significant heterogeneity was observed (I^2 = 79%).

3.3. Toxicities

Overall, 47% of patients treated in the PROPEL study with olaparib + AAP experienced G3–4 TEAEs (vs 38% in the control arm); the most common G3–4 AEs in the combination arm were anaemia (15% vs 3.3%), hypertension (3.8 vs 3.5%), and fatigue (2.3% vs 1.5) [16]. Fifty-five patients (14%) discontinued olaparib and 31 patients (7.8%) discontinued placebo because of an AE. Discontinuation of AAP as a result of AEs occurred in 34 patients (8.5%) in the olaparib + AAP arm and 35 patients (8.8%) in the AAP + placebo arm.

In the MAGNITUDE study, 67% of patients experienced G3–4 TEAEs in the combination arm, versus 46% in the AAP + placebo arm, with anaemia (30% vs 7.6%), hypertension (15% vs 13%), and thrombocytopenia (6.6% vs 2.4%) being the most common. Discontinuation of niraparib or placebo due to an AE occurred in only 11% and 4.7% of cases, respectively [17].

For the talazoparib + enzalutamide combination, the most common G3–4 TEAES were anaemia (47% vs 4.2%), neutropenia (18% vs 1.5%), and thrombocytopenia (7.3% vs 0.9%). However, 49% of patients started the treatment with G1–2 anaemia at baseline. Overall, 72% of patients had at least one G3–4 TEAE in the combination arm, versus 41% in the enzalutamide arm [18]. Discontinuation of talazoparib or placebo due to an AE occurred in 19% versus 12% of cases, respectively.

All three phase 3 trials [4–6] included in our systematic review reported the incidence of G3–4 TEAEs in the PARPi + ARSI and control arms (Fig. 4). Moderate heterogeneity (I^2 = 60%) was detected in the HRR$^+$ subgroup analysis.

The pooled RR was 1.47 (95% CI 1.18–1.83), indicating a significantly higher probability of developing G3–4 TEAEs with PARPi + ARSI treatment. High heterogeneity among the three studies was observed (I^2 = 83%).

