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Review

Impact of performance status on efficacy of systemic therapy for prostate cancer: a meta-analysis

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Objective

To evaluate the efficacy of systemic therapies in patients with worse performance status (PS) treated for high-risk non-metastatic prostate cancer (PCa), metastatic hormone-sensitive PCa (mHSPC), and non-metastatic/metastatic castration-resistant PCa (nmCRPC/mCRPC), as there is sparse pooled data showing the effect of PS on oncological outcomes in patients with PCa.

Methods

Three databases were queried in June 2022 for randomised controlled trials (RCTs) analysing patients with PCa treated with systemic therapy (i.e., adding androgen receptor signalling inhibitor [ARSI] or docetaxel [DOC] to androgen-deprivation therapy [ADT]). We analysed the oncological outcomes of patients with PCa with worse PS, defined as Eastern Cooperative Oncology Group PS ≥ 1, treated with combination therapies and compared these to patients with good PS. The main outcomes of interest were overall survival (OS), metastasis-free survival (MFS), and progression-free survival.

Results

Overall, 25 and 18 RCTs were included for systematic review and meta-analyses/network meta-analyses, respectively. In all clinical settings, combination systemic therapies significantly improved OS in patients with worse PS as well as in those with good PS, while the MFS benefit from ARSI in the nmCRPC setting was more pronounced in patients with good PS than in those with worse PS ($P = 0.002$). Analysis of treatment ranking in patients with mHSPC revealed that triplet therapy had the highest likelihood of improved OS irrespective of PS; specifically, adding darolutamide to DOC + ADT had the highest likelihood of improved OS in patients with worse PS. Analyses were limited by the small proportion of patients with a PS ≥ 1 (19%–28%) and that the number of PS 2 was rarely reported.

Conclusions

Among RCTs, novel systemic therapies seem to benefit the OS of patients with PCa irrespective of PS. Our findings suggest that worse PS should not discourage treatment intensification across all disease stages.

Keywords

performance status, Eastern Cooperative Oncology Group, metastatic hormone-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, metastatic castration-resistant prostate cancer

Introduction

The treatment landscape of combination systemic therapies for all prostate cancer (PCa) stages including high-risk non-metastatic PCa (nmPCa), non-metastatic/metastatic castration-resistant PCa (nmCRPC/mCRPC), and metastatic hormone-sensitive PCa (mHSPC), has been rapidly evolving in the past decade [1]. Today, combination therapies using an androgen receptor signalling inhibitor (ARSI) and/or docetaxel (DOC) plus androgen-deprivation therapy (ADT) are the guideline-endorsed treatment strategies across the metastatic disease states [2–6]. However, in the clinical setting, treatment intensification should be tailored towards each patient's condition and account for the toxicity, and possible limited survival benefit in patients with worse performance status (PS) [7,8]. Therefore, choosing the appropriate candidates more likely to benefit from systemic therapies may improve overall survival (OS). In this context, the benefit of intensified therapy in patients with worse PS needs further assessment [9]. The Eastern Cooperative Oncology Group (ECOG) PS is widely used to discriminate the patients' general health condition in clinical practice and trials. Poor ECOG PS has been recognised as a prognostic factor of worse OS across multiple malignancies [10–12]. However, to date, there is no robust data regarding the differential survival outcomes of patients with PCa treated with systemic therapy stratified by PS. Therefore, we conducted this systematic review, meta-analysis, and network meta-analysis (NMA) to assess the impact of PS on the efficacy of combination systemic therapies in patients with PCa. Moreover, we compared the outcomes of patients with worse PS (≥ 1) with patients with good PS.

Methods

The protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42022339754).

Search Strategy

This systematic review, meta-analysis, and NMA were performed following the guidelines of the Preferred Reporting Items for Meta-Analyses of Observational Studies in Epidemiology Statement (Table S1) [13]. PubMed®, Web of Science™, and Scopus® databases were queried in June 2022 to identify studies evaluating the oncological outcomes of systemic therapy for PCa. The detailed search strategy is described in Appendix S1. The primary outcome of measurement was OS. Secondary outcomes were progression-free survival (PFS) for mCRPC and mHSPC, as well as metastasis-free survival (MFS) for nmPCa. Two investigators independently screened the titles and abstracts for eligibility and performed a full-text review of potentially relevant studies. In addition, we performed manual searches of relevant reference lists to identify additional studies of interest. Disagreements were resolved by consensus with co-authors.

Inclusion and Exclusion Criteria

Studies were included if they analysed patients with high-risk nmPCa, nmCRPC, mCRPC, and mHSPC stratified by ECOG PS (Patients), and compared the efficacy of the currently guideline-endorsed combination systemic therapy (Interventions) with the efficacy of standard systemic treatment at the time of study enrolment (Comparisons) to assess the differential effects of treatment on OS, PFS or MFS (Outcome) in randomised controlled trials (RCTs) (Study design), i.e., PICOS approach. Studies lacking original patient data, reviews, letters, editorial comments, replies from authors, case reports, and articles not written in English were excluded.

Data Extraction

Two authors independently extracted the following data: the studies and first author's name, publication year, inclusion criteria, agents, number of patients, follow-up duration, the cut-off value of PS outcomes, number of patients and median OS stratified by ECOG PS. Subsequently, the hazard ratios (HRs) and 95% CIs from Cox regression models for OS, PFS, and MFS were retrieved. All discrepancies were resolved by consensus with co-authors. We defined the patients with ECOG PS ≥ 1 as 'worse PS' and those with ECOG PS 0 as 'good PS'.

Risk of Bias Assessment

We assessed a study quality and risk of bias was based on the Cochrane Handbook for Systematic Reviews of Interventions risk-of-bias tool (RoB version 2) (Fig. S1) [14]. The risk-of-bias figure was depicted using Review Manager 5.3 Software (RevMan; The Cochrane Collaboration, Oxford, UK). Two independent authors performed the risk-of-bias assessment of each study.

Statistical Analyses

Meta-Analysis

Forest plots with HRs were used to analyse the association between systemic therapy and survival outcomes. PFS was defined as the time from treatment initiation to radiological progression, clinical progression, or death. MFS was defined as the time from randomisation to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first. We divided patients with mHSPC into three groups depending on treatment and control arms: triplet therapy (ARSI + DOC + ADT vs DOC + ADT), ARSI-based doublet therapy (ARSI + standard of care [SOC] vs SOC), DOC-based doublet therapy (DOC + ADT vs ADT). In the mCRPC setting, we divided the patients into two groups: pre-ARSI/pre-DOC and pre-ARSI/post-DOC settings. A fixed-effect model was used for calculations of HRs [15]. Heterogeneity among the outcomes of included studies in this meta-analysis was assessed using Cochrane's Q test. When significant heterogeneity ($P < 0.05$ in the Cochrane's Q test) was observed, we attempted to investigate the cause of heterogeneity [16]. All analyses were conducted using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria), and the statistical significance level was set at $P < 0.05$.

Network Meta-Analysis

We applied random-effects models with a frequentist approach to analyse the direct and indirect comparisons between treatment regimens [17,18]. Contrast-based analyses were applied with estimated differences in the log HR and the standard error calculated from the published HR and CI [19]. The relative ranking of the different regimens for oncological outcomes was estimated using the surface under the cumulative ranking (SUCRA) [17]. Network plots were utilised to illustrate the connectivity of the treatment networks. Cochrane's Q test was used to assess the heterogeneity. All statistical analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing).

