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ORIGINAL ARTICLE

Prostate Cancer

Network meta-analysis of combination strategies in metastatic hormone-sensitive prostate cancer

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This study compared different doublet and triplet therapies for efficacy and safety in metastatic hormone-sensitive prostate cancer (mHSPC). PubMed, EMBASE, and the Cochrane Library were comprehensively searched for eligible randomized controlled trials (RCTs) published from inception to October 2023. Interventions included abiraterone, apalutamide, enzalutamide, docetaxel, darolutamide, and androgen deprivation therapy (ADT), either as doublet or triplet therapies. The outcomes examined were overall survival (OS), progression-free survival (PFS), castration-resistant prostate cancer (CRPC)-free survival, time to symptomatic skeletal event (SSE), and toxicity. The surface under the cumulative ranking curve (SUCRA) was determined to identify the preferred treatments. Ten RCTs were included. The combination of darolutamide, docetaxel, and ADT had the highest SUCRA of 84.3 for OS, followed by combined abiraterone, docetaxel, and ADT (SUCRA = 71.6). The highest SUCRAs for PFS were observed for triplet therapies (abiraterone, docetaxel, and ADT [SUCRA = 74.9], followed by enzalutamide, docetaxel, and ADT [SUCRA = 74.3]) and other androgen receptor axis-targeted therapy-based doublet therapies (SUCRAs: 26.5–59.3). Darolutamide, docetaxel, and ADT had the highest SUCRAs, *i.e.*, 80.8 and 84.0 regarding CRPC-free survival and time to SSE, respectively. Regarding Grade >3 adverse events (AEs), the SUCRAs of triplet therapies (SUCRAs: 14.8–31.5) were similar to that of docetaxel and ADT (SUCRA = 39.5). Three studies had a low risk of bias in all categories; the remaining studies had at least an unclear risk of bias in at least one category. Triplet therapy demonstrated potentially enhanced effectiveness than doublet therapy in mHSPC, with acceptable safety concerns. Darolutamide might be the optimal option for triplet therapy in combination with docetaxel and ADT.

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men worldwide (annual age-standardized incidence of 29.3/100 000 men)[1] and the most prevalent malignancy in men in the USA (annual age-adjusted incidence of 109.8/100 000 men).[2,3] Metastatic PCa includes *de novo* metastatic hormone-sensitive prostate cancer (mHSPC) and cancers progressing during or after androgen deprivation therapy (ADT), referred to as castration-resistant prostate cancer (mCRPC).[4] An interval of <12 months between ADT initiation and castration resistance (*i.e.*, progression to mCRPC) is associated with poor prognosis.[5] Hence, providing the optimal treatment timely in patients with mHSPC may delay progression to mCRPC and improve prognosis.[2,3,6,7]

Among common therapeutic regimens for mHSPC, ADT prevents testosterone production and deprives the cancer cells of the inducing effects of testosterone;[8] docetaxel prevents mitosis and induces apoptosis,[9] and androgen receptor axis-targeted therapies (ARATs) act on different components of the androgen receptor axis.[10] According to patient characteristics and prognosis, doublet treatment options for mHSPC include ADT combined with ARATs (*i.e.*, abiraterone, apalutamide, or enzalutamide) and ADT combined with docetaxel.[2,3,6,7,11,12] In addition, adding abiraterone,[13] apalutamide,[14] or enzalutamide[15] to ADT provides survival benefits to mHSPC cases. In a network meta-analysis, all combination regimens had better efficacy compared with ADT alone.[16]

Still, initial triplet therapy is becoming a trend in clinical trials and clinical practice because of the unsatisfactory efficacy of doublet therapy in many patients.[2] Indeed, combined darolutamide, docetaxel, and ADT significantly prolonged overall survival (OS) in clinical mHSPC, with no additional safety concerns compared with combined ADT and docetaxel.[17] Consistently, triplet therapy with abiraterone had similar benefits.[18] Triplet therapies have been included in the most recent National Comprehensive Cancer Network (NCCN) guidelines[2] and the European Association of Urology guidelines.[19] On the other hand, a meta-analysis detected no survival benefit of triplet therapy versus doublet regimens, except for the ADT and docetaxel combination.[20] In another network meta-analysis, triplet therapy was the highest-ranked treatment option in terms of efficacy.[21] Unfortunately, previous meta-analyses only compared triplet therapy with doublet therapy,[20,21] not considering comparisons among various triplet therapies. In addition, the potential safety concerns of different triplet therapies must be examined. Therefore, this network meta-analysis including large-scale phase II/III randomized controlled

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trials (RCTs), aimed to compare different doublet and triplet therapies for efficacy and safety in mHSPC.

