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Platinum Priority – Review – Prostate Cancer

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Androgen Receptor Signaling Inhibitors in Addition to Docetaxel with Androgen Deprivation Therapy for Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Recent randomized controlled trials (RCTs) examined the role of adding androgen receptor signaling inhibitors (ARSIs), including abiraterone acetate (ABI), apalutamide, darolutamide (DAR), and enzalutamide (ENZ), to docetaxel (DOC) and androgen deprivation therapy (ADT) in patients with metastatic hormone-sensitive prostate cancer (mHSPC).

Objective: To analyze the oncologic benefit of triplet combination therapies using ARSI + DOC + ADT, and comparing them with available treatment regimens in patients with mHSPC.

Evidence acquisition: Three databases and meetings abstracts were queried in April 2022 for RCTs analyzing patients treated with first-line combination systemic therapy for mHSPC. The primary interests of measure were overall survival (OS) and progression-free survival (PFS). Subgroup analyses were conducted to assess the differential outcomes in patients with low- and high-volume disease as well as de novo and metachronous metastasis.

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Evidence synthesis: Overall, 11 RCTs were included for meta-analyses and network meta-analyses (NMAs). We found that the triplet combinations outperformed DOC + ADT in terms of OS (pooled hazard ratio [HR]: 0.74, 95% confidence interval [CI]: 0.65–0.84) and PFS (pooled HR: 0.49, 95% CI: 0.42–0.58). There was no statistically significant difference between patients with low- and high-volume disease in terms of an OS benefit from adding an ARSI to DOC +ADT (both HR: 0.79; $p = 1$). Based on NMAs, triplet therapy also outperformed ARSI + ADT in terms of OS (DAR + DOC + ADT: pooled HR: 0.74, 95% CI: 0.55–0.99) and PFS (ABI + DOC + ADT: HR: 0.68, 95% CI: 0.51–0.91, and ENZ + DOC + ADT: HR: 0.70, 95% CI: 0.53–0.93). An analysis of treatment ranking among de novo mHSPC patients showed that triplet therapy had the highest likelihood of improved OS in patients with high-volume disease; however, doublet therapy using ARSI + ADT had the highest likelihood of improved OS in patients with low-volume disease.

Conclusions: We found that the triplet combination therapy improves survival endpoints in mHSPC patients compared with currently available doublet treatment regimens. Our findings need to be confirmed in further head-to-head trials with longer follow-up and among various patient populations.

Patient summary: Our study suggests that triplet therapy with androgen receptor signaling inhibitor, docetaxel, androgen deprivation therapy prolongs survival in patients with metastatic hormone-sensitive prostate cancer compared with the current standard doublet therapy.

1. Introduction

The management of metastatic hormone-sensitive prostate cancer (mHSPC) is rapidly evolving [1–7]. The current standard of care combines androgen deprivation therapy (ADT) with other systemic therapies, either docetaxel (DOC) or an androgen receptor signaling inhibitor (ARSI) [1–7]. Today, there is no clear consensus on their comparative efficacy [8–11]. Although limited evidence of the STAMPEDE trial did not show a superior benefit of any combination [12], network meta-analyses (NMAs) have reported that ARSIs might be the best treatment option regarding overall survival (OS) [8–11]. ARSIs, DOC, and ADT have different mechanisms of targeting androgen receptors and prostate cancer cells, thus potentiating the effect of combination therapy [13]. Some evidence could also be derived from the recent trials that aimed to assess the impact of ARSI + ADT versus ADT for mHSPC, which allowed the use of DOC before or at the time of randomization [1,3,14]. In addition, recent randomized controlled trials (RCTs), such as the PEACE-1 or ARASENS trials, aiming directly at analyzing the impact of triplet combination therapies showed a significant OS benefit with ARSI + DOC + ADT compared with DOC + ADT [15,16]. However, as most of these data are preliminary, the clinical impact of the triplet treatment for mHSPC remains unproven. Furthermore, there are no head-to-head comparisons regarding triplet therapy versus ARSI + ADT, and little is known regarding the true treatment benefit of DOC in these combinations. We believe that clarification of these controversies may provide an immense impact on future trials. Therefore, we conducted this systematic review, meta-analysis, and NMA to analyze the oncologic outcomes of combination therapy with ARSI + DOC + ADT and to compare its efficacy with currently available treatments.

2. Evidence acquisition

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42022298107).

2.1. Search strategy

This meta-analysis and NMA was conducted based on the guidelines of the Preferred Reporting Items for Meta-analyses of Observational Studies in Epidemiology Statement (Supplementary Fig. 1) [17]. In April 2022, a literature search was performed in the PubMed, Web of Science, and Scopus databases to identify studies investigating the oncologic outcomes of systemic therapy for mHSPC. The detailed search strategy is shown in the Supplementary material. Furthermore, we also reviewed abstracts presented at recent major conferences, such as the American Society of Clinical Oncology and the European Society for Medical Oncology, to include unpublished RCTs and trial updates. The primary outcome of interest was OS; secondary outcomes were progression-free survival (PFS) and adverse events (AEs). Two investigators performed initial screening based on the titles and abstracts to identify eligible studies. Potentially relevant studies were subjected to a full-text review. Additionally, manual searches of the reference lists of relevant articles were performed to identify additional studies of interest. Disagreements were resolved by consensus with coauthors.

2.2. Inclusion and exclusion criteria

Studies were deemed eligible if those analyzed patients with mHSPC (patients), who were treated with triplet combination therapy using ARSI + DOC + ADT (interventions), and compared them with patients treated with other

currently available treatment strategies (comparisons), to assess the differential effects of treatment on OS, PFS, and AEs (outcome) only in RCTs (study design). Studies lacking original patient data, reviews, letters, editorial comments, replies from authors, case reports, and articles not written in English were excluded. In cases of duplicate cohorts, the higher-quality or most recent publication was selected. Thus, we solely selected the arm C versus arm G of the STAMPEDE trial, reported by Sydes et al [12], to avert the cohort's duplication. However, this study did not provide subgroup analyses based on disease volume (high- vs low-volume); thus, we selected the other two studies from the STAMPEDE trial for subgroup analyses [6,18,19]. Regarding the ARSI + ADT arm, we included only abiraterone acetate (ABI) + ADT from the LATITUDE trial, as none of the patients received DOC [4]. References of all included papers were scanned for additional studies of interest.

2.3. Data extraction

Data were extracted independently by two authors. The first author's name, publication year, inclusion criteria, agents, agent dosage, number of patients, age, de novo disease, disease volume, number of patients treated with DOC, and follow-up periods were extracted. Subsequently, the hazard ratios (HRs) and 95% confidence intervals (CIs) form Cox regression models for OS and PFS, and the number of any AEs, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–5), and other drug-specific events were retrieved. For a fair comparison of AE rates between different treatment exposure durations, in severe AEs, we calculated the exposure-adjusted incidence rates (EAIRs); an EAIR is defined as the number of patients with a given event divided by the total treatment duration of all patients in years, if treatment duration data were available. All discrepancies were resolved by consensus with coauthors.

2.4. Risk of bias assessment

An assessment of study quality and risk of bias was carried out using the *Cochrane Handbook for Systematic Reviews of Interventions* risk-of-bias tool (version 2; Supplementary Fig. 2) [20]. The risk-of-bias figure was created using Review Manager 5.3 software (RevMan; The Cochrane Collaboration, Oxford, UK). The risk-of-bias assessment of each study was performed independently by two authors.

2.5. Statistical analyses

2.5.1. Meta-analysis

Forest plots with HRs were used to analyze the relationships between combination therapy and survival outcomes. PFS was defined as the time from treatment initiation to radiological progression, clinical progression, or death. For OS and PFS, subgroup analyses were conducted among patients with high- versus low-volume disease and de novo versus metachronous metastasis. High-volume disease was defined following the CHARRTED trial as the presence of visceral metastases, or four or more bone metastases, of which at least one must be located outside the vertebral column or pelvic bone [7,21]. Odds ratios (ORs) were calculated to compare AEs of the triplet treatment arms with those of the DOC + ADT arms. A fixed-effect model was used for calculations of HRs and ORs [22]. 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 [23]. All analyses were conducted using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and the statistical significance level was set at $p < 0.05$.