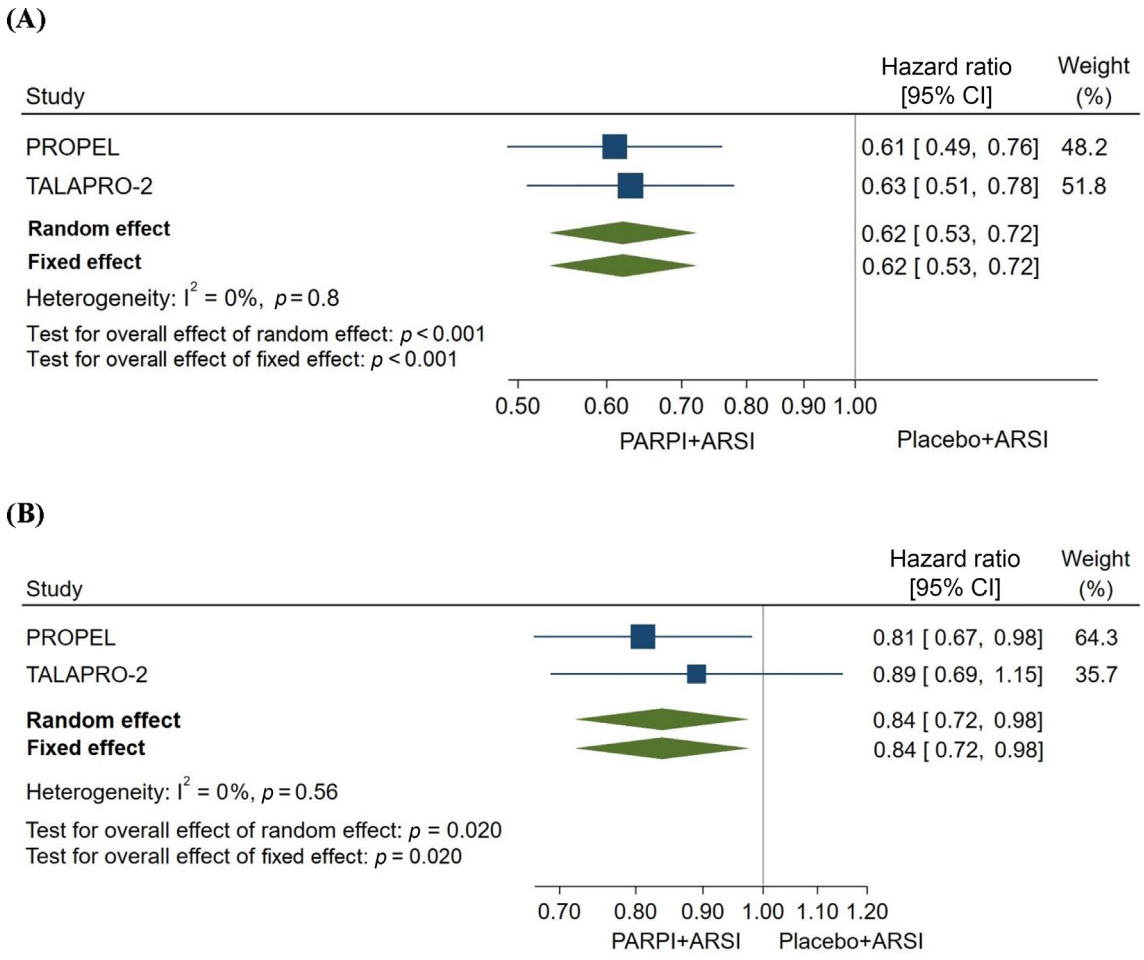


Fig. 2 – Forest plots of hazard ratios for (A) progression-free survival and (B) overall survival in two randomised trials comparing PARPI+ ARSI versus placebo + ARSI in an intention-to-treat mCRPC population with metastatic castration-resistant prostate cancer in the first-line setting. Pooled hazard ratios were computed using both fixed-effect and random-effect models. The bars indicate the 95% confidence interval (CI). ARSI = androgen receptor signalling inhibitor; PARPI = PARP inhibitor.