Results

Study Selection and Characteristics

Our initial search identified 4794 records. After removing duplicates, 2536 records remained for screening titles and abstracts (Fig. S2). After screening, 129 articles remained eligible for a full-text review. Finally, 25 RCTs were eligible for systematic review [2–6,20–53], and 18 were eligible for meta-analyses and NMAs [2–6,20–38,40,43,46,47,49,50,53]. The demographics of each included study are summarised in Table S2. Of the 25 RCTs, one, three, 10, and 11 studies included patients with high-risk nmPCa, nmCRPC, mHSPC, and mCRPC, respectively. Among the included studies providing absolute numbers of patients of different ECOG PS groups, patients with worse PS constantly constituted a minority of the included populations (Table 1 [2–6,20–53]). A higher prevalence of ECOG ≥ 1 patients was noted among studies that analysed mCRPC (28%), the lowest in nmPCa (19%) studies. The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trials applied WHO PS [28,33–35], and the Groupe d'Etude des Tumeurs Uro-Génitales (GETUG)-AFU 15 (ClinicalTrials.gov Identifier: NCT00104715) [31,32] and the TAX-327 [51] trials applied Karnofsky PS (KPS) as inclusion criteria. We translated the value of WHO PS into ECOG PS owing to the same definition. The GETUG-AFU 15 trial provided survival data stratified by ECOG PS; thus, these trials were included in meta-analyses and NMAs.

Oncological Outcomes

The oncological outcomes of the included studies are described in Table 1. The results of our meta-analyses and NMAs are summarised in Table 2.

High-Risk nmPCa

Only the STAMPEDE trial which compared the ARSI (abiraterone [ABI] ± enzalutamide [ENZ]) + ADT combination vs ADT alone in addition to radiation therapy for high-risk nmPCa, provided data on MFS stratified by PS. In this trial, patients with ECOG PS 0 had a benefit in MFS (HR 0.47, 95% CI 0.38–0.5), whereas, it did not reach statistical significance in patients with ECOG PS 1–2 (HR 0.86, 95% CI 0.58–1.28). There was a statistically significant difference between the two groups ($P = 0.007$).

Non-metastatic CRPC

Meta-analyses of the effect of ARSI combination therapies stratified by PS Three studies comprising 4117 patients provided data on OS and MFS in patients with nmCRPC treated with ARSI + ADT vs ADT alone. As shown in Fig. 1, adding ARSI to ADT reduced the risk of death in both patients with ECOG PS 1 (pooled HR 0.78, 95% CI 0.63–0.98) and those with ECOG PS 0 (pooled HR 0.67, 95% CI 0.56–0.80); there were no statistical differences between the two groups ($P = 0.3$). Adding ARSI to ADT also reduced the risk of metastasis in both patients with ECOG PS 1 (pooled HR 0.45, 95% CI 0.36–0.56) and those with ECOG PS 0 (pooled HR 0.30, 95% CI 0.26–0.35). There was a significant difference between patients with poor vs good PS in terms of combination systemic therapy efficacy ($P = 0.002$). The

Table 1 Oncological outcomes of included 25 RCTs.

Study name and first author	Year	Median follow-up period, months	Comparison of ECOG PS outcomes	Number of patients, (%) (treatment/control arm)		Median OS, months (treatment/control arm)		HR (95% CI) of survival outcomes (treatment vs control arm)	
				Good PS	Worse PS	Good PS	Worse PS	Good PS	Worse PS
1. High-risk nmPCa									
STAMPEDE, Attard et al. [52]	2022	72	0 vs 1–2	711 (79)/ 810 (82)	187 (21)/ 178 (18)	ND	ND	MFS: 0.47 (0.38–0.5)	MFS: 0.86 (0.58–1.28)
2. nmCRPC									
SPARTAN, Smith et al. [23] and Small et al. [24]	2018/2019	41	0 vs 1	623 (77)/ 311 (78)	183 (23)/ 89 (22)	NR/NR	NR/45.7	OS: 0.69 (0.51–0.93) MFS: 0.27 (0.21–0.34)	OS: 0.87 (0.58–1.31) MFS: 0.40 (0.27–0.60)
ARAMIS, Fizazi et al. [20,21]	2019/2020	29	0 vs 1	1041 (69)	468 (31)	ND	ND	OS: 0.62 (0.45–0.87) MFS: 0.38 (0.30–0.48)	OS: 0.74 (0.50–1.08) MFS: 0.50 (0.36–0.69)
PROSPER, Hussain et al. [22] and Sternberg et al. [25]	2018/2020	48	0 vs 1	747 (80)/ 382 (82)	185 (20)/ 85 (18)	ND	ND	OS: 0.71 (0.57–0.88) MFS: 0.27 (0.22–0.34)	OS: 0.76 (0.52–1.09) MFS: 0.43 (0.28–0.66)
3. mHSPC									
3.1. Triplet therapy									
PEACE-1, Fizazi et al. [4]	2022	45.7	0 vs 1–2	250 (70)/ 246 (69)	105 (30)/ 109 (31)	ND	ND	OS: 0.75 (0.56–1.02) rPFS: 0.50 (0.32–0.78)	OS: 0.74 (0.50–1.09) rPFS: 0.50 (0.27–0.93)
ARASENS, Smith et al. [5]	2022	43	0 vs 1	466 (72)/ 462 (71)	185 (28)/ 190 (29)	ND	ND	OS: 0.75 (0.61–0.93)	OS: 0.58 (0.43–0.77)
3.2. Doublet therapy with ARSI + ADT									
ARCHES, Armstrong et al. [2,26]	2019/2022	44.6	0 vs 1	448 (78)/ 443 (77)	125 (22)/ 133 (23)	NR/NR	NR/45.9	OS: 0.67 (0.52–0.86) rPFS: 0.38 (0.29–0.51)	OS: 0.65 (0.44–0.97) rPFS: 0.43 (0.27–0.70)
ENZAMET, Davis et al. [29,53]	2019/2022	34	0 vs 1–2	405 (72)/ 405 (72)	158 (28)/ 157 (28)	ND	ND	OS: 0.68 (0.54–0.85) cPFS: 0.38 (0.3 –0.48)	OS: 0.72 (0.53–0.97) cPFS: 0.44 (0.32–0.6)
TITAN, Chi et al. [3,27]	2019/2021	44	0 vs 1	328 (62)/ 348 (66)	197 (38)/ 178 (34)	NR/52.2	NR/32.3	OS: 0.68 (0.52–0.89) rPFS: 0.52 (0.39–0.68)	OS: 0.56 (0.42–0.76) rPFS: 0.42 (0.30–0.59)
LATITUDE, Fizazi et al. [6,30]	2017/2019	51.8	0 vs 1–2	ND	ND	NR/38.2	NR/31.3	OS: 0.64 (0.48–0.86) rPFS: 0.40 (0.32–0.50)	OS: 0.61 (0.46–0.79) rPFS: 0.55 (0.44–0.70)
STAMPEDE Arm G, James et al. [34] and Hoyle et al. [33]	2017/2019	40	0 vs 1–2	744 (78)/ 745 (78)	213 (22)/ 215 (22)	ND	ND	OS: 0.69 (0.56–0.87)	OS: 0.50 (0.35–0.72)
3.3. Doublet therapy with DOC + ADT									
CHAARTED, Sweeney et al. [37] and Kyriakopoulos et al. [36]	2015/2018	53.7	0 vs 1–2	549 (69)	241 (31)	ND	ND	OS: 0.75 (0.61–0.93)	OS: 0.58 (0.41–0.83)
STAMPEDE Arm BCG, James et al. [35] and Clarke et al. [28]	2016/2019	78.2	0 vs 1–2	521 (72)/ 269 (75)	203 (28)/ 92 (25)	ND	ND	OS: 0.83 (0.68–1.00)	OS: 0.79 (0.59–1.05)
GETUG-AFU 15, Gravis et al. [31,32]	2013/2016	83.9	0 vs 1–2	357 (98)	9 (2.5)	ND	ND	OS: 0.84 (0.66–1.14)	OS: 1.21 (0.11–13)
4. mCRPC									
4.1. Pre-ARSI									
TAX 327, Tannock et al. [51] and Berthold et al. [39]	2004/2008	ND	KPS ≥ 90 vs ≤ 80	410 (41)	595 (59)	21	13.5	OS: 0.75 (0.60–0.93)	OS: 0.82 (0.65–1.05)
PREVAIL, Beer et al. [38]	2014	22	0 vs 1	584 (67)/ 585 (69)	288 (33)/ 260 (31)	NR/32.4	27.9/26.9	OS: 0.7 (0.56–0.87) rPFS: 0.15 (0.11–0.2)	OS: 0.69 (0.53–0.9) rPFS: 0.27 (0.19–0.37)