MATERIALS AND METHODS

We report this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22,23]

Search strategy

PubMed, EMBASE, and the Cochrane Library were comprehensively and systematically searched for potentially eligible articles published from inception to October 2023. Furthermore, the reference lists of all selected studies or related reviews were reviewed to identify additional relevant trials. The utilized search terms were combinations of subject and free words: [(prostatic neoplasms] or [metastatic hormone-sensitive prostate cancer]) and ([abiraterone] or [apalutamide] or [enzalutamide] or [docetaxel] or [darolutamide] or [nonsteroidal anti-androgens]) and (randomized controlled trial). The study was restricted to English publications examining humans. The detailed search strategy is shown in **Supplementary Table 1**.

Eligibility criteria

Inclusion criteria were (1) trials that enrolled patients with mHSPC (PCa confirmed by histological examination with radiologically proven metastases) with no age restriction, previously administered local treatment or diagnosed with *de novo* metastatic disease; (2) the interventions of interest included the combination of abiraterone, apalutamide, enzalutamide, docetaxel, darolutamide, and ADT; (3) trials that reported at least one of the clinical outcomes including OS, progression-free survival (PFS), radiographic PFS (rPFS), clinical PFS (cPFS), prostate-specific antigen (PSA) PFS, CRPC-free survival, time to symptomatic skeletal event (SSE), or toxicity; and (4) phase II or III RCTs.

Exclusion criteria were (1) trial with combination approaches used as maintenance, neoadjuvant or sequential treatment, or dose-escalation trials; (2) trial that compared any two or more different arms mixed with other therapeutic agents, except prednisone or abiraterone; or (3) trial with the same trial registry number or subgroup analysis of a previously published trial (in case of multiple reports for the same trial, *e.g.*, interim and final analyses, reports with complete outcomes were selected).

Based on the above inclusion and exclusion criteria, titles and abstracts were selected for the initial screening, and the full texts of potentially eligible articles were sequentially assessed for final inclusion. The screening was carried out by two investigators (SSW and JLW) independently.

Data extraction and quality assessment

Data extraction and risk of bias assessment were carried out by two investigators independently (SSW and XJB). Any disagreements were resolved by the involvement of a third investigator (JLW).

A standardized form for data extraction was designed and included: (1) basic information (first author's name, publication year, study site, study period, and trial registry number); (2) trial design (type of design, baseline characteristics of participants, sample size, follow-up time, and treatment strategies); and (3) primary outcome (OS) and secondary outcomes including PFS, PSA PFS, CRPC-free survival, time to SSE and adverse events (AEs).

The risk of bias was assessed with the Cochrane Collaboration tool,[24] based on the presence of a randomization sequence, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases.

Statistical analyses

The R 4.1.3 (http://www.Rproject.org) packages "gemtc" and Stata/SE 15.0 (StataCorp., College Station, TX, USA) were employed for statistical analysis. The network meta-analysis was conducted in a Bayesian framework by the Markov chain Monte Carlo method for parameter estimation. Four chains fitted with 20 000 burn-ins, 50 000 iterations, and a thinning interval of 1 were applied. Network plots were generated to illustrate the connectivity of treatment networks. Direct and indirect evidence was obtained to compare different treatments in terms of efficacy and toxicity, with data reported as hazard ratios (HRs) for efficacy outcomes (OS, PFS, PSA PFS, CRPC-free survival, and time to SSE) along with the respective 95% credible intervals (CrIs). The 95 CrIs not including 1 were considered statistically significant. The surface under the cumulative ranking curve (SUCRA) was assessed according to the rank probability to identify the preferred treatments. The rank probability was determined by calculating the proportion of iterations in the Markov chain to rank each treatment's HR or relative risk (RR). The larger the SUCRA, the better the rank. Heterogeneity analysis was carried out visually applying the I^2 statistic. An I^2 >50% was considered to indicate statistically significant heterogeneity. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Selection and characteristics of studies

A total of 4219 hits were obtained from PubMed, EMBASE, and the Cochrane Library and two additional from other sources. After removing duplicates, 3275 reports were screened, and 2956 were excluded. Consequently, 319 full-text articles were retrieved and assessed for eligibility, excluding 309 articles. The screening, inclusion, and exclusion details are shown in **Figure 1**. Therefore, 10 studies were finally included in the present network meta-analysis.