2.5.2. Network meta-analysis

For OS and PFS, an NMA using random-effect models with a frequentist approach was performed for direct and indirect treatment comparisons [24,25]. In the assessment of OS and PFS, contrast-based analyses were applied with estimated differences in the log HR, and the standard error was calculated from the published HR and CI [26]. The relative effects were presented as HRs and 95% CIs [24]. For OS and PFS, subgroup analyses for high- versus low-volume disease and de novo versus metachronous metastasis were conducted. For comparing AEs, arm-based analyses were performed to estimate the ORs of the AEs (and 95% CIs) from the available data presented in the included articles. We also estimated the relative ranking of the different treatments for each outcome using the surface under the cumulative ranking (SUCRA) [24]. Network plots were utilized to illustrate the connectivity of the treatment networks in terms of OS, PFS, and AEs. Heterogeneity was assessed using Cochrane's Q test when more than one trial was available for a given comparison. All statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing).

3. Evidence synthesis

3.1. Study selection and characteristics

Our initial search identified 671 records. After removing duplicates, 554 records remained for screening of titles and abstracts (Fig. 1). After screening, 526 articles were excluded and a full-text review of 28 articles/abstracts was performed. According to our inclusion criteria, we finally identified 11 RCTs comprising 7679 patients eligible for meta-analyses and NMAs [1–7,12,14–16,18,19,27–30]. The demographics of each included study are shown in Table 1. Of 11 RCTs, only the ARASENS trial assessed the OS difference between darolutamide (DAR) + DOC + ADT and DOC + ADT as a primary endpoint [16]. The patients treated with DOC in addition to ARSI + ADT in the PEACE-1, ARCHES, ENZAMET, and TITAN trials were extracted from their subgroup analyses [14,27,31,32]. The percentage of high-volume disease patients was the highest at 82% in the LATITUDE trial, owing to the inclusion of high-risk patients only [4]. The percentages of patients with high-volume disease included in the other trials ranged from 48% to 66%. The median follow-up duration ranged from 34 to 83.9 mo.

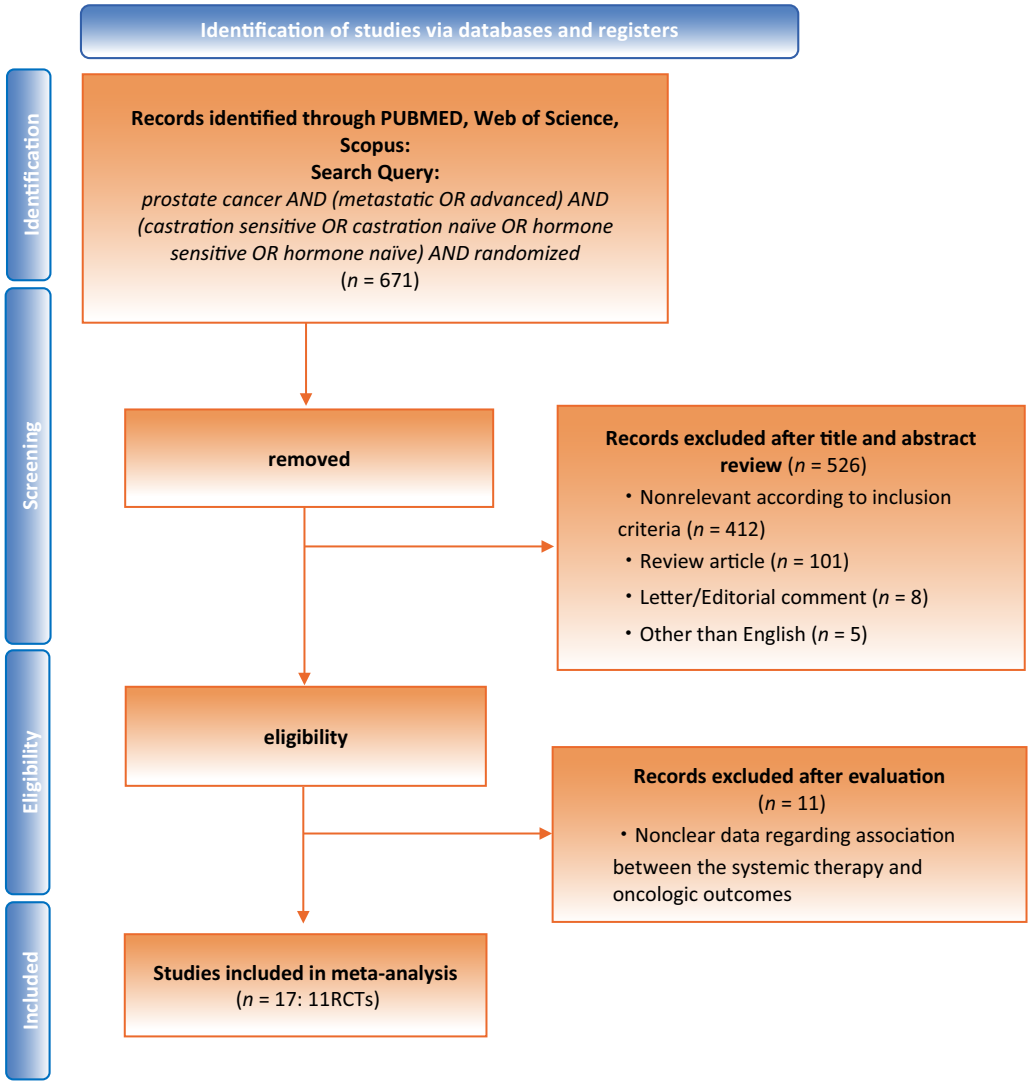


Fig. 1 – The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart, detailing the article selection process. RCT = randomized controlled trial.

3.2. *Risk of bias assessment*

The risk of bias judgments of each domain for each included study is summarized in Supplementary Figure 1. All included studies had a low risk of bias owing to the nature of the selected studies, that is, prospective randomized phase 3 trials.

3.3. *Meta analysis of ARSIs with DOC plus ADT versus DOC plus ADT*

The results of the meta-analysis are described and summarized in Figure 2 and Table 2.

3.3.1. *OS and PFS*

Five studies comprising 2837 patients provided data on OS and PFS in mHSPC patients treated with systemic therapy, ARSI + DOC + ADT versus DOC + ADT. As shown in Table 2, addition of an ARSI to DOC + ADT reduced the risk of death (pooled HR: 0.74, 95% CI: 0.65–0.84, $p < 0.001$) and progression (pooled HR: 0.49, 95% CI: 0.42–0.58, $p < 0.001$; Fig. 2). Among de novo mHSPC patients, addition of an ARSI to DOC + ADT also reduced the risk of death (pooled HR: 0.72, 95% CI: 0.62–0.84, $p < 0.001$; Supplementary Fig. 2). There were no statistical differences in HRs for OS and PFS between the concomitant and sequential use of DOC ($p = 0.4$; Supplementary Fig. 3). The Cochrane's Q tests revealed no significant heterogeneity among all analyses of OS and PFS.

3.3.2. *Differences of OS and PFS between patients with high- and low-volume disease*

Two studies comprising 1213 patients provided data on OS and PFS in mHSPC patients separately for high- and low-volume disease. Addition of an ARSI to DOC + ADT reduced the risk of death in patients with high-volume disease (pooled HR: 0.79, 95% CI: 0.63–0.99, $p = 0.039$); it did not reach statistical significance in terms of OS in patients with low-volume disease (pooled HR: 0.79, 95% CI: 0.50–1.23, $p = 0.3$; Supplementary Fig. 4). However, there was no statistically significant difference between patients with