Table 1 (continued)

Study name and first author	Year	Median follow-up period, months	Comparison of ECOG PS outcomes	Number of patients, (%) (treatment/control arm)		Median OS, months (treatment/control arm)		HR (95% CI) of survival outcomes (treatment vs control arm)	
				Good PS	Worse PS	Good PS	Worse PS	Good PS	Worse PS
COU-AA-302, Ryan et al. [46,47]	2013/2015	49.2	0 vs 1	416 (76)/ 414 (76)	130 (24)/ 128 (24)	35.4/32.0	27.9/26.4	OS: 0.79 (0.66–0.93) rPFS: 0.56 (0.47–0.67)	OS: 0.87 (0.65–1.16) rPFS: 0.43 (0.3–0.61)
TERRAIN, Shore et al. [50]	2016	20/16.7	0 vs 1	130 (71)/ 146 (76)	54 (29)/45 (24)	16.5/6.8*	15.3/5.3*	cPFS: 0.43 (0.32–0.59)	cPFS: 0.42 (0.25–0.71)
ALSYMPCA, Parker et al. [45]	2013	ND	0–1 vs 2	536 (87)/ 265 (87)	77 (13)/41 (13)	15.4/11.9	10.0/8.4	OS: 0.68 (0.56–0.82)	OS: 0.82 (0.50–1.35)
AFFIRM, Scher et al. [49]	2012	ND	0–1 vs 2	1097 (91)	102 (8.5)	NR/14.2	10.5/7.2	OS: 0.62 (0.52–0.75)	OS: 0.65 (0.39–1.07)
COU-AA-301, de Bono et al. [40] and Fizazi et al. [43]	2011/2012	12.8	0–1 vs 2	715 (90)/ 353 (89)	82 (10)/45 (11)	17.0/12.3	7.3/7.0	OS: 0.74 (0.63–0.86)	OS: 0.77 (0.50–1.17)
TROPIC, de Bono et al. [41]	2010	12.8	0–1 vs 2	694 (92)	61 (8.1)	ND	ND	OS: 0.68 (0.57–0.82)	OS: 0.81 (0.48–1.38)
4.2. Post-ARSI									
PROfound, Hussain et al. [44]	2021	ND	0 vs 1	84 (52)/34 (41)	78 (48)/49 (59)	ND	ND	OS: 0.94 (0.55–1.66)	OS PS 1: 0.55 (0.35–0.88) PS 2: 0.98 (0.30–4.37)
CARD, de Wit et al. [42]	2019	9.2	0–1 vs 2	242 (95)	13 (5.1)	ND	ND	OS: 0.56 (0.41–0.75)	OS: 0.33 (0.10–1.12)
VISION, Sartor et al. [48]	2021	20.9	0–1 vs 2	510 (93)/ 258 (92)	41 (7.4)/ 22 (7.9)	ND	ND	OS: 0.61 (0.50–0.74)	OS: 0.63 (0.35–1.13)

*cPFS, clinical PFS; ND, no data; NR, not reached; rPFS, radiographic PFS. *This study only analysed PFS.*

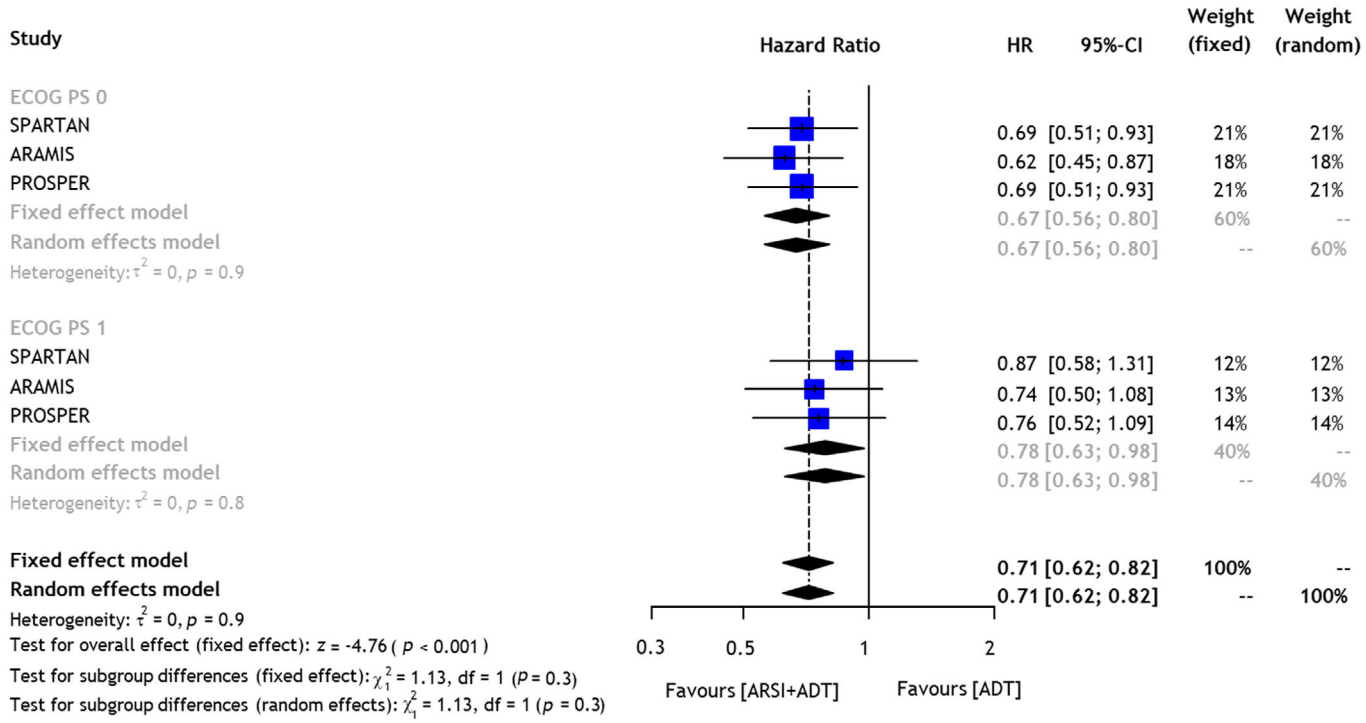
Table 2 Summary of differential oncologic outcomes stratified by performance status.

		Meta-analysis of oncological outcomes stratified by PS		NMA	
1. nmCRPC					
		OS, pooled HR (95% CI)	MFS, pooled HR (95% CI)	Treatment ranking for OS	
ARSI vs ADT	Good PS (PS 0)	0.67 (0.56–0.80)	0.30 (0.26–0.35)	DAR: 76% > APA: 64% > ENZ: 58%	
	Worse PS (PS 1)	0.78 (0.63–0.98)	0.45 (0.36–0.56)	DAR: 76% > ENZ: 67% > APA: 38%	
2. mHSPC					
		OS, pooled HR (95% CI)	PFS, pooled HR (95% CI)	Treatment ranking for OS	
Triplet therapy (ARSI + DOC + ADT vs DOC + ADT)	Good PS (PS 0)	0.75 (0.63–0.90)	NA	Good PS (PS 0)	ABI + DOC: 79% > DAR + DOC: 73% > ABI: 62% > ENZ: 58% > APA: 52% > DOC: 26%
	Worse PS (PS ≥ 1)	0.63 (0.50–0.79)			
Doublet therapy with ARSI (ARSI + SOC vs SOC)	Good PS (PS 0)	0.68 (0.60–0.76)	0.42 (0.38–0.48)	Worse PS (PS ≥ 1)	DAR + DOC: 94% > ABI + DOC: 75% > APA: 63% > ABI: 53% > ENZ: 35% > DOC: 30%
	Worse PS (PS ≥ 1)	0.61 (0.53–0.70)	0.49 (0.43–0.57)		
Doublet therapy with DOC (DOC + ADT vs ADT)	Good PS (PS 0)	0.81 (0.71–0.93)	NA		
	Worse PS (PS ≥ 1)	0.70 (0.56–0.87)			
3. mCRPC					
		OS, pooled HR (95% CI)	PFS, pooled HR (95% CI)	Treatment ranking for OS	
Pre-ARSI and pre-DOC (ARSI + ADT vs ADT)	Good PS (PS 0)	0.75 (0.66–0.86)	0.29 (0.08–1.06)	ABI: 75% = ENZ: 75%	
	Worse PS (PS ≥ 1)	0.77 (0.68–0.93)	0.34 (0.26–0.43)	ENZ: 95% > ABI: 46%	
Pre-ARSI and post-DOC (ARSI + ADT vs ADT)	Good PS (PS 0–1)	0.69 (0.61–0.78)	NA	ENZ: 96% > ABI: 54%	
	Worse PS (PS ≥ 2)	0.72 (0.52–0.99)		ENZ: 84% > ABI: 56%	