The characteristics of the included trials are summarized in **Table 1**. Totally, 3 studies compared docetaxel with ADT *vs* ADT,[11,12,25]

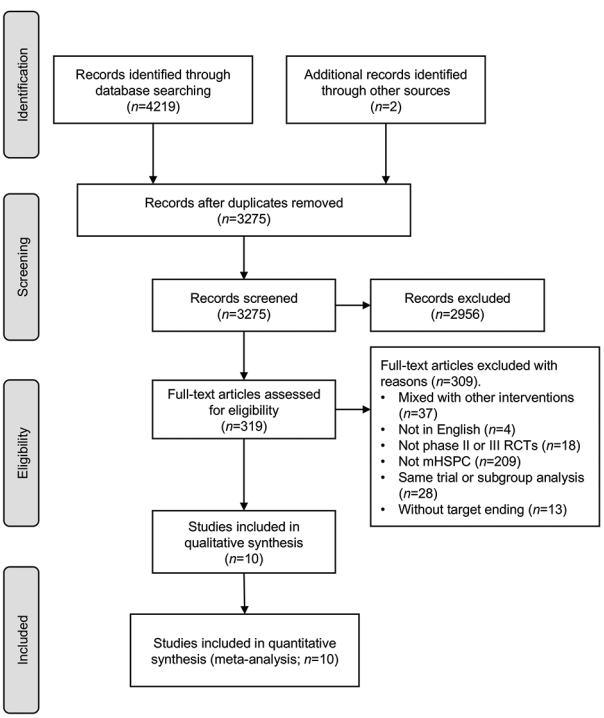

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. RCTs: randomized controlled trials; mHSPC: metastatic hormone-sensitive prostate cancer.

2 examined abiraterone with ADT *vs* ADT,[13,26] 1 examined apalutamide with ADT *vs* ADT,[14] 1 compared abiraterone with docetaxel and ADT (with or without radiotherapy) *vs* docetaxel with ADT (with or without radiotherapy),[18] 1 compared darolutamide with docetaxel and ADT *vs* docetaxel with ADT,[17] 1 compared enzalutamide with ADT *vs* ADT,[15] 1 compared enzalutamide and ADT with or without docetaxel *vs* ADT with or without docetaxel,[27] and 1 compared abiraterone plus enzalutamide and ADT with or without docetaxel *vs* ADT with or without docetaxel.[26] The median patient age ranged from 63 years to 69 years. The median follow-up ranged between 14.4 months and 96 months.

OS

All 10 studies reported OS data and were included in the network meta-analysis for OS (**Figure 2a**). Compared with ADT alone, marked benefits were detected for combined abiraterone and ADT (HR = 0.62, 95% CrI: 0.47–0.82), abiraterone combined with docetaxel and ADT (HR = 0.58, 95% CrI: 0.36–0.96), abiraterone combined with enzalutamide and ADT (HR = 0.65, 95% CrI: 0.44–0.96), darolutamide combined with docetaxel and ADT (HR = 0.53, 95% CrI: 0.33–0.85), and the combination of enzalutamide and ADT (HR = 0.68, 95% CrI: 0.51–0.91), as shown in **Figure 3a**. The combination of darolutamide, docetaxel, and ADT had the highest probability of ranking first, with the largest SUCRA (84.3), followed by abiraterone with docetaxel and ADT (SUCRA = 71.6) and abiraterone with ADT (SUCRA = 64.8; **Table 2**).

Secondary outcomes

Totally 6 studies were eligible for PFS analysis (**Figure 2b**). Regarding cumulative ranking, the highest SUCRAs were obtained for triplet therapies (abiraterone, docetaxel, and ADT, SUCRA = 74.9; followed by enzalutamide, docetaxel, and ADT, SUCRA = 74.3), followed by ARAT-based doublet therapies (SUCRAs: 26.5–59.3; **Table 2**). For CRPC-free survival analysis, 4 studies were assessed (**Figure 2c**). Pairwise comparisons yielded no significant differences (**Figure 3b**). Darolutamide, docetaxel, and ADT had the highest SUCRA (80.8), followed by abiraterone, docetaxel, and ADT (SUCRA = 77.8) and enzalutamide and ADT (SUCRA = 54.3; **Table 2**). Regarding PSA PFS, 2 distinct networks were generated (**Figure 2d**). Pairwise comparisons yielded no significant differences (**Figure 3b**). SUCRAs were 87.1 for darolutamide containing triplet therapy and 63.9 for apalutamide and ADT (**Table 2**).

Finally, regarding time to SSE, 6 studies were included in the network meta-analysis (**Figure 2e**). Darolutamide, docetaxel, and ADT had the highest SUCRA (84.0), followed by enzalutamide and ADT (SUCRA = 75.7) and docetaxel and ADT (SUCRA = 56.4; **Table 2**).

Pairwise comparisons of PFS, CRPC-free survival, PSA PFS, and time to SSE yielded no significant differences (**Figure 3a**–**3c**).

Safety

All 10 trials were included in the network meta-analysis for safety analysis (**Figure 2f** and **2g**). The safety data of the included studies are summarized in **Supplementary Table 2**.