Table 1 – Study demographics of included studies

	PEACE-1	ARASENS	ARCHES	ENZAMET	TITAN	LATITUDE	STAMPEDE (arm G)	STAMPEDE (arms C, G)	STAMPEDE (arm B, C, E)	CHAARTED	GETUG-AFU15
Author	Fizazi [15]	Smith [16]	Armstrong [1]/Azad [28]	Davis [3]	Chi [14]]	Fizazi [4]	James [19]/ Hoyle [6]	Sydes [12]	Clarke [18]	Kyriakopoulos [7]	Gravis [29]/ Gravis [5]
Year	2022	2022	2019/2022	2019	2021	2019	2017/2019	2018	2019	2018	2013/2016
Treatment arm	Abiraterone + SOC (±RT)	Darolutamide + docetaxel + ADT	Enzalutamide + ADT	Enzalutamide + ADT	Apalutamide + ADT	Abiraterone + ADT	Abiraterone + ADT	Abiraterone + ADT	Docetaxel + ADT	Docetaxel + ADT	Docetaxel + ADT
Dosage	1000 mg	Darolutamide: 600 mg Docetaxel: 75 mg/m^2	160 mg	160 mg	240 mg	1000 mg	1000 mg	1000 mg	75 mg/m^2	75 mg/m^2	75 mg/m^2
Control arm	SOC (±RT)	Placebo + docetaxel + ADT	Placebo + ADT	NSAA + ADT	Placebo + ADT	Placebo + ADT	ADT	Docetaxel + ADT	ADT	ADT	ADT
Inclusion criteria	De novo mHSPC	mHSPC	mHSPC	mHSPC	mHSPC	High-risk de novo mHSPC [a]	mHSPC [b]	mHSPC [b]	mHSPC	mHSPC	mHSPC
Number of patients	1172	1306	1150	1125	1152	1199	1917 (990 [b])	566 (392 [b])	1086	790	385
Treatment	583	651	574	563	525	597	960 (493 [b])	377 (277 [b])	362	397	192
Control	589	655	576	562	527	602	957 (497 [b])	189 (115 [b])	724	393	193
Age (yr), median											
Treatment	66 (IQR: 60–70)	67 (range: 41–89)	70 (range: 46–92)	69.2 (IQR: 63.2–74.5)	69 (range: 45–94)	67.3 ± 8.5 (mean ± SD)	67 (IQR: 63–72)	66 (IQR: 61–70)	65 (IQR: 60–70)	64 (range: 36–88)	63 (IQR: 57–68)
Control	66 (IQR: 59–70)	67 (range: 42–86)	70 (range: 42–92)	69 (IQR: 63.6–74.5)	68 (range: 43–90)	66.8 ± 8.7 (mean ± SD)	67 (IQR: 63–72)	66 (IQR: 62–71)	65 (IQR: 60–71)	63 (range: 39–91)	64 (IQR: 58–70)
De novo disease (%)											
Treatment	100	86	73	58	82	100	94	93	96	73	68
Control	100	87	72	58	85	100	96	97	95	73	66
Disease volume (high/low [c]; %)											
Treatment	63/37	NA	62/38	52/48	62/38	82/18	54/46	NA	54/46	66/34	48/52
Control	65/35	NA	65/35	53/47	64/36	78/22	51/49	NA	57/43	64/36	47/53
No. of docetaxel patients											
Treatment	355	All	103	254	58	No use	No use	NA	NA	NA	NA
Control	355		102	249	55						
HR for OS (95% CI)											
All	0.82 (0.69–0.98)	0.68 (0.57–0.80)	0.66 (0.53–0.81)	0.6 (0.52–0.86)	0.67 (0.51–0.89)	0.66 (0.56–0.78)	0.61 (0.49–0.75)	1.13 (0.77–1.66)	0.81 (0.69–0.95)	0.72 (0.59–0.89)	0.88 (0.68–1.14)
De novo metastasis		0.71 (0.59–0,85)	NA	0.65 (0.47–0.89)	0.68 (0.55–0.85)		0.59 (0.47–0.74)	NA	NA	0.68 (0.54–0.85)	0.93 (0.69–1.25)
Prior local treatment	NA	0.65 (0.35–1.05)	NA	0.7 (0.47–1.09)	0.39 (0.22–0.69)	NA	NA	NA	NA	0.97 (0.58–1.62)	0.83 (0.47–1.47)
Docetaxel cohort	0.75 (0.59–0.95)	0.68 (0.57–0.80)	0.74 (0.46–1.2)	0.9 (0.62–1.31)	1.12 (0.59–2.12)	NA	NA	NA	NA	NA	NA
HR for PFS (95% CI)	rPFS	Time to CRPC	rPFS	cPFS	rPFS	rPFS	PFS	rPFS	rPFS	cPFS	rPFS
All	0.54 (0.44–0.67)	0.36 (0.30–0.42)	0.39 (0.3–0.5)	0.40 (0.33–0.49)	0.48 (0.39–0.60)	0.47 (0.39–0.55)	0.45 (0.37–0.54)	0.69 (0.50–0.95)	0.69 (0.59–0.81)	0.62 (0.51–0.75)	0.69 (0.55–0.87)
Docetaxel cohort	0.5 (0.4–0.62)	0.36 (0.30–0.42)	0.52 (0.3–0.89)	0.48 (0.37–0.62)	0.47 (0.22–1.01)	NA	NA	NA	NA	NA	NA
Follow-up (mo), median (treatment/control arm)	45.7 (46.2/45.0)	43 (43.7/42.4)	44.6	34	44	51.8	40	48	78.2	53.7	83.9

ADT = androgen deprivation therapy, APA = apalutamide; CI = confidential interval; cPFS = clinical PFS; CRPC = castration-resistant prostate cancer; DOC = docetaxel; HR = hazard ratio; IQR = interquartile range; mHSPC = metastatic hormone-sensitive prostate cancer; NA = not applicable; NSAA = nonsteroidal antiandrogen; OS = overall survival; PFS = progression-free survival; rPFS = radiographic PFS; RT = radiotherapy; SD = standard deviation; SOC = standard of care.

[a] High risk was defined with at least two of the following risk factors: (1) Gleason score ≥8, (2) at least three bone metastases, and (3) visceral metastasis.

[b] HR was included only for mHSPC patients in this meta-analysis.

[c] High volume was defined with one of the two following risk factors: (1) at least four bone metastases (with one or more beyond the vertebral bodies and pelvis) and (2) visceral metastasis.