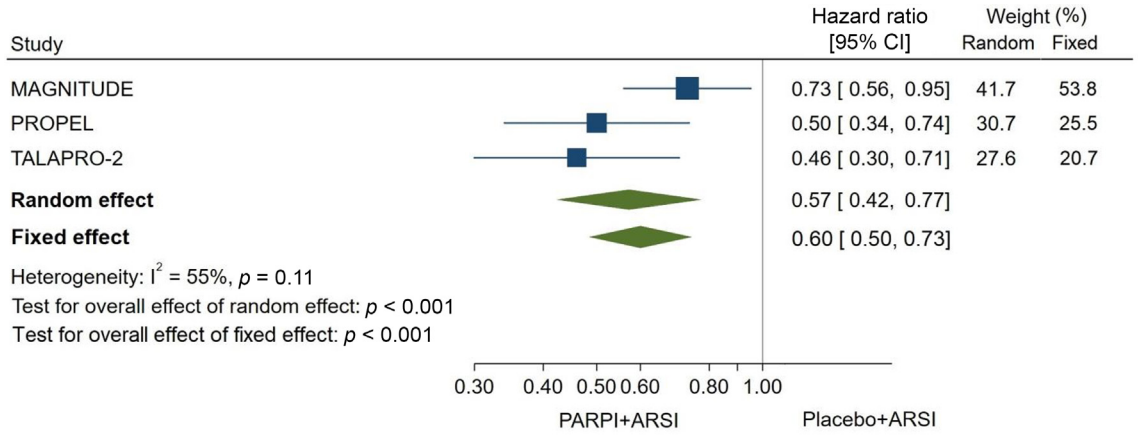
3.4. *Discussion*

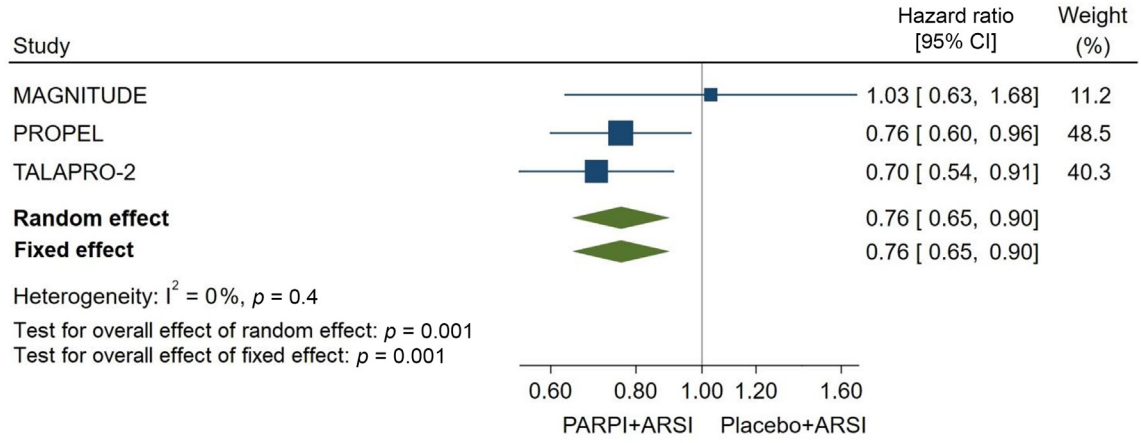
The role of PARPi in HRR-deficient mCRPC was first established in the TOPARP adaptive phase 2 study. TOPARP-B was the first biomarker-led trial to prospectively determine that nearly one-third of advanced prostate cancers harbour somatic genomic alterations in the DNA repair machinery [19], and to clinically support the synthetic lethality concept, whereby proteins that are synthetically lethal are targeted with specific tumour suppressor gene defects to elicit tumour cell–specific death without deleterious effects on normal cells [6].

However, it is worth pointing out that in HHR^+ prostate cancer, inhibition of PARP might impair not only DNA repair but also the modulatory activity of the AR [7] via actions on two distinct pathways. Conversely, in HHR^- prostate cancers, PARPi efficacy might only rely on modulation of the AR and/or on the genomic instability probably induced by the concomitant ARSI [7–8,20]. This could potentially explain why the benefit seen in HRR-proficient mCRPC in PROPEL and TALAPRO-2 is present but not as profound as for *BRCA2*-mutated or HRR-deficient prostate cancer [16,18].

TOPARP-B is the only phase 2 trial so far to perform next-generation sequencing (NGS) on mandatory prestudy fresh biopsies from metastatic sites, highlighting that sequencing failure is low when an adequate tissue sample is used for analysis [19]. This could be extremely relevant in selecting patients with *BRCA2* alterations. There is now compelling evidence that prostate cancers harbouring *BRCA2* homozygous loss, identified on tissue sequencing, derive the greatest benefit from PARPi [21,22]. Although the concordance between tissue and cell-free DNA sequencing results is high (approximately 80%%), it is highly likely that blood-based testing may miss *BRCA2* homozygous loss [22,23]. Therefore, it is possible that basing patient selection on cell-free DNA might hinder the identification of homozygous *BRCA2* loss, missing patients who would benefit the most from PARPi-based therapies.

Differences in the design of the three trials, especially with regard to their genomic sequencing approaches, may account for the heterogeneity observed for the outcomes. MAGNITUDE is the only trial in which a priori genomic sequencing of patient samples dictated trial arm allocation. Genomic sequencing was preplanned for PROPEL but was conducted after randomisation. TALAPRO-2 had two