Regarding AEs, the highest SUCRA was detected for ADT alone (SUCRA = 82.1), followed by ARAT-based doublet therapies (SUCRAs: 57.3–78.9), docetaxel with ADT (SUCRA = 21.3), and triplet therapies (SUCRAs: 12.3–20.4), as shown in **Table 2**. For Grade ≥3 AEs, the highest SUCRA was obtained with ADT alone (SUCRA = 88.0),

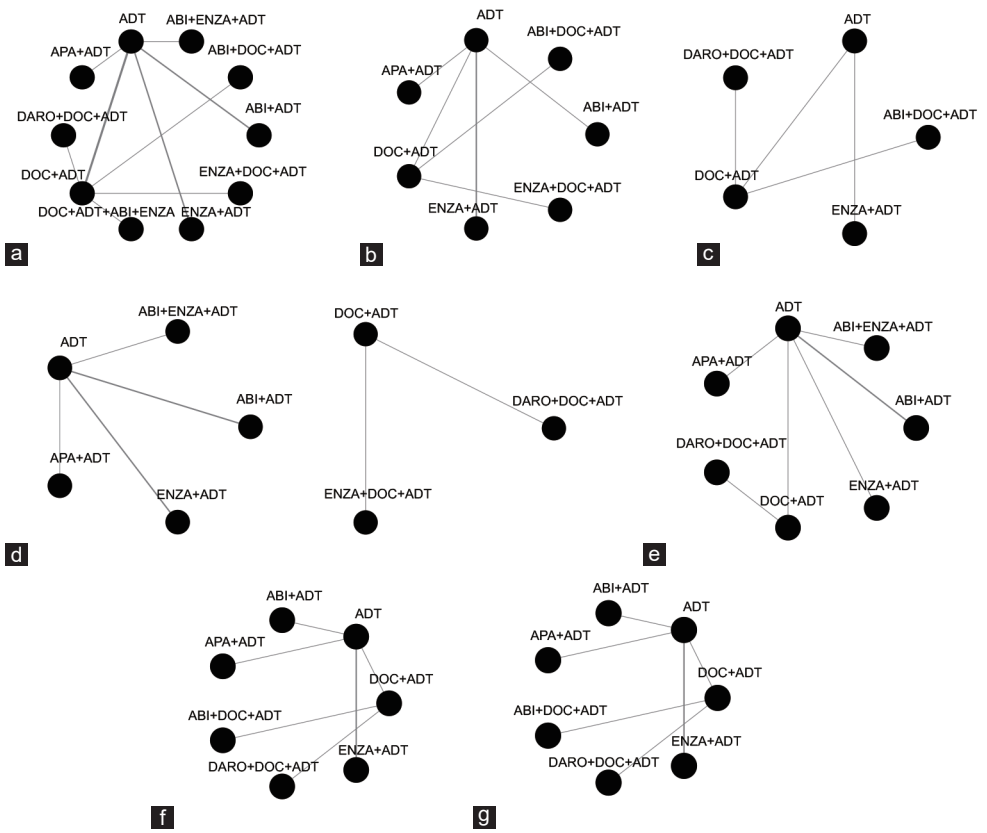

Figure 2: Network meta-analysis. (**a**) Overall survival. (**b**) Progression-free survival. (**c**) Castration-resistant prostate cancer-free survival. (**d**) Prostate-specific antigen progression-free survival. (**e**) Time to symptomatic skeletal events. (**f**) Adverse events. (**g**) Grade ≥3 adverse events. ADT: androgen deprivation therapy; APA: apalutamide; DOC: docetaxel; ABI: abiraterone; ENZA: enzalutamide; DARO: darolutamide.