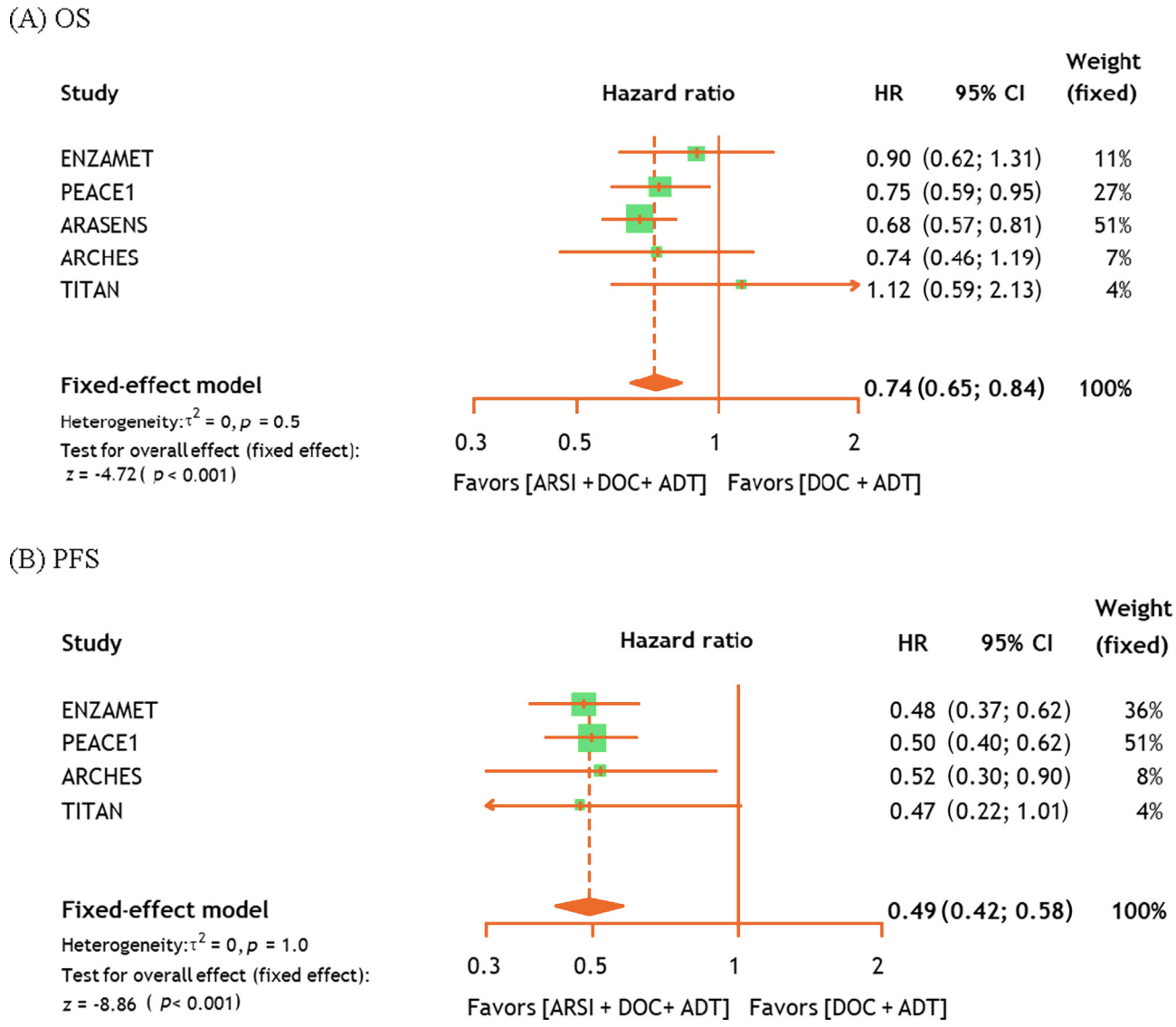


Fig. 2 – Forest plots showing association of ARSI + DOC + ADT versus DOC + ADT with (A) OS and (B) PFS in mHSPC patients. ADT = androgen deprivation therapy; ARSI = androgen receptor signaling inhibitor; CI = confidence interval; DOC = docetaxel; HR = hazard ratio; mHSPC = metastatic hormone-sensitive prostate cancer; OS = overall survival; PFS = progression-free survival.

Table 2 – Summary of oncologic impact of triplet therapy and its differential outcomes stratified by clinical settings

	Meta-analysis of ARSI + DOC + ADT vs DOC + ADT		Network meta-analysis
	OS, pooled HR (95% CI)	PFS, pooled HR (95% CI)	Best treatment probability ranking for OS
All patients	0.74 (0.65–0.84)	0.49 (0.42–0.84)	DAR + DOC: 88% > ABI + DOC: 79% > ENZ + DOC: 66% > ABI: 50% > DOC: 41%
High-volume	0.79 (0.63–0.99)	0.49 (0.40–0.59)	ABI + DOC: 91% > ABI: 74% > ENZ + DOC: 47% > DOC: 36%
Low-volume	0.79 (0.50–1.23)	0.50 (0.36–0.70)	ENZ + DOC: 84% > ABI: 67% > ABI + DOC: 49% > DOC: 28%
Patients with de novo metastasis	0.72 (0.62–0.84)	NA	DAR + DOC: 84% > ABI + DOC: 76% > ABI: 61% > DOC: 29%
High-volume	NA		ABI + DOC: 97%> ABI: 56% > DOC: 48%
Low-volume			ABI: 83% > ABI + DOC: 59% > DOC: 43%
Patients with metachronous metastasis	NA		APA: 91% > DAR + DOC: 74% > ENZ: 55% > DOC: 40% > ABI: 22% [a]

ABI = abiraterone acetate; ADT = androgen deprivation therapy; APA = apalutamide; ARSI = androgen receptor signaling inhibitor; CI = confidence interval; DAR = darolutamide; DOC = docetaxel; ENZ = enzalutamide; HR = hazard ratio; NA = not applicable; OS = overall survival; PFS = progression-free survival.
[a] Analysis included docetaxel cohort in the ARCHES, TITAN, and ENZAMET trials.

low- and high-volume disease in terms of an OS benefit from adding an ARSI to DOC +ADT ($p = 1$). In addition, addition of an ARSI to DOC + ADT reduced the risk of progression irrespective of tumor burden (Supplementary Fig. 5). The Cochrane's Q tests revealed no significant heterogeneity among all analyzed endpoints.

3.3.3. Adverse events

The AE profiles, including the EAIRs of severe AEs (CTCAE grade ≥3) are shown in Table 3. Three studies comprising 2498 patients with concomitant use of ARSIs and DOC provided data on the incidence of clinically relevant AE profiles (Supplementary Fig. 6). Addition of an ARSI to DOC + ADT increased the incidence of severe AEs (pooled OR: 1.28, 95% CI: 1.06–1.54, $p = 0.009$; Supplementary Fig. 6B). On the contrary, pooled EAIRs of severe AEs were comparable between ARSI + DOC + ADT (25%) and DOC + ADT (33%). Regarding hematologic AEs, addition of an ARSI to DOC + ADT did not increase the incidence of febrile neutropenia (FN) and severe neutropenia (Supplementary Fig. 6C and 6D). On the contrary, for nonhematologic AEs, addition of an ARSI to DOC + ADT increased the incidence of severe hypertension (CTCAE grade ≥3; pooled OR: 1.96, 95% CI: 1.42–2.70, $p < 0.001$; Supplementary Fig. 6I). There were no differences in the rates of the other AEs. The Cochrane's Q tests revealed no significant heterogeneity among the endpoints analyzed, except for the rate of peripheral neuropathy.

3.4. NMA of differential oncologic and safety outcomes between DOC with/without ARSI plus ADT

3.4.1. Study selection

All 11 included studies were eligible for this NMA to compare the OS of available systemic combination treatment regimens. However, the ARASENS trial was ineligible for the analyses of PFS, lacking data for this endpoint [16]. In the ENZAMET, ARCHES, and TITAN trials, only patients treated with DOC were extracted and analyzed for the NMAs [14,27,32]. As previously mentioned, arm C versus arm G of the STAMPEDE trial, reported by Sydes et al [12], was selected to analyze OS and PFS of all cohorts to avoid data duplication. As for a subgroup analysis of high- and low-volume disease patients, the PEACE-1, ENZAMET, GETUG-15, CHARRTED, and LATITUDE trials, and two studies from the STAMPEDE trial assessing the differential effect between oncologic outcomes and tumor burden were selected for NMAs [3–7,18,31]. For a subgroup analysis of patients with de novo or metachronous metastasis, the PEACE-1, ARASENS, ARCHES, TITAN, ENZAMET, GETUG-15, CHARRTED, and LATITUDE trials, and one study from the STAMPEDE trial were selected for NMAs [3–7,14–16,27]. The networks of eligible comparisons are graphically described as network plots addressing all survival endpoints (Supplementary Fig. 7). Results of NMAs comparing the combinations and currently available regimens are depicted in Table 2.

For analyses of AEs, ten RCTs reporting any and severe (CTCAE grade ≥3) AEs, and clinically relevant AEs were eligible for NMAs [1–4,12,15,16,19,29,30]. We extracted the data of DOC cohort from the ENZAMET trial and included all cohorts from the TITAN and ARCHES trials for an AE analysis owing to the use of DOC before randomization.

3.4.2. All patients

3.4.2.1. Overall survival. Nine studies were included in this NMA to assess the primary outcome of OS. As shown in Table 2 and Figure 3, addition of an ARSI to DOC + ADT reduced the risk of death (DAR + DOC + ADT: HR: 0.68, 95% CI: 0.56–0.82, and ABI + DOC + ADT: HR: 0.75, 95% CI: 0.58–0.97; Fig. 3B). Furthermore, addition of DOC to ARSI + ADT also reduced the risk of death (DAR + DOC + ADT: HR: 0.74, 95% CI: 0.55–0.99; Fig. 3C). Based on the SUCRA analysis of treatment rankings for OS, triplet therapy had a high likelihood of providing the maximal OS benefit (DAR + DOC + ADT: 88%, ABI + DOC + ADT: 79%; Supplementary Fig. 8A). We did not find any significant heterogeneity for all results.

3.4.2.2. Progression-free survival. Eight studies were included in this NMA to assess the PFS. The results are shown in Table 2 and Figure 4. Addition of an ARSI to DOC + ADT reduced the risk of progression (enzalutamide [ENZ] + DOC + ADT: HR: 0.49, 95% CI: 0.39–0.61, and ABI + DOC + ADT: HR: 0.50, 95% CI: 0.40–0.62; Fig. 4B). Furthermore, addition of DOC to ARSI + ADT also reduced the risk of progression (ENZ + DOC + ADT: HR: 0.68, 95% CI: 0.51–0.91, and ABI + DOC + ADT: HR: 0.70, 95% CI: 0.53–0.93; Fig. 4C). Based on the SUCRA analysis of treatment rankings for OS, triplet therapy had a high likelihood of providing the maximal PFS benefit (apalutamide [APA] + DOC + ADT: 85%, ENZ + DOC + ADT: 74%, ABI + DOC + ADT: 72%; Supplementary Fig. 8B). We did not find any significant heterogeneity for all results.