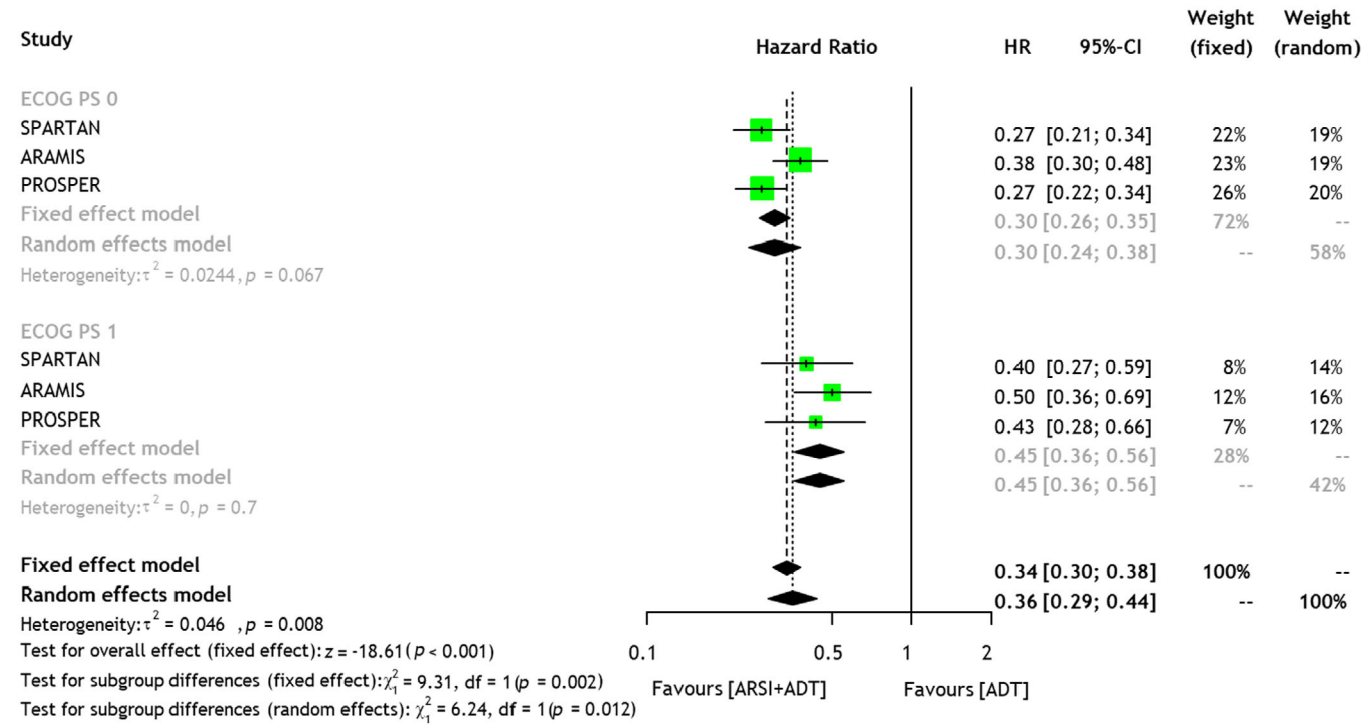
NA, not applicable.

Fig. 1 Forest plots showing association of ARSI + ADT vs ADT alone with (**A**) OS, (**B**) MFS in patients with nmCRPC stratified by ECOG PS.

(A) OS



(B) MFS



Cochrane's Q tests revealed no significant heterogeneity among all analyses.

Network meta-analyses of the effect of ARSI combination therapies stratified by PS Three different agents were included in this NMA to assess the outcome of OS and MFS. The networks of eligible comparisons are graphically described as network plots addressing all survival endpoints (Fig. S3).

Efficacy of combination systemic therapies in terms of OS in patients with nmCRPC

All combination therapies, including adding darolutamide (DAR), apalutamide (APA), or ENZ to ADT, resulted in significantly improved OS in patients with ECOG PS 0. However, it did not reach statistically significant in patients with ECOG PS 1 primarily due to the limited number of patients (Fig. 2A). Based on the SUCRA analysis of treatment rankings for OS, among patients with ECOG PS 1, DAR + ADT had the highest likelihood of providing the maximal OS benefit (76%; Fig. 2B, Table 2). Among patients with ECOG PS 0, DAR + ADT had the highest likelihood of providing the maximal OS benefit (76%; Fig. 2B, Table 2). The results of MFS are summarised in Fig. S4. We did not find any significant heterogeneity in all analyses.

Metastatic HSPC

Meta-analyses Effect of DOC combination therapies stratified by PS

Three studies comprising 2261 patients provided data on OS in patients with mHSPC treated with DOC + ADT vs ADT alone. As shown in Fig. 3A, adding DOC to ADT reduced the risk of death in both patients with ECOG PS ≥ 1 (pooled HR 0.70, 95% CI 0.56–0.87) and those with ECOG PS 0 (pooled HR 0.81, 95% CI 0.71–0.93). There was no significant difference between patients with poor vs good PS in terms of combination systemic therapy efficacy for OS (P = 0.3). The Cochrane's Q tests revealed no significant heterogeneity in this analysis.

Effect of ARSI combination therapies stratified by PS

Five studies comprising 6443 patients provided data on OS and PFS in patients with mHSPC treated with ARSI + SOC vs SOC. As shown in Fig. 3B, adding ARSI to SOC reduced the risk of death in both patients with ECOG PS ≥ 1 (pooled HR 0.61, 95% CI 0.53–0.70) and those with ECOG PS 0 (pooled HR 0.68, 95% CI 0.60–0.76) with a comparable degree (P = 0.24). The results of PFS are summarised in Fig. S5. The Cochrane's Q tests revealed no significant heterogeneity among all analyses.

Effect of triplet therapies stratified by PS

Two studies comprising 2015 patients provided data on OS in patients with mHSPC treated with ARSI + DOC + ADT vs DOC + ADT. Figure 3C shows that adding ARSI to DOC + ADT reduced the risk of death in both patients with ECOG PS ≥ 1 (pooled HR 0.63, 95% CI 0.50–0.79) and those with ECOG PS 0 (pooled HR 0.75, 95% CI 0.63–0.90) with a comparable degree (P = 0.2). The Cochrane's Q tests revealed no significant heterogeneity in this analysis.

Network meta-analyses of the effect of combination therapies stratified by PS Seven different agents were included in this NMA to assess the outcome of OS. All combinations outperformed ADT alone in terms of OS in both patients with worse and good PS (Fig. 4A). Compared to DOC + ADT, only the DAR + DOC +ADT combination resulted in significantly improved OS regardless of ECOG PS (Fig. 4A). Based on the SUCRA analysis of treatment rankings for OS, among patients with ECOG PS ≥ 1, DAR + DOC + ADT had the highest likelihood of providing the maximal OS benefit (94%). Among patients with ECOG PS 0, ABI + DOC + ADT had the highest likelihood of providing the maximal OS benefit (79%), followed by DAR + DOC + ADT (73%). We did not find any significant heterogeneity in all analyses.