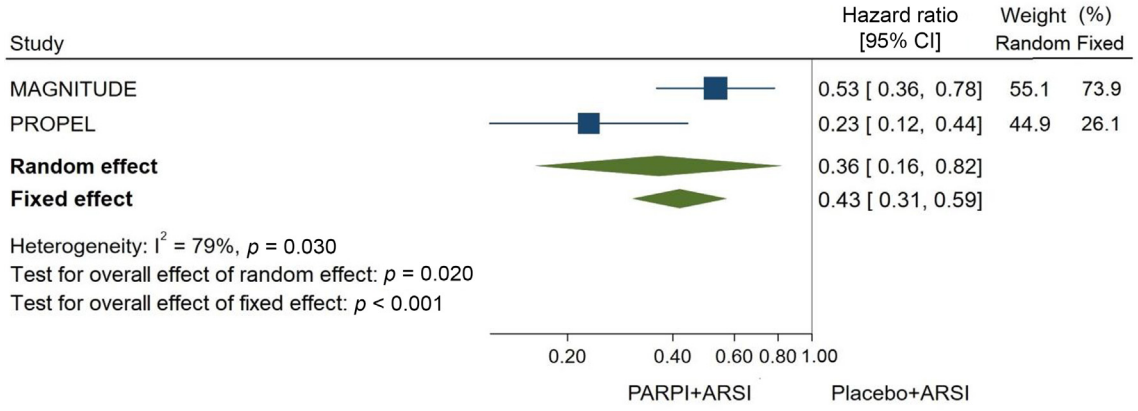


Fig. 3 – Forest plots of hazard ratios for progression-free survival in randomised trials comparing PARPI + ARSI versus placebo + ARSI in (A) homologous recombination repair (HRR)-deficient, (B) HRR-proficient, and (C) *BRCA*-mutated metastatic castration-resistant prostate cancer in the first-line setting. Pooled hazard ratios were computed using both fixed-effect and random-effect models. The bars indicate the 95% confidence interval (CI). It should be noted that the HRR-proficient group in the TALAPRO-2 study also included patients for whom it was not possible to define biomarker status. ARSI = androgen receptor signalling inhibitor; PARPI = PARP inhibitor.

cohorts, one with prospective and the other with retrospective genomic sequencing to detect HRR deficiency. In assessing HRR status after randomisation, patients with unassessable HRR status and those for whom only one sample (blood or tissue) was assessable might be considered as biomarker-negative. This bears the risk of including de facto HRR-positive patients in the biomarker-negative population. However, in PROPEL only 2.3% of patients had unknown HRR status due to sequencing failure because of insufficient sample quantity or quality or other technical issues, and these patients were not included in the biomarker-negative cohort, in contrast to TALAPRO-2. Nev-

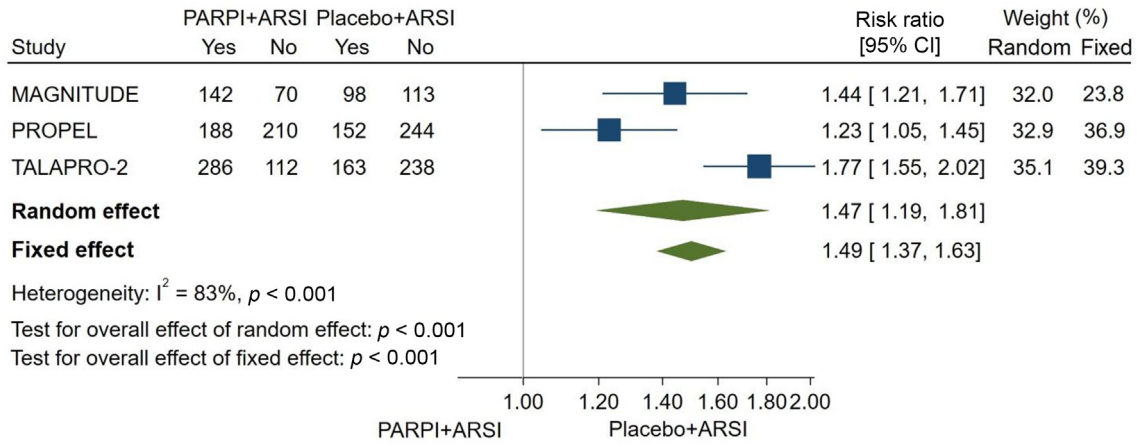


Fig. 4 – Forest plot of risk ratios for grade ≥3 treatment-emergent adverse events in three randomised trials comparing PARPI + ARSI versus placebo + ARSI. Pooled risk ratios were computed using both fixed-effect and random-effect models. The bars indicate the 95% confidence interval (CI). ARSI = androgen receptor signalling inhibitor; PARPI = PARP inhibitor.

ertheless, among the limited number of patients with undetermined/single-assay negative HRR status, considering the concordance between tissue- and blood-based sequencing, the expected rate of misclassified *BRCA2* mutation carriers should not exceed 9%, as the generally accepted prevalence of this mutation. In MAGNITUDE, for patients with a negative result via blood testing only required sequencing of tissue to confirm their biomarker-negative status, but 75/247 patients (30%) were deemed biomarker-negative only on the basis of circulating tumour DNA (ctDNA) sequencing [17]. In PROPEL, 186/552 patients (33.7%) in the HRR-proficient cohort had only ctDNA available for sequencing. Considering that the negative predictive value in PROPEL was 94% using tissue testing as the reference, approximately 12 of these patients may potentially be misclassified. This equates to ∼2% of patients in the total HRR$^-$ subgroup [24]. It is thus unlikely that the limited number of false-HRR$^-$ cases would explain the rPFS benefit seen in the biomarker-negative trial groups. Importantly, the proportion of patients for whom HRR biomarker status cannot be defined is a challenge in real-world practice, as preservation of tissue samples, quality standards in pathology and sequencing hubs, and national testing policies may differ significantly across countries.