3.4.3. Patients with de novo or metachronous metastasis

All six studies were included in this NMA to assess the outcome of OS in de novo and metachronous mHSPC patients. In patients with de novo mHSPC patinets, addition of an ARSI to DOC + ADT reduced the risk of death (DAR + DOC + ADT: HR: 0.71, 95% CI: 0.55–0.92; Supplementary Fig. 9B). Based on the SUCRA analysis of treatment rankings for OS, triplet therapies had a high likelihood of providing the maximal OS benefit (DAR + DOC + ADT: 84% and ABI + DOC + ADT: 76%; Supplementary Fig. 9C). The outcomes of OS in metachronous mHSPC patients are depicted in Supplementary Figure 10. Treatment rankings revealed that ARSI (APA) + ADT had the highest likelihood of providing the maximal benefit on OS (91%); however, these findings are limited due to a low number of available studies and patients, resulting in a wide range of 95% CIs of HRs for OS. We did not find any significant heterogeneity for all results.

3.4.4. Patients with high-volume disease

Seven and four studies were included in this NMA to assess the OS and PFS stratified by tumor burden in all and de novo mHSPC patients, respectively.

3.4.4.1. Overall survival. Among patients with high-volume mHSPC, addition of an ARSI to DOC + ADT reduced the risk of death (ABI + DOC + ADT: HR: 0.72, 95% CI:

0.55–0.95; Supplementary Fig. 11). As shown in Table 2, triplet therapy had the highest likelihood of providing the maximal OS benefit in both all and de novo mHSPC patients based on treatment rankings for OS (ABI + DOC + ADT: 91% and 97%, respectively; Supplementary Fig. 11C and 12C). We did not find any significant heterogeneity for all results.

3.4.4.2. Progression-free survival. Addition of an ARSI to DOC + ADT reduced the risk of progression (ABI + DOC + ADT: HR: 0.47, 95% CI: 0.37–0.60, and ENZ + DOC + ADT: HR: 0.51, 95% CI: 0.38–0.69; Supplementary Fig. 13). In addition, addition of DOC to ARSI +ADT also reduced the risk of progression (ABI + DOC + ADT: HR: 0.62, 95% CI: 0.45–0.85, and ENZ + DOC + ADT: HR: 0.67, 95% CI: 0.47–0.97; Supplementary Fig. 13). Treatment rankings showed that triplet therapies had a high likelihood of providing the maximal PFS benefit (ABI + DOC + ADT: 92% and ENZ + DOC + ADT: 83%; Supplementary Fig. 13). We did not find any significant heterogeneity for all results.

3.4.5. Patients with low-volume disease

3.4.5.1. Overall survival. As shown in Table 2 and Supplementary Figure 14, addition of an ARSI to DOC + ADT did not improve OS significantly (ENZ + DOC + ADT: HR: 0.65, 95% CI: 0.25–1.71, and ABI + DOC + ADT: 0.83, 95% CI 0.50–1.38). This was also seen in patients with de novo mHSPC. Treatment rankings revealed that ARSI + ADT had the highest likelihood of providing the maximal OS benefit in patients with de novo metastasis (ABI + ADT: 86%; Supplementary Fig. 15). We did not find any significant heterogeneity for all results.

3.4.5.2. Progression-free survival. Addition of an ARSI to DOC + ADT reduced the risk of progression (ENZ + DOC + ADT: HR: 0.37, 95% CI: 0.20–0.68, and ABI + DOC +ADT: HR: 0.58, 95% CI: 0.38–0.89); however, addition of DOC to ARSI +ADT did not reduce the risk of progression (Supplementary Fig. 16). Triplet therapies had a high likelihood of providing the maximal benefit for PFS based on treatment rankings (ENZ + DOC + ADT: 96%, followed by ABI + DOC + ADT: 73%; Supplementary Fig. 16). We did not find any significant heterogeneity for all results.

3.4.6. Adverse events

The available results from eight studies were included in this NMA. Compared with ADT alone, combination therapies with DOC, such as DOC + ADT and ARSI + DOC + ADT, had a higher likelihood of any and severe AEs (Fig. 5). Based on the SUCRA analyses, triplet therapy had the lowest likelihood of safety concerning any and severe AEs (Supplementary Fig. 17). Other relevant AE profiles are summarized in Supplementary Figure 18.

3.5. Discussion

This is the first meta-analysis and NMA to analyze and compare the novel promising triplet combination therapies in patients with mHSPC. There are several key findings to our study. First, triplet therapy, addition of an ARSI to DOC + ADT, improved both OS and PFS. Second, triplet therapy improved PFS compared with any available doublet combination. Third, our NMAs revealed that triplet therapy (eg, DAR + DOC + ADT) was associated with better OS than ARSI-based doublet therapy. Third, based on treatment ranking analysis, triplet therapy demonstrated the highest likelihood of an OS benefit in patients with high-volume disease; this was not true for patients with de novo low-volume disease who were most likely to benefit from ARSI-based doublet therapy.

Our analysis showed that the triplet therapy outperformed DOC + ADT in terms of OS and PFS in mHSPC patients. In recent years, combination treatment with DOC or ARSIs plus ADT has become the first treatment option for mHSPC patients [33]. Despite limited direct comparisons, data from separate RCTs showed that DOC + ADT and ARSI + ADT decreased the risk of death by 12–28% [5,7,18] and 33–39% [1,3,4,6,14,19,28], respectively, when compared with ADT alone. Four NMAs, assessing the comparative effectiveness of the currently available treatment options, concluded that the oncologic benefit of DOC + ADT was likely inferior to all ARSI + ADT combinations [8–11]. Moreover, cost effectiveness and quality-adjusted life-year assessments suggested more favorable results for ARSI combination therapies than DOC + ADT [34–36]. On the contrary, initial data from the STAMPEDE trial directly comparing ABI + ADT (n = 377) to DOC + ADT (n = 189) showed no clear advantage of any specific treatment strategy with comparable OS; however, better PFS was provided with ABI + ADT [12]. Considering their mechanisms of action and the differences in treatment applications, the hypothesis has arisen that triplet combination of ARSI + DOC + ADT might lead to even better survival than any doublet combination.

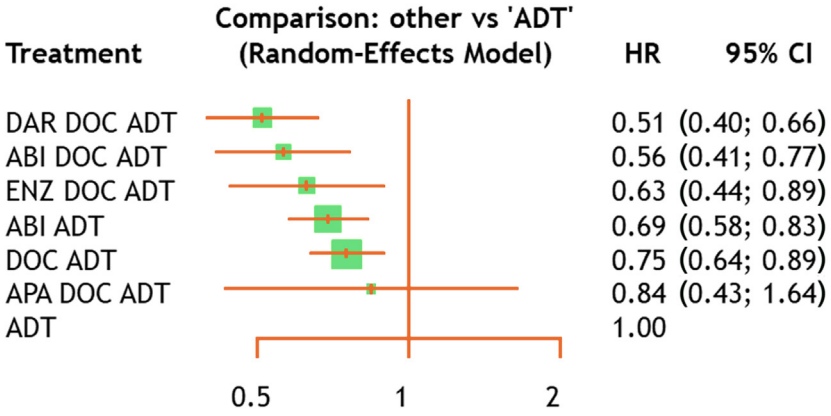
Our NMAs revealed that triplet therapy was the best treatment combination among the currently available combinations with regard to an OS benefit. The PEACE-1 study, which assessed the efficacy of adding ABI to ADT ± DOC, revealed that the combination treatment with ABI + DOC + ADT was associated with better radiographic PFS and OS [31]. More recently, the ARASENS study, which assessed the impact of adding DAR to DOC + ADT, demonstrated an OS benefit for DAR + DOC + ADT compared with DOC + ADT [16]. Based on these trials and our NMAs, one can conclude that DAR + DOC + ADT and ABI + DOC + ADT significantly improve OS compared with DOC + ADT. Furthermore, triplet therapy using DAR + DOC + ADT was associated with better OS than ARSI-based doublet therapy, the current standard treatment. The population selection of the LATITUDE trial, which assessed the impact of ABI + ADT versus ADT alone in high-risk mHSPC patients, was the strictest among included studies, including 100% de novo patients and the highest number of high-volume disease patients [4]. These aspects need to be considered in the interpretation of our analyses; nevertheless, triplet therapy demonstrated improved OS compared with ABI + ADT (ARSI + ADT arm); these findings could change clinical practice and stimulate the future clinical trials. Furthermore, triplet combination regimens outperformed ARSI + ADT in terms of PFS. Indeed, our results suggest that the addition of DOC to ARSI + ADT improves PFS in mHSPC patients. It has to be acknowledged that PFS has not been found to be