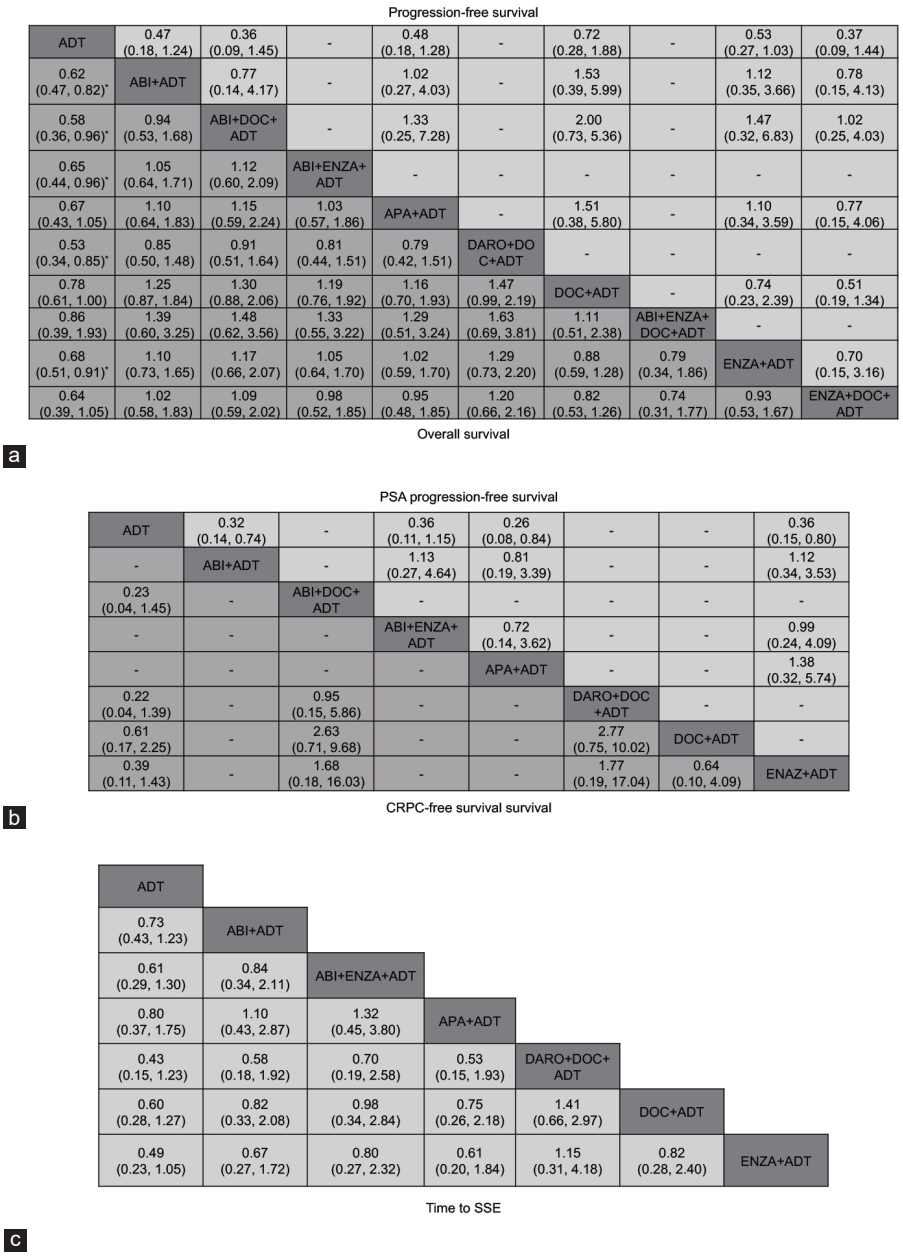

Figure 3: Pairwise comparisons of the treatments. (**a**) Overall survival and progression-free survival. (**b**) Castration-resistant prostate cancer (CRPC)-free survival and prostate-specific antigen (PSA) progression-free survival. (**c**) Times to first skeletal-related event (SSE). Data in each cell, presented as HR (95% CrI), are the comparison of column-defining treatment versus row-defining treatment. $^{*}P < 0.05$. ADT: androgen deprivation therapy; APA: apalutamide; DOC: docetaxel; ABI: abiraterone; ENZA: enzalutamide; DARO: darolutamide; -: not available; HR: hazard ratio; 95% CrI: 95% credible interval.

followed by ARAT-based doublet therapies (SUCRAs: 44.4–80.9), docetaxel with ADT (SUCRA = 39.6), and triplet therapies (SUCRAs: 14.8–31.5), as shown in **Table 2**.

Risk of bias

A total of 3 studies had a low risk of bias in all categories,[13,14,17] while the remaining ones had at least an unclear risk of bias in at least one category (**Supplementary Figure 1**).

DISCUSSION

This network meta-analysis, including large-scale phase II/III RCTs, aimed to compare different doublet and triplet therapies for efficacy and safety in mHSPC. Triplet therapies had a higher probability of ranking higher than doublet therapies in terms of SSE, PFS, and OS. Based on SUCRA, darolutamide might be the optimal option for triplet therapy in combination with docetaxel and ADT. The safety profiles of triplet therapies were similar to that of the ADT and docetaxel combination. These findings might provide evidence for regimen selection in clinical practice.