It is still a matter of debate why the MAGNITUDE study showed no rPFS benefit in the HRR$^-$ population [17], in contrast to the other two studies. After futility analysis based on biochemical or radiographic progression, whatever occurred first, the HRR$^-$ mCRPC treatment arm was suspended. Interestingly, PSA progression was used as a stopping criterion only in this part of the study. The number of PSA progression events (n = 83) was numerically higher than the number of radiographic progression events (n = 65) in this cohort, meaning that the treatment might have been interrupted prematurely in the absence of meaningful progression [17]. Moreover, MAGNITUDE allowed prior 4 mo of AAP before the combination was started, which could have had a negative impact on outcomes. Indeed, patients who had previously received AAP for more than 2 mo during the combination run-in period (n = 40) achieved no rPFS benefit (HR 1.47, 95% CI 0.66–3.30) [25].

In terms of side effects, haematological toxicities, including anaemia, thrombocytopenia, and neutropenia, were the most common G3–4 toxicities in the three studies and can be attributed to the PARPi [26]. Among the PARPi options, niraparib as a single agent is associated with a lower incidence of anaemia, while olaparib is associated with lower thrombocytopenia [27]. The most common severe nonhaematological toxicity for all combinations is hypertension, a well-known side effect of ARSI, especially AAP [26]. Among other nonhaematological TEAEs, fatigue and nausea are commonly reported by patients undergoing PARPi treatment. It has been reported that olaparib may potentially lead to a greater degree of fatigue than other PARPi agents, while niraparib can potentially cause more nausea [27]. Importantly, the toxicities emerging from combination treatments are not particularly different from those associated with PARPi monotherapies [26]. However, it is worth pointing out that for these three combinations, only olaparib was given at the full dose, and both niraparib and talazoparib were given at a lower dose than when administered as monotherapy (200 mg niraparib when combined with AAP vs 300 mg as a single agent; 0.5 mg talazoparib when combined with enzalutamide vs 1 mg as a single agent) on the basis of dose-limiting toxicity for niraparib and pharmacokinetic studies for talazoparib [17,18]. Nevertheless, the olaparib + AAP combination led to the lowest numerical rate of severe side effects (all grade ≥3 TEAEs: 47.2% in PROPEL vs 75.1% in TALAPRO-2 vs 66.9% in MAGNITUDE); the percentage of patients who discontinued the study arm because of toxicities is comparable between studies (13.8% vs 19.1% vs 10.8, respectively).

4. Conclusions

Taken together, the results from our meta-analysis confirm that PARPi + ARSI combination is beneficial in prolonging

rPFS for patients with mCRPC harbouring *BRCA2/1* and HRR gene mutations, irrespective of the PARPi agent used. This is extremely relevant since a significant benefit with single-agent PARPi has only been observed in *BRCA2/1*-mutant mCRPC, highlighting synergistic activity of PARPi + ARSI combinations. Moreover, the data presented here show a modest but statistically significant OS benefit in HRR^{-} mCRPC. However, the results should be interpreted with caution since they are derived from only two of the three studies analysed, and the OS analysis is still immature for the combination of talazoparib + enzalutamide.

The clinical utility of these results might also be challenged by the recent change in the treatment landscape for advanced prostate cancer. Novel ARSIs, including AAP and enzalutamide, in addition to LHRH analogues have shown a survival benefit in patients with metastatic hormone-sensitive prostate cancer (mHSPC), while addition of docetaxel to ARSI is mainly beneficial in mHSPC with a high burden of disease [28]. Therefore, in the near future, only a small proportion of patients will be ARSI-naïve in the mCRPC setting.

Moreover, results from these trials should not discourage molecular characterisation studies of mCRPC. Despite PARPi treatment, virtually all patients experience disease progression sooner or later because of intrinsic or acquired PARPi resistance, highlighting the need for further molecularly targeted treatment approaches. Beside HRR gene mutations, there are other alterations that could potentially be targeted in advanced prostate cancer, such as mismatch repair deficiency and aberrant activation of the PI3K/AKT/PTEN signalling pathway or molecular features of neuroendocrine differentiation [29–32]. Although treatments for these variants have not been established as standard of care, they could be offered within research protocols in dedicated cancer centres.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.07.013.

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