Table 3 – Profile of adverse events in included studies

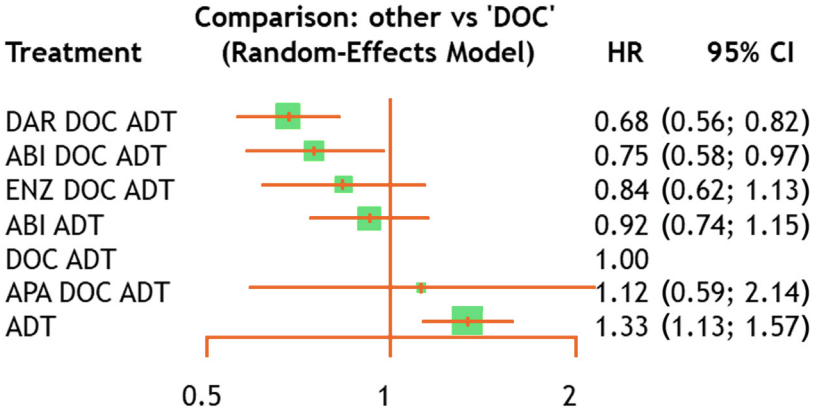
Study name	Year	Treatment duration (mo)		Adverse events, number of patients (%)					
				Any		Grade 3–5		Details and drug-specific events	
		Treatment arm	Control arm	Treatment arm	Control arm	Treatment arm	Control arm	Treatment arm	Control arm
PEACE-1	2022	32.0	21.3	346/347 (99.7%)	349/350 (99.7%)	217/347 (63%) EAIR: 23%	181/350 (52%) EAIR: 29%	FN: 18/346 (5.2%) Neutropenia (G3): 34/346 (9.8%) Hepatotoxicity (G3): 20/347 (5.8%) Fatigue (any): 146/347 (42%) Neuropathy (any): 140/347 (40%)	FN: 19/350 (5.4%) Neutropenia (G3): 32/350 (9.1%) Hepatotoxicity (G3): 2/350 (0.6%) Fatigue (any): 134/350 (38%) Neuropathy (any): 125/350 (36%)
ARASENS	2022	31.8	22.2	649/652 (99.5%)	643/650 (98.9%)	458/652 (70%) EAIR: 27%	439/650 (68%) EAIR: 37%	FN: 51/652 (7.8%) Neutropenia (G3): 220/652 (34%) Anemia (any): 181/652 (28%) Cardiovascular (any): 71/652 (11%) Fatigue (any): 216/652 (33%) Neuropathy (any): 76/652 (12%)	FN: 48/650 (7.4%) Neutropenia (G3): 222/650 (34%) Anemia (any): 163/650 (25%) Cardiovascular (any): 76/650 (12%) Fatigue (any): 214/650 (33%) Neuropathy (any): 67/650 (10%)
ARCHES	2019	40.2	13.8	487/572 (85%)	493/574 (86%)	139/572 (24%) EAIR: 7.2%	147/574 (26%) EAIR: 22%	Cardiovascular (any): 23/572 (4.0%) Fatigue (any): 112/572 (20%) Hot flush (any): 155/572 (27%)	Cardiovascular (any): 17/574 (3.0%) Fatigue (any): 88/574 (15%) Hot flush (any): 128/574 (22%)
ENZAMET	2019	NA	NA	563/563 [a] (100%)	548/558 [a] (98%)	321/563 [a] (57%)	241/558 [a] (43%)	FN: 35/254 (14%) [b] Fatigue (any): 199/254 (78%) [b] Neuropathy (any): 117/254 (46%) [b]	FN: 32/246 (13%) [b] Fatigue (any): 166/246 (67%) [b] Neuropathy (any): 172/246 (29%) [b]
TITAN	2021	39.3	20.2	507/524 [a] (96.8%)	509/527 [a] (96.6%)	221/524 [a] (42%) EAIR: 13%	215/527 [a] (41%) EAIR: 24%	Cardiovascular (any):31/524(5.9%) [a] Fatigue (any): 103/524 (20%) [a] Rash (any): 142/ 524 (27%) [a]	Cardiovascular (any): 11/527 (2.1%) [a] Fatigue (any): 88/527 (17%) [a] Rash (any): 45/ 527 (8.5%) [a]
LATITUDE	2019	25.8	14.4	558/597 (93.5%)	557/602 (92.5%)	374/597 (63%) EAIR: 29%	287/602 (48%) EAIR: 40%	Cardiovascular (any): 74/597 (12%) Hypertension (G3): 121/597 (20%) AST increase (G3): 26/597 (4.4%) Fatigue (any): 77/597 (13%)	Cardiovascular (any): 47/602 (7.8%) Hypertension (G3): 60/602 (10%) AST increase (G3): 9/602 (1.5%) Fatigue (any): 86/602 (14%)
STAMPEDE (arm G)	2017	33.2	NA	943/948 [a] (99.4%)	950/960 [a] (99.0%)	443/948 [a] (47%) EAIR: 17%	315/960 [a] (33%)	Cardiovascular (any): 168/948 (18%) [a] Hypertension (G3): 44/948 (4.6%) [a] Hepatotoxicity (G3): 70/948 (7.4%) [a] Fatigue (any): 551/948 (58%) [a]	Cardiovascular (any): 105/960 (11%) [a] Hypertension (G3): 13/960 (1.4%) [a] Hepatotoxicity (G3): 12/960 (1.3%) [a] Fatigue (any): 648/960 (68%) [a]
STAMPEDE [c] (arms C, G)	2018	NA	NA	370/373 (99.1%)	172/172 (100%)	180/373 (48%)	86/172 (50%)	FN: 3/373 (0.8%) Cardiovascular (any): 32/373 (8.6%) Hepatotoxicity (G3): 32/373 (8.6%) Fatigue (G3): 8/373 (2.1%)	FN: 29/172 (17%) Cardiovascular (any): 6/172 (3.5%) Hepatotoxicity (G3): 1/172 (0.6%) Fatigue (G3): 7/172 (4.1%)
STAMPEDE (arms B, C, E)	2019	NA	NA	362/362 (100%)	703/724 (97%)	141/362 (39%)	179/724 (25%)	Neutropenia (G3): 65/362 (18%) Cardiovascular (any): 27/331 (8.2%) Hepatotoxicity (G3): 2/331 (0.6%)	Neutropenia (G3): 8/724 (1.1%) Cardiovascular (any): 64/735 (8.7%) Hepatotoxicity (G3): 8/734 (1.1%)
CHARRTED	2015	NA	NA	ND	ND	114/390 (29%)	ND	FN: 24/390 (6.2%) Neutropenia (G3): 47/390 (12%) Fatigue (G3): 16/390 (4.1%)	ND
GETUG-AFU15	2013	NA	NA	ND				FN: 15/189 (8%) Fatigue (any): 140/189 (74%) Neuropathy: 54/189 (29%)	FN: 0/186 (0%) Fatigue (any): 37/186 (20%) Neuropathy: 7/186 (3.8%)

AST = aspartate aminotransferase; EAIR = exposure-adjusted incidence rates; FN = febrile neutropenia; NA = not applicable; ND = no data.
EAIR was defined as the number of patients with a given event divided by the total treatment duration of all patients in years; the rate is expressed in 100 patient-years.
[a] Described as entire cohort.
[b] Described as docetaxel cohort.
[c] Defined treatment arm as abiraterone.