Previous studies have suggested that adding a cytotoxic agent to ADT could help eliminate castration-resistant clones and enhance treatment efficacy.[28–30] In addition, docetaxel addition to ADT and ARAT can maximize the therapeutic window because symptomatic progression may occur rapidly with the doublet therapy, and many patients would then be unfit for docetaxel administration.[29] The initial

Table 1: Characteristics of the included studies

Characteristic	*GETUG-AFU15, 2013*[25]	*CHAARTED, 2015*[11]	*STAMPEDE, 2016*[26]	*LATITUDE, 2017*[13]	*TITAN, 2019*[14]	*PEACE1, 2022*[18]	*ARASENS, 2022*[17]	*ARCHES, 2022*[15]	*ENZAMET, 2023*[27]	*STAMPEDE, 2023*[26]	
Study design	Open-label, phase 3	NR	NR	Phase 3	Phase 3	Open-label, phase 3	Phase 3	Open-label, phase 3	Open-label, phase 3	Open-label, phase 3	
Study period	2004–2008	2006–2012	2005–2013	2013–2014	2015–2017	2013–2018	2016–2018	2016–2018	2014–2017	2011–2014	2014–2016
Study site	29 centers in 2 countries	NR	NR	235 sites in 34 countries	260 sites in 23 countries	77 sites in 7 countries	286 centers in 23 countries	202 centers in 4 countries	83 sites in 6 countries	117 sites in 2 countries	
Treatment	DOC+ADT	DOC+ADT	DOC+ADT	ABI+ADT	APA+ADT	ABI+DOC+ADT (with or without radiotherapy)	DARO+DOC+ADT	ENZA+ADT	ENZA+ADT with or without DOC	ADT+ABI	DOC with or without ADT+ABI+ENZA
Control	ADT	ADT	ADT	ADT	ADT	DOC+ADT with or without RT	DOC+ADT	ADT	ADT with or without DOC	ADT	DOC with or without ADT
Participants (*n*), treatment/control	192/193	397/393	592/1184	597/602	525/527	355/355	651/654	574/576	563/562	501/502	462/454
Median PSA (ng ml^{-1}), treatment/control	26.7/25.58	50.9/52.1	67/70	NR	5.97/4.02	14/12	30.3/24.2	5.4/5.1	NR	96/97	85/97
Median follow-up (month)	50	28.9	43	30.4	22.7	52.8	43.7/42.4	44.6	68	96	72

ABI: abiraterone; ENZA: enzalutamide; APA: apalutamide; DARO: darolutamide; NSAA: nonsteroidal antiandrogen; ADT: androgen deprivation therapy; DOC: docetaxel; RT: radiotherapy; PSA: prostate-specific antigen; NR: no reports in studies included

triple combination strategies might attack cancer cells from multiple fronts simultaneously and be more effective in controlling mHSPC. In a previous network meta-analysis, although no OS differences were detected between doublet and triplet therapies, triplet therapies ranked higher than commonly administered doublet therapies.[21] However, the ranking between different triplet regimens was not in the scope of the previously reported meta-analysis. Similarly, in the present study, triplet therapies had advantages over doublet therapies in terms of OS. Furthermore, the combination of darolutamide, docetaxel, and ADT ranked the highest, followed by the abiraterone, ADT, and docetaxel combination, suggesting that addition of an ARAT to ADT and docetaxel, especially darolutamide, might provide OS benefits in patients with mHSPC. Notably, in the subpopulation of Chinese patients in the ARASENS study, the risk of death was decreased by 36% (HR = 0.64, 95% CrI: 0.41–0.99) with darolutamide compared to placebo,[31] which highlights a consistent and even possibly greater benefit of darolutamide in Chinese patients compared with the global population (HR = 0.68, 95% CrI: 0.57–0.80).[17] Therefore, in mHSPC cases, triplet therapies should be administered whenever the primary treatment goal is to prolong OS, and darolutamide might be the optimal option, especially in Chinese individuals.

In this study, seven treatment regimens besides darolutamide-containing triplet therapies were analyzed for PFS, and combined enzalutamide, docetaxel, and ADT and combined abiraterone, docetaxel, and ADT ranked the highest. In addition, in terms of CRPC-free survival and time to SSE, combined darolutamide, docetaxel, and ADT had the highest SUCRA. These data suggest that the triplet regimen confers benefits to patients with mHSPC in terms of disease progression and bone-related events, and among them, darolutamide-containing combination regimens had the best efficacy. Although these findings are supported by the pivotal studies that led to the approval of those drugs by regulatory agencies,[15,17] subsequent trials with further head-to-head comparisons are warranted to provide more definitive evidence, especially among triplet therapies.