Metastatic CRPC

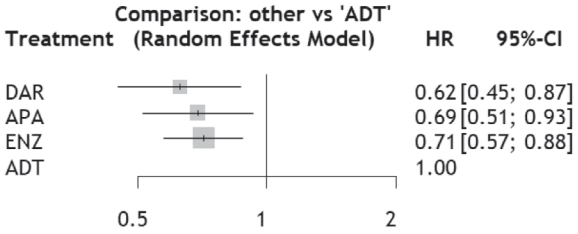
Meta-analyses of the effect of ARSI combination therapies stratified by PS In the pre-DOC setting, two studies comprising 2805 patients provided data on OS and three studies comprising 3180 patients provided data on PFS in patients with mCRPC treated with ARSI + ADT vs ADT alone. Adding ARSI to ADT reduced the risk of death in both patients with ECOG PS ≥ 1 (pooled HR 0.77, 95% CI 0.61–0.93) and those with ECOG PS 0 (pooled HR 0.75, 95% CI 0.66–0.86) with a comparable degree (P = 0.9, Fig. S6). The results for PFS are shown in Fig. S7. The Cochrane's Q tests revealed significant heterogeneity in the analysis of PFS in patients with ECOG PS 0 (P < 0.001). Sensitivity analysis revealed that the results from the PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer) trial [38] was the primary cause of heterogeneity.

In the post-DOC setting, two studies comprising 2394 patients provided data on OS in patients with mCRPC treated with ARSI + ADT vs ADT alone. Fig. S6B revealed that adding ARSI to ADT reduced the risk of death in both patients with ECOG PS 2 (pooled HR 0.72, 95% CI 0.52–0.99) and those with ECOG PS 0–1 (pooled HR 0.69, 95% CI 0.61–0.78) with a comparable degree (P = 0.8). The Cochrane's Q tests revealed no significant heterogeneity among analyses.

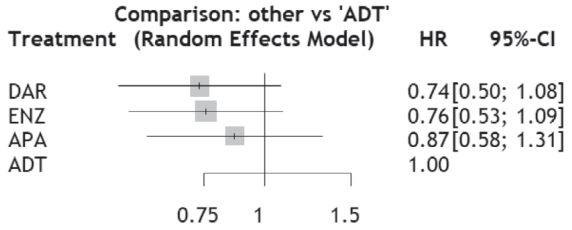
Fig. 2 Network meta-analysis for OS in patients with nmCRPC stratified by ECOG PS; (**A**) Forest plots, (**B**) SUCRA graph showing the treatment ranking for OS.

(A) Forest plots

1) ECOG PS 0

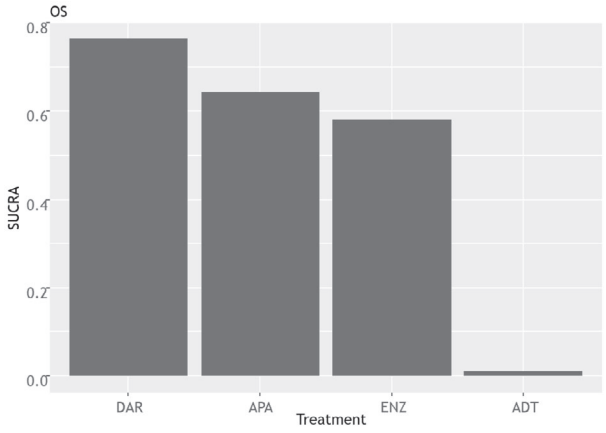


2) ECOG PS 1



(B) SUCRA graph showing the treatment ranking for OS

1) ECOG PS 0



2) ECOG PS 1

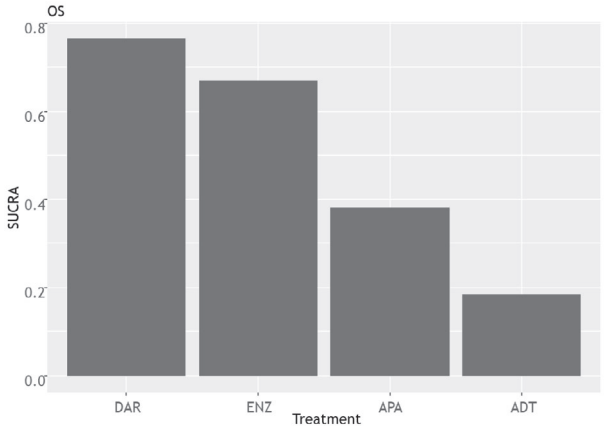
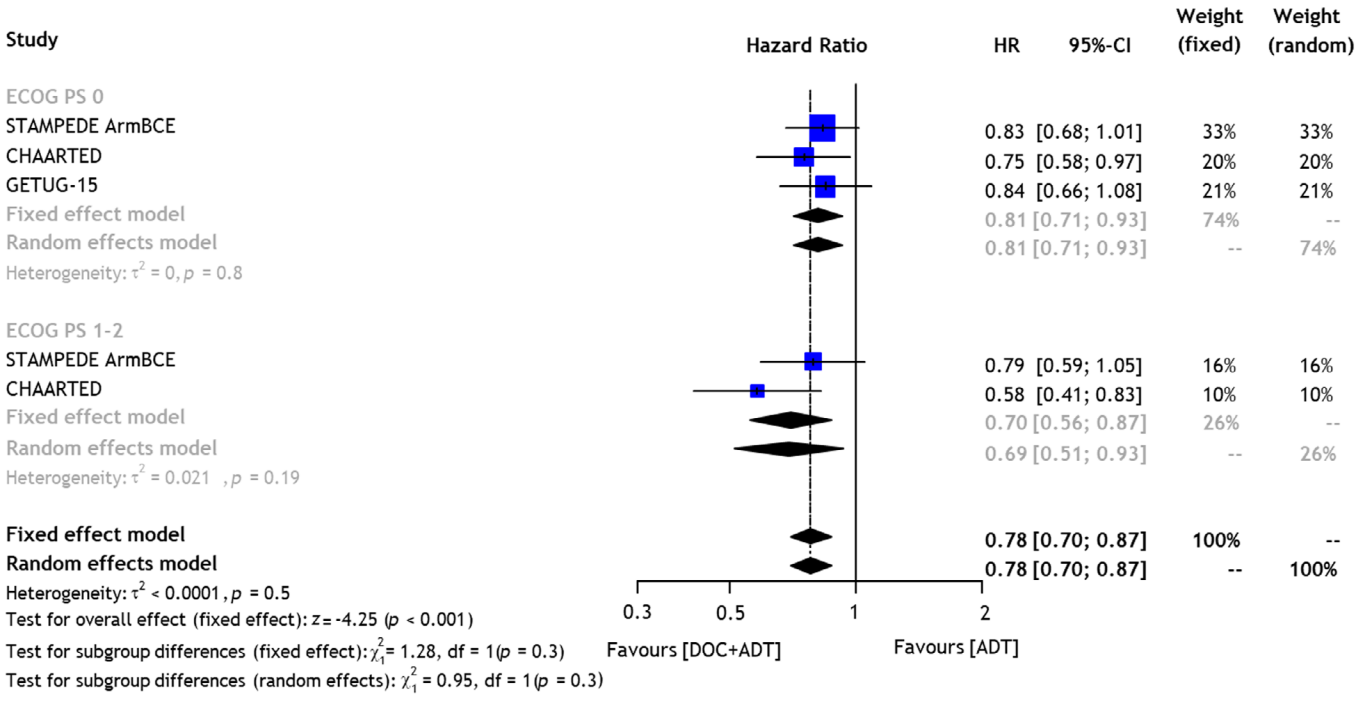


Fig. 3 Forest plots showing association of systemic therapy for mHSPC with OS stratified by performance status; (**A**) DOC + ADT vs ADT, (**B**) ARSI + SOC vs SOC, (**C**) ARSI + DOC +ADT vs DOC + ADT.