(A) Comparison to ADT alone



(B) Comparison to DOC + ADT



(C) Comparison to ARSI + ADT (ABI +ADT)

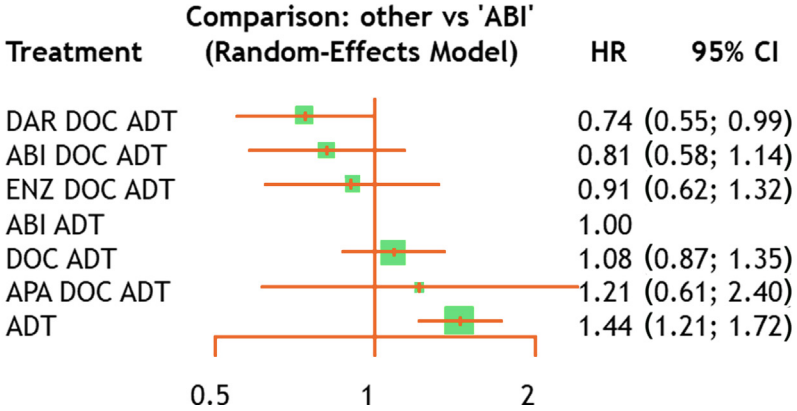
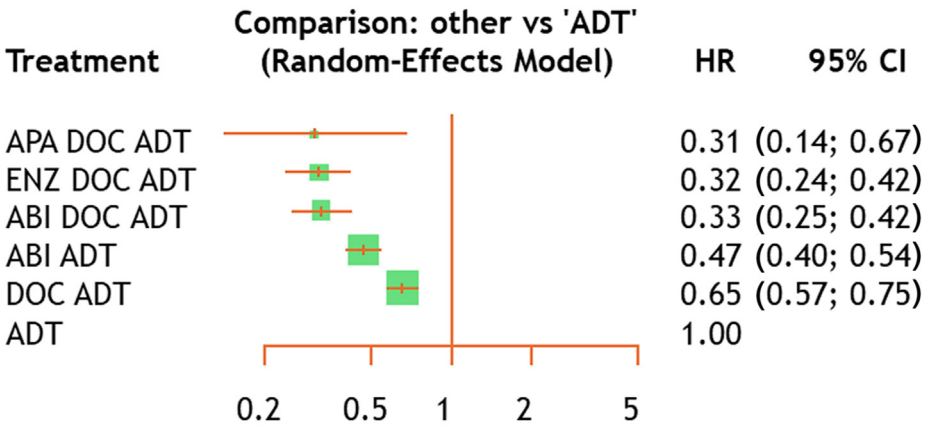


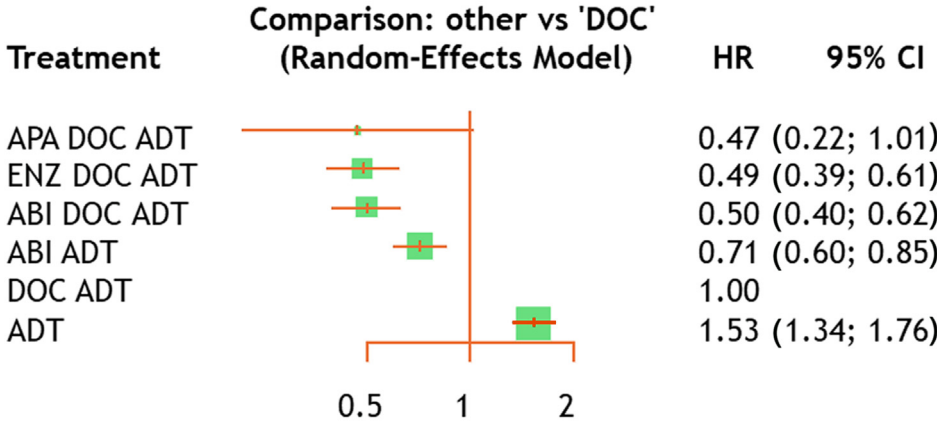
Fig. 3 – Forest plots showing the association of systemic therapy for mHSPC with OS: (A) comparison with ADT alone, (B) comparison with DOC + ADT, and (C) comparison with ARSI (ABI) + ADT. ABI = abiraterone; ADT = androgen deprivation therapy; APA = apalutamide; ARSI = androgen receptor signaling inhibitors; CI = confidence interval; DAR = darolutamide; DOC = docetaxel; ENZ = enzalutamide; HR = hazard ratio; mHSPC = metastatic hormone-sensitive prostate cancer; OS = overall survival.

a surrogate endpoint for OS in mHSPC [37]. Nevertheless, PFS is an important endpoint itself, as it leads to a change of therapy. Thus, taken together, our data signal that triplet therapy could improve distant oncologic outcomes in patients with mHSPC with a significant impact on long-term oncologic outcomes.

(A) Comparison to ADT alone



(B) Comparison to DOC + ADT



(C) Comparison to ARSI (ABI) + ADT

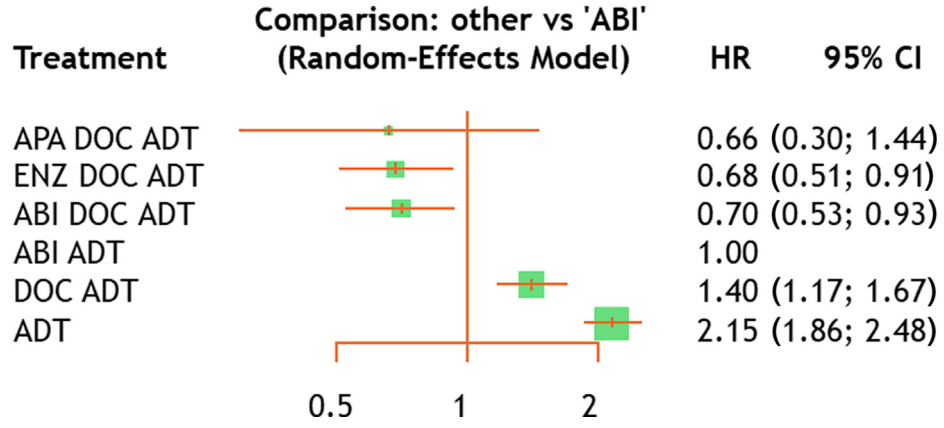


Fig. 4 – Forest plots showing the association of systemic therapy for mHSPC with PFS: (A) comparison with ADT alone, (B) comparison with DOC + ADT, and (C) comparison with ARSI (ABI) + ADT. ABI = abiraterone; ADT = androgen deprivation therapy; APA = apalutamide; ARSI = androgen receptor signaling inhibitors; CI = confidence interval; DOC = docetaxel; ENZ = enzalutamide; mHSPC = metastatic hormone-sensitive prostate cancer; PFS = progression-free survival.