Compared with the common doublet regimens, triplet regimens use additional docetaxel or ARATs. Among them, the safety issues induced by the additional use of docetaxel are key concerns. Indeed, docetaxel is associated with significant side effects such as infusion reactions, myelosuppression, febrile neutropenia, fatigue, diarrhea, and fluid retention.[9] A network meta-analysis reported that docetaxel and ADT are associated with worse health-related quality of life compared with abiraterone and ADT.[32] On the other hand, in the phase III ARAMIS and ARASENS trials, addition of darolutamide to docetaxel and ADT resulted in a comparable occurrence of AEs compared to docetaxel and ADT.[17,33] Increased incidence of AEs with docetaxel addition to ARAT and ADT was observed in the ENZAMET trial[34] but not in ARASENS trial.[17] In this study, despite the low SUCRAs detected for AEs and ≥Grade 3 AEs with triplet regimens, a pairwise comparison showed a similar safety risk for triplet regimens compared to docetaxel and ADT. The safety ranking of triplet regimens containing darolutamide was higher than that of triplet regimens containing abiraterone. This finding suggested that addition of ARATs, especially darolutamide, to the original recommended dual regimen (docetaxel and ADT) might not increase the risk of toxicity. On the other hand, addition of docetaxel to ARAT + ADT should be decided after considering the patient's tolerance and comorbidities.

This study had limitations. A meta-analysis utilizes statistical tools to compare the included treatments, but no head-to-head comparisons are actually carried out among the included studies, and the comparison of some specific treatment pairs solely relies on statistics. In addition,

Table 2: The surface under the cumulative ranking curve of different treatment regimens

Outcome	*DARO+DOC+ADT*	*ABI+DOC+ADT*	*ENZA+DOC+ADT*	*ABI+ADT*	*ENZA+ADT*	*APA+ADT*	*DOC+ADT*	*ADT*
OS	84.3	71.6	59.6	64.8	48.7	52.0	27.9	5.7
PFS	NR	74.9	74.3	59.3	50.3	57.7	26.5	7.1
CRPC-free survival	80.8	77.8	NR	NR	54.3	NR	29.5	7.6
PSA PFS	87.1	52.3	53.4	63.9	52.5	79.5	9.5	1.8
Time to first SSE	84.0	NR	NR	38.4	75.7	31.1	56.4	8.3
AEs	12.3	20.4	NR	77.6	57.3	78.9	21.3	82.1
Grade ≥3 AEs	31.5	14.8	NR	50.8	44.4	80.9	39.6	88.0

ABI: abiraterone; ENZA: enzalutamide; APA: apalutamide; DARO: darolutamide; ADT: androgen deprivation therapy; DOC: docetaxel; OS: overall survival; PFS: progression-free survival; CRPC: castration-resistant prostate cancer; PSA PFS: prostate-specific antigen PFS; SSE: symptomatic skeletal-related event; AEs: adverse events; NR: no reports in studies included

the quality of a meta-analysis entirely depends on the quality of the included studies, of which some had an uncertain or even high risk of bias in at least one bias category. Furthermore, not all triplet therapies were represented (*e.g.*, triplet regimen containing apalutamide). Finally, because of the limited data available, no subgroup analysis could be performed. Future studies should carry out such subgroup analyses since the efficacy of docetaxel addition to ADT and ARAT appears to differ between patients with low-volume disease and those with metachronous presentation.[35–37] In the ARCHES,[15] ENZAMET,[34] PEACE-1,[18] and TITAN[14] trials, prior administration of docetaxel was a stratification factor. It is therefore likely that tumor characteristics were worse in patients receiving docetaxel compared with cases without docetaxel administration. This might bias survival and the present meta-analysis, as well as highlighting the need for direct comparisons of triplet therapies in future clinical trials. Further studies are required to determine the patients who might benefit the most from a triplet regimen, and factors such as comorbidities, fitness, treatment goals, quality of life, and kinetics of treatment response should be considered.

In this network meta-analysis, triplet therapy had potentially enhanced effectiveness than doublet therapy in mHSPC patients, with acceptable safety profile. Darolutamide might be the optimal option for triplet therapy in combination with docetaxel and ADT. Further head-to-head studies are warranted to confirm the benefit of triplet therapy in mHSPC.

AUTHOR CONTRIBUTIONS

DWY proposed the idea and design of this meta-analysis. SSW and XJB performed database screening independently. JLW resolved disagreements. BHW and SZ were involved in manuscript drafting. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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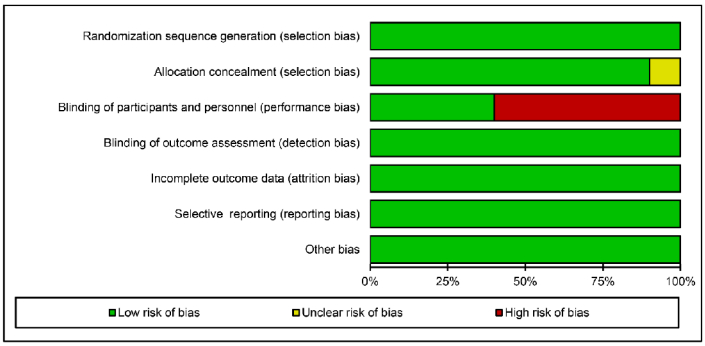