(A) DOC + ADT vs. ADT



(B) ARSI + SOC vs. SOC

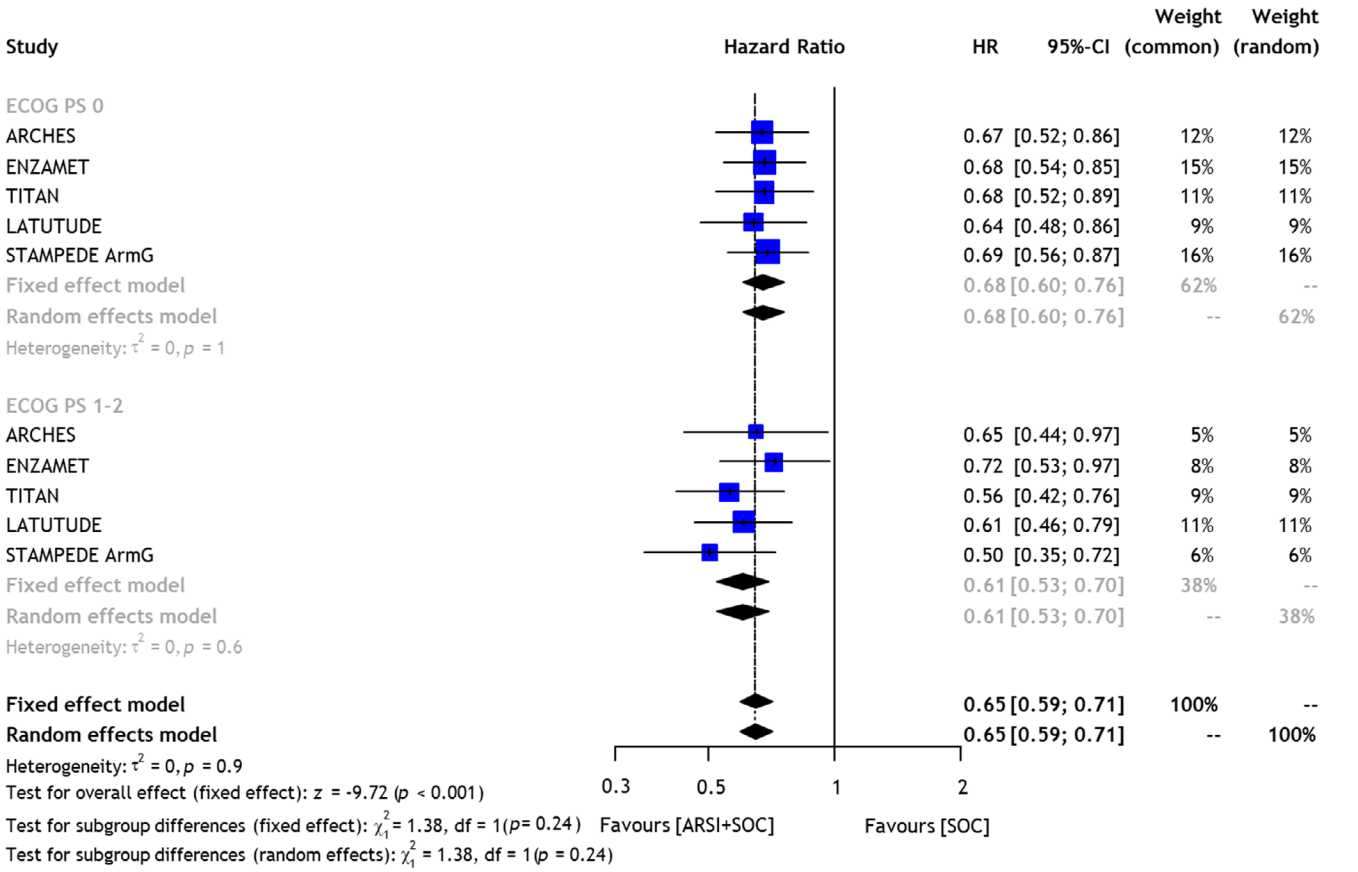
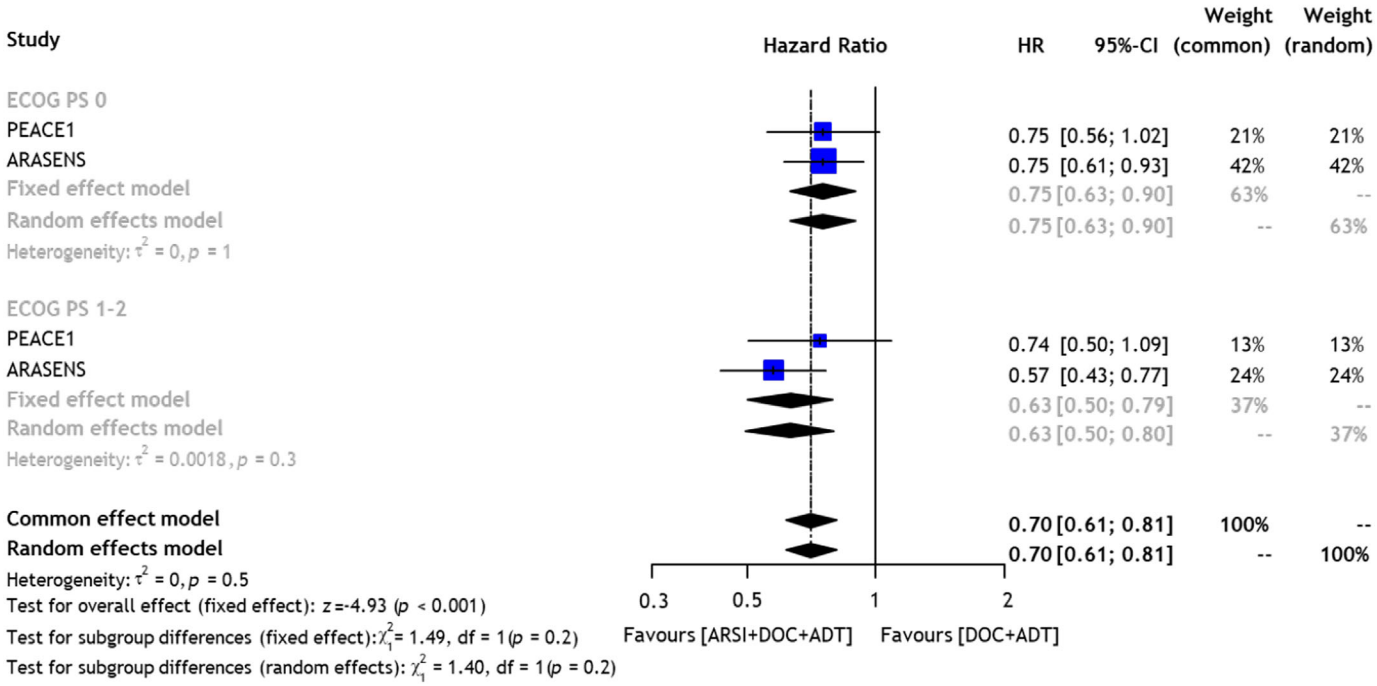


Fig. 3 (continued).