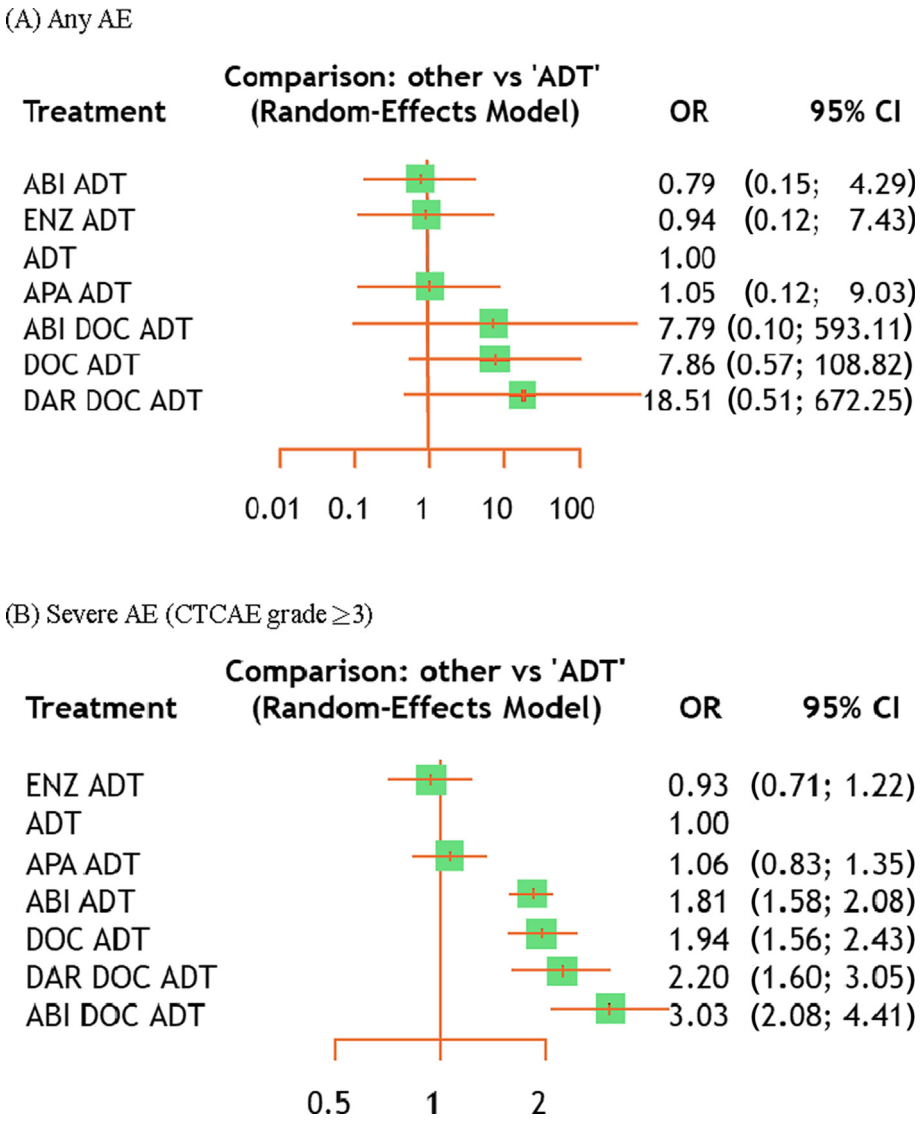


Fig. 5 – Forest plots showing the association of systemic therapy for mHSPC with AE: (A) any AE and (B) severe AE (CTCAE grade ≥3). ABI = abiraterone; ADT = androgen deprivation therapy; AE = adverse event; APA = apalutamide; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; DAR = darolutamide; DOC = docetaxel; ENZ = enzalutamide; mHSPC = metastatic hormone-sensitive prostate cancer; OR = odds ratio.

Based on our NMAs, our sensitivity analysis among de novo metastasis patients suggested the limited utility of adding DOC to ARSI (ABI) + ADT for low-volume disease (Table 2). High-volume disease generally represents an aggressive feature of disease with a higher likelihood of involving androgen receptor–independent cells [38]. In line with this scenario, the CHARRTED trial showed that the OS benefit of DOC + ADT was most prominent in mHSPC patients with high-volume disease [21]. Hence, it seems rational that addition of DOC to ARSI + ADT in patients with high-volume disease might lead to better outcomes.

By contrast, low-volume disease generally has longer survival and less heterogeneous tumor biology. The results from the STAMPEDE trial with long-term follow-ups (78 mo) demonstrated comparable impact of DOC + ADT combination therapy on OS between patients with low-volume (HR: 0.76, 95% CI: 0.54–1.07) and high-volume (HR: 0.81, 95% CI: 0.64–1.02) disease [18]. In addition, a recent meta-analysis using individual participant data from the GETUG-15, CHARRTED, and STAMPEDE trials with a median 6 yr of follow-up showed that an OS benefit from DOC + ADT was seen in patients with both high-volume (HR: 0.60, 95% CI: 0.52–0.68) and low-volume (HR: 0.78, 95% CI: 0.64–0.94) disease [39]. However, the authors concluded that patients with low-volume and metachronous disease should be managed differently based on less survival benefit than those with high-volume and/or de novo disease [39]. Therefore, longer follow-ups are needed to clarify a survival benefit from adding DOC to ARSI + ADT in patients with low-volume disease; notably, a head-to-head comparison of DOC + ARSI + ADT versus ARSI + ADT are awaited.

On the contrary, our meta-analyses showed no statistically significant difference between patients with low- and high-volume disease in terms of an OS benefit from adding an ARSI to DOC +ADT. Indeed, the ARASENS trial lacks data of differential OS stratified by tumor burden. Therefore, limited available data and insufficient statistical power make drawing conclusions uncertain. In the

PEACE-1 trial, 5-yr OS was 60% for DOC + ADT and 68% for ARSI + DOC + ADT in low-volume disease compared with 31% for DOC + ADT and 50% for ARSI + DOC + ADT in high-volume disease [15]. These differences in absolute estimates might suggest that the addition of an ARSI to DOC + ADT actually work better in high-volume disease. The potential OS benefit from triplet therapy in mHSPC patients with low-volume disease remains controversial. However, together with our results from NMAs, the benefit seems to be reliable in those with high-volume disease.

Finally, regarding AEs, our findings indicate that DOC-related hematologic AEs such as FN and severe neutropenia do not increase when adding an ARSI to DOC + ADT. However, ARSI + DOC + ADT was associated with a higher incidence of severe AEs compared with DOC + ADT. Furthermore, our NMAs revealed that triplet therapy had the lowest likelihood of safety concerning AEs compared with doublet therapy. By contrast, treatment duration of the treatment arm was obviously longer than that of the control arm (Table 1). Therefore, for a fair comparison of AE rates between different treatment exposure duration, recent RCTs proposed the evaluation of EAIRs [15,16]. Our results showed that the pooled EAIRs of severe AEs were higher for DOC-based combination therapy than for ARSI-based combination therapy (29 vs 17 per 100 patient-year), while those were comparable between triplet therapy and DOC + ADT. A recent published meta-analysis assessing the benefit-harm balance in mHSPC treatment showed that ARSI-based doublet therapy had high probabilities for a net clinical benefit; however, DOC-based doublet as well as triplet therapy appeared unlikely to be beneficial [40]. The authors also highlighted that any combination systemic therapy did not show a clear benefit of health-related quality of life compared with to ADT alone [40]. Although our analyses showed a survival benefit of triplet therapy, precise comprehension of AE rates (ie, using EAIRs) and weighing up the risks and benefits are mandatory to provide a personalized treatment approach and guide clinical decision-making.

The present study has several limitations that need to be considered. First, this meta-analysis and NMA included RCTs that differed in patient populations, such as the proportion with de novo disease, disease burden, and rate and type of sequential therapies. Therefore, we conducted sensitivity analyses of de novo/metachronous metastasis and tumor burden. However, results need to be interpreted with caution due to the limited number of patients, events, and included studies, thus decreasing statistical power. In addition, NMAs have a limited role in facilitating proper patient selection for current treatment options. Thus, this approach cannot substitute for a direct comparison of each treatment and is mostly hypothesis generating; our findings need to be validated in head-to-head, well-designed RCTs. Second, the follow-up duration of each included study was somewhat different, thus affecting the number of survival events. Further follow-ups of recently published RCTs are warranted to clarify the potential benefit of triplet therapy for low-volume disease. Third, despite showing an OS benefit of triplet therapy compared with ARSI + ADT, our analyses have a limited role for assessing which combination regimens is the best for each clinical setting due to the limited number of studies assessing the outcomes stratified by de novo/metachronous or tumor burden. In addition, we need to wait for the results of the ARANOTE trial (ClinicalTrials.gov identifier: NCT04736199) assessing DAR + ADT versus ADT alone in mHSPC patients, in order to conclude the comparative efficacy of DAR with other ARSIs. Fourth, as mentioned above, for the ARSI (ABI) + ADT arm, we included only the LATITUDE trial as no patient received DOC in the control arm. To prevent a serious selection bias, we did not include the control cohorts from the ENZAMET, ARCHES, and TITAN trials, as a significant proportion of patients in the arms either received or did not receive DOC. Finally, the ENZAMET trial included the use of nonsteroidal antiandrogen therapy with ADT in the control arm. This might provide a differential survival benefit in the control arm, therefore weighing against the survival outcomes of ENZ.

4. Conclusions

We found that the triplet therapy reduces the risk of death and progression endpoints in patients with mHSPC compared with currently available doublet treatment regimens. The efficacy of triplet therapy appears to be reliable in patients with high-volume disease, while the potential benefit in patients with low-volume disease is still controversial. However, triplet therapy had the highest likelihood of increased rates of AEs. Based on efficacy and AEs, further studies with long-term follow-up are needed to select mHSPC patient populations, which are most likely to benefit from triplet therapy in terms of quality-adjusted survival.

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

Study concept and design: Yanagisawa, Rajwa, Shariat.
Acquisition of data: Yanagisawa, Rajwa.
Analysis and interpretation of data: Yanagisawa, Rajwa.
Drafting of the manuscript: Yanagisawa, Rajwa.
Critical revision of the manuscript for important intellectual content: Thibault, Gandaglia, Mori, Kawada, Mostafaei, Motlagh, Quhal, Laukhtina, Pallauf, Pradere.
Statistical analysis: Yanagisawa, Rajwa, Fukuokaya, Shim.
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Supervision: Kimura, Egawa, Shariat.
Other: None.

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Peer Review Summary

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