(C) ARSI + DOC +ADT vs. DOC + ADT



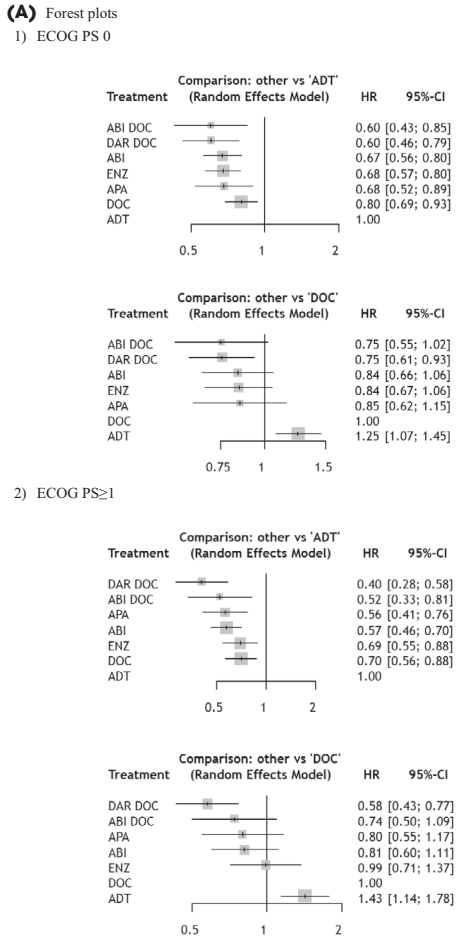
Network meta-analyses of the effect of ARSI combination therapies stratified by PS Three and four different agents were included in this NMA to assess the outcome of OS and PFS (Figs S8–S10). In the pre-DOC setting, based on the SUCRA analysis of treatment rankings for OS, ENZ + ADT had the highest likelihood of providing the maximal OS benefit (95%) among patients with ECOG PS 1 (Fig. S8B, Table 2). On the other hand, ABI + ADT and ENZ + ADT had the highest likelihood of providing the maximal OS benefit (both 75%) among patients with ECOG PS 0 (Fig. S8B, Table 2).

In the post-DOC setting, ENZ + ADT had the highest likelihood of providing the maximal OS benefit in both patients with ECOG PS 0–1 (96%) and those with ECOG PS 2 (84%) (Fig. S10B, Table 2). We did not find any significant heterogeneity among all analyses.

Systematic review of other clinical settings and novel agents available in the context of mCRPC Detailed oncological outcomes are summarised in Table 2. In the pre-ARSI setting, the TAX 327 trial [39,51], which assessed the efficacy of adding DOC compared to mitoxantrone to ADT in patients who experienced disease progression after ADT monotherapy, showed that patients with a KPS of ≥ 90% lived ~8 months longer compared to those with a KPS of ≤80%; however, the HRs for these groups were within a similar range at 0.75 and 0.82, respectively. On the other hand, in the pre-DOC setting, the ALSYMPCA trial (NCT00699751) [45], which assessed the efficacy of adding radium-223 to ADT, reported an OS benefit only in patients with ECOG PS 0–1 (HR 0.68, 95% CI: 0.56–0.82); however, that in patients with ECOG PS 2 did not reach statistical significance (HR 0.82, 95% CI0.50–1.35). In addition, the TROPIC trial (NCT00417079) [41], which assessed the efficacy of cabazitaxel vs mitoxantrone after progression with DOC, showed the same trend with OS benefit only seen in patients with ECOG PS 0–1 (HR 0.68, 95% CI 0.57–0.82); it did not reach statistical significance in patients with ECOG PS 2 (HR 0.81, 95% CI0.48–1.38). In both trials, this non-significant effect among patients with poor PS could be partly explained by the low number of events and patients (wide HRs).

On the other hand, the CARD trial (NCT02485691) [42], which assessed the sequential impact of cabazitaxel over other ARSIs in patients who experienced disease progression after DOC and ARSI, showed a better HR for OS in patients with ECOG PS 2; however, the small number of patients resulted in a wide range of 95% CI (HR 0.33, 95% CI 0.10–1.12). More recently, the VISION trial (NCT03511664) [48], which assessed the efficacy of 177-Lu prostate-specific membrane antigen-617 vs SOC (including ARSI) in patients with mCRPC who experienced disease progression after ARSI and taxane chemotherapy, reported that the HR for OS was similar between patients with ECOG PS 2 and those with ECOG PS 0–1; however, the small number of patients with ECOG PS 2 also resulted in a wide range of 95% CI (HR

Fig. 4 Network meta-analysis for OS in patients with mHSPC with/without good PS; (**A**) Forest plots, (**B**) SUCRA graph showing the treatment ranking for OS.



0.63, 95% CI 0.35–1.13). Interestingly, the PROfound trial (NCT02987543) [44], which assessed the efficacy of olaparib vs ARSI in patients with mCRPC who had qualifying alterations in homologous recombination repair genes and whose disease had progressed during previous ARSI treatment, reported that olaparib was associated with better OS in patients with ECOG PS 1 (HR 0.55, 95% CI 0.35–0.88) compared to those with ECOG PS 0 (HR 0.94, 95% CI 0.55–0.82).

Discussion

We analysed and compared the differential survival benefit of ARSI and/or DOC-based combination therapies in patients with PCa stratified by PS across all disease states. There are several key findings in our study. First, in all clinical settings, novel systemic therapies with ARSI and/or DOC significantly improved OS in patients with worse PS as well as in those with good PS, while the MFS benefit was significantly larger in patients with good PS in the nmPCa setting. Second, among patients with nmCRPC, our treatment ranking analysis revealed that the combination with DAR had the highest likelihood of improved OS irrespective of PS. Third, among patients with mHSPC, DAR + DOC + ADT had the highest likelihood of improved OS in patients with worse PS; on the other hand, ABI + DOC + ADT and DAR + DOC + ADT had a similar likelihood of improved OS in patients with good PS. Fourth, in post-DOC patients with mCRPC, despite several studies showing limited OS benefit from combination therapy to patients with worse PS, our analyses revealed that combination therapy with ARSI improves OS regardless of PS. Considering the trend towards intensified systemic treatment for each PCa state [54–56], our analyses might be valuable in enriching the shared decision-making process with patients of a specific PS group; overall it supports the administration of combination systemic therapy in patients with worse PS.

In the nmCRPC setting, our analyses revealed that, compared to ADT alone, ARSI-based combination therapy resulted in a 22% risk reduction of overall mortality in patients with worse PS and a 33% risk reduction of that in patients with good PS. These findings are in line with subgroup analysis from a recent meta-analysis [57]. Moreover, we found that patients with good PS have significantly better MFS compared to those with poor PS. However, in a view of limited accuracy of conventional imaging in the context of nmCRPC, these results should be taken with caution, especially while entering the molecular imaging era [58]. A similar trend was seen in our analyses of the STAMPEDE data in high-risk nmPCa; MFS benefit was only seen in patients with ECOG PS 0 [52]. Therefore, we hypothesise that these differential survival benefits in favour of patients with ECOG PS 0 might be based on longer life expectancy in patients with good PS at baseline. Owing to the nature of the non-metastatic setting,

patients with ECOG PS 1–2 might have more lethal comorbidities other than PCa.

On the other hand, in the mHSPC setting, our analyses revealed that, compared to ADT alone or SOC, DOC- and/or ARSI-based combination therapy resulted in a better degree of risk reduction of overall mortality in patients with worse PS (30%–37%) compared to that in those with good PS (19%–32%). That a more favourable OS benefit was obtained in patients with worse PS was in contrast to the findings in the nmCRPC setting. One possible rationale is that patients with mHSPC with worse PS are likely to have symptoms from PCa, resulting in an increasing proportion of high-volume disease in that group. Despite these differences in HR for OS not being statistically significant, we found that OS benefits from upfront intensive therapies in patients with mHSPC with worse PS were not inferior to that of those with good PS. Taken together, patients with nmCRPC with good PS seem to be appropriate candidates for ARSI treatment, and patients with mHSPC with worse PS appear to have a larger benefit from upfront intensive therapies compared to those with good PS.

Based on treatment ranking analysis, we found that DAR had the highest likelihood of improved OS irrespective of PS in patients with nmCRPC. A previous NMA demonstrated a comparable likelihood of improved OS among APA, DAR, and ENZ owing to immature OS data [54]. On the other hand, the authors demonstrated that regarding safety, DAR was the likely best option [54]. Our analyses with updated OS data could be more reliable, supporting the clinical benefit of DAR to patients with nmCRPC. In addition, among patients with mHSPC, ABI + DOC + ADT and DAR + DOC + ADT had a similar likelihood of improved OS in patients with good PS; on the other hand, DAR + DOC + ADT had the highest likelihood of improved OS (94%) in patients with worse PS. Our analyses confirmed the utility of triplet therapy even for patients with mHSPC with worse PS and the highest clinical benefit of triplet therapy with DAR + DOC + ADT in such patients [59]. These results are likely to facilitate clinical decision-making.

In the post-DOC mCRPC setting, all RCTs included patients with ECOG PS 0–2, allowing the analysis of the differential survival outcomes of patients with ECOG PS 0–1 vs those with ECOG PS 2. Indeed, the median OS of patients with mCRPC with ECOG PS 2 treated with ARSI after DOC is about 7–10 months shorter compared to those with ECOG PS 0–1 [47,49]. In the AFFIRM trial (NCT00974311) [49], ECOG PS 2 was an independent prognostic factor of poor OS on multivariable analysis. In addition, a recent meta-analysis, including real-world data, showed that patients with mCRPC with ECOG PS 2 had a significantly increased mortality risk compared to those with ECOG PS 0–1 on ARSI, DOC, as well as cabazitaxel treatment [60]. Therefore, in the later line of mCRPC treatments, patients with ECOG PS 2 had shorter life expectancy, theoretically leading to a lower range of OS benefit from life-prolonging treatment. Nevertheless, our analysis revealed that combination therapy with ARSI improved OS compared to ADT alone in post-DOC patients with mCRPC with ECOG PS 2, as well as those with ECOG PS 0–1. On the other hand, the TROPIC trial [41] showed that the HR of OS in patients with ECOG PS 2 was higher compared to those with ECOG PS 0–1, hypothesising that the efficacy of chemotherapy for patients with poor PS might be limited. In addition, several studies demonstrated that patients with ECOG PS 2 or comorbidities had an increased risk of chemotherapy-associated haematological adverse events, including DOC [61–63]. Taken together, weighing the risks and benefits is essential to provide the optimal personalised treatment for later-line mCRPC treatment, specifically for chemotherapy.

There are several limitations in this study. First, despite categorising the subgroups of each clinical setting and agent, RCTs differed in their patient populations, such as the proportion of patients with a specific disease status/burden and the rate and type of sequential therapies. Especially for analyses of the mHSPC setting, apart from disease burden, the proportion of de novo/metachronous metastases differed. Additionally, the ENZAMET (NCT02446405) [29,53], ARCHES (NCT02677896) [2,26], and TITAN (NCT02489318) [3,27] trials include some patients treated with DOC in both arms; this must create a potential bias despite categorising the control arm as SOC. Second, our analyses were conducted based on subgroup analyses of each RCT and, therefore, had a limited number of patients, decreasing the statistical power. Third, we found significant heterogeneity in the analysis of PFS in patients with good PS with pre-DOC mCRPC. This might be caused by differential pharmaceutical action of ENZ and ABI. Additionally, the TERRAIN trial (NCT01288911) [50] (as well as ENZAMET [29,53] trial) set non-steroidal anti-androgen (NSAA) + ADT as the control arm. Although a NSAA + ADT has been recognised to have marginal or no potential OS benefit compared to ADT alone for mHSPC, this differential difference might underestimate the efficacy of ENZ [64,65]. Fourth, NMAs cannot substitute for a direct comparison of each treatment; our findings of NMAs need to be validated in head-to-head, well-designed RCTs. Fourth, RCTs potentially have strict inclusion criteria, indeed, resulting in excluding patients with ECOG PS 2 in most trials. Studies expanding the inclusion criteria, as well as a large number of real-world data, are needed to improve our understanding of the impact of PS on the likelihood to benefit from intensified therapies across each clinical PCa state. Finally, although ECOG PS is widely used in clinical trials, it has serious limitations as it does not distinguish the causes of the symptoms, comorbidities, or whether it is cancer-related. In addition, it

does not consider the patient's age. To draw reliable conclusions regarding the association between health status and systemic therapy benefit in PCa, all potential variables impacting the patient's health must be considered [66,67]. Therefore, further studies should include these variables in their study design.

Conclusions

Among RCTs, systemic combination therapy with an ARSI and/or DOC provides comparable OS benefit between patients with worse PS vs those with good PS across all PCa states. PS should not be a stand-alone exclusion criterion for combination systemic therapies. Based on our treatment ranking analyses for mHSPC, triplet therapy showed the highest likelihood of improved OS irrespective of PS; in particular, DAR + DOC + ADT had a great value of likelihood of improved OS in patients with worse PS. However, as the populations of current RCTs do not reflect the clinical practice, real-world data and further RCTs, including the entire range of patient comorbidity and frailty, are needed to draw proper conclusions for daily clinical practice.

Disclosure of Interests

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Author Contributions

Takafumi Yanagisawa contributed to protocol/project development, data collection and management, data analysis, and manuscript writing. Tatsushi Kawada and Keiichiro Mori contributed to data analysis and manuscript writing/editing. Sung Ryul Shim contributed to statistical analysis and supervision. Hadi Mostafaei, Reza Sari Motlagh, Fahad Quhal, Ekaterina Laukhtina, Markus von Deimling, Alberto Bianchi, Muhammad Majdoub, Maximilian Pallauf, and Benjamin Pradere contributed to manuscript writing/editing. Takahiro Kimura contributed to manuscript editing. Shahrokh F. Shariat and Pawel Rajwa contributed to supervision, protocol/project development/management and manuscript editing.

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Abbreviations: ABI, Abiraterone; ADT, Androgen deprivation therapy; APA, Apalutamide; ARSI, Androgen receptor signalling inhibitor; DAR, Darolutamide; DOC, Docetaxel; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ENZ, Enzalutamide; GETUG, Groupe d'Etude des Tumeurs Uro-Génitales; HR, Hazard ratio; KPS, Karnofsky Performance Status; mCRPC, metastatic castration-resistant prostate cancer; MFS, Metastasis-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; NMA, Network meta-analysis; nmCRPC, non-metastatic castration-resistant prostate cancer; nmPCa, non-metastatic prostate cancer; NSAA, non-steroidal anti-androgen; OS, Overall survival; PCa, Prostate cancer; PFS, Progression-free survival; PS, Performance status; RCT, Randomised controlled trial; SOC, Standard of care; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; SUCRA, Surface under the cumulative ranking.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy for meta-analysis.

Table S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2020.

Table S2. Study demographics of the included 25 RCTs.

Fig. S1. Risk-of-bias assessment of the included RCTs.

Fig. S2. The PRISMA flow chart, detailing the article selection process.

Fig. S3. Network plots of NMA for OS in patients with nmCRPC, mHSPC, and mCRPC.

Fig. S4. NMA for MFS in patients with nmCRPC with/without good PS; (**A**) Forest plots, (**B**) SUCRA graph showing the treatment ranking for MFS.

Fig. S5. Forest plots showing association of adding ARSI to SOC for mHSPC with PFS stratified by PS.

Fig. S6. Forest plots showing association of ARSI treatment for mCRPC with OS stratified by PS; (**A**) Pre-DOC setting, (**B**) Post-DOC setting.

Fig. S7. Forest plots showing association of adding ARSI to ADT for pre-DOC mCRPC with PFS stratified by PS.

Fig. S8. NMA for OS in pre-DOC patients with mCRPC with/without good PS; (**A**) Forest plots, (**B**) SUCRA graph showing the treatment ranking for OS.

Fig. S9. NMA for PFS in pre-DOC patients with mCRPC with/without good PS; (**A**) Forest plots, (**B**) SUCRA graph showing the treatment ranking for PFS.

Fig. S10. NMA for OS in post-DOC patients with mCRPC with/without good PS; (**A**) Forest plots, (**B**) SUCRA graph showing the treatment ranking for OS.