Study	Randomization sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
GETUG-AFU15, 2013	Low	Low	High	Low	Low	Low	Low
CHAARTED, 2015	Low	Unclear	Low	Low	Low	Low	Low
STAMPEDE, 2016	Low	Low	High	Low	Low	Low	Low
LATITUDE, 2017	Low	Low	Low	Low	Low	Low	Low
TITAN, 2019	Low	Low	Low	Low	Low	Low	Low
PEACE1, 2022	Low	Low	High	Low	Low	Low	Low
ARASENS, 2022	Low	Low	Low	Low	Low	Low	Low
ARCHES, 2022	Low	Low	High	Low	Low	Low	Low
ENZAMET, 2023	Low	Low	High	Low	Low	Low	Low
STAMPEDE, 2023	Low	Low	High	Low	Low	Low	Low

Supplementary Figure 1: Risk of bias.

Supplementary Table 1: Search strategies

Search	*Search query*
	PubMed
#1	"Prostatic Neoplasms"[Mesh]
#2	"prostatic neoplasms"[Title/Abstract] OR "prostate neoplasms"[Title/Abstract] OR "prostate neoplasm"[Title/Abstract] OR "prostatic neoplasm"[Title/Abstract] OR "prostate cancer"[Title/Abstract] OR "prostate cancers"[Title/Abstract] OR "prostatic cancer"[Title/Abstract] OR "prostatic cancers"[Title/Abstract] OR "prostatic tumor"[Title/Abstract] OR "prostatic tumors"[Title/Abstract] OR "prostate tumor"[Title/Abstract] OR "prostate tumors"[Title/Abstract]
#3	(#1) OR (#2)
#4	"Docetaxel"[Mesh]
#5	"Docetaxel"[Title/Abstract] OR "docetaxel trihydrate"[Title/Abstract] OR "Docetaxol"[Title/Abstract] OR "docetaxel hydrate"[Title/Abstract] OR "taxoltere metro"[Title/Abstract] OR "RP-56976"[Title/Abstract] OR "RP 56976"[Title/Abstract] OR "RP56976"[Title/Abstract] OR "Taxotere"[Title/Abstract] OR "docetaxel anhydrous"[Title/Abstract] OR "nsc 628503"[Title/Abstract]
#6	(#4) OR (#5)
#7	"enzalutamide" [Supplementary Concept]
#8	"enzalutamide"[Title/Abstract] OR "HC-1119"[Title/Abstract] OR "HC 1119"[Title/Abstract] OR "Xtandi"[Title/Abstract] OR "MDV-3100"[Title/Abstract] OR "MDV3100"[Title/Abstract] OR "MDV 3100"[Title/Abstract]
#9	(#7) OR (#8)
#10	("Abiraterone Acetate"[Mesh]) OR "abiraterone" [Supplementary Concept]
#11	"Abiraterone"[Title/Abstract] OR "Zytiga"[Title/Abstract] OR "CB-7630"[Title/Abstract] OR "CB 7630"[Title/Abstract] OR "CB7630"[Title/Abstract] OR "CB-7598"[Title/Abstract] OR "CB 7598"[Title/Abstract] OR "CB7598"[Title/Abstract]
#12	#10 or #11
#13	"darolutamide" [Supplementary Concept]
#14	"Darolutamide"[Title/Abstract] OR "Nubeqa"[Title/Abstract] OR "ODM-201"[Title/Abstract]
#15	(#13) OR (#14)
#16	"apalutamide" [Supplementary Concept]
#17	"apalutamide"[Title/Abstract] OR "ARN-509"[Title/Abstract] OR "Erleada"[Title/Abstract]
#18	(#16) OR (#17)
#19	"Nonsteroidal Anti-Androgens"[Mesh]
#20	"nonsteroidal antiandrogen"[Title/Abstract] OR (("androgen antagonists"[Pharmacological Action] OR "androgen antagonists"[MeSH Terms] OR ("androgen"[All Fields] AND "antagonists"[All Fields]) OR "androgen antagonists"[All Fields] OR ("Anti"[All Fields] AND "Androgens"[All Fields]) OR "Anti-Androgens"[All Fields]) AND "Nonsteroidal"[Title/Abstract]) OR "nonsteroidal anti androgens"[Title/Abstract] OR "nonsteroidal antiandrogens"[Title/Abstract] OR (("androgen antagonists"[Pharmacological Action] OR "androgen antagonists"[MeSH Terms] OR ("androgen"[All Fields] AND "antagonists"[All Fields]) OR "androgen antagonists"[All Fields] OR "antiandrogen"[All Fields] OR "Antiandrogens"[All Fields] OR "antiandrogenic"[All Fields] OR "antiandrogenicity"[All Fields]) AND "Nonsteroidal"[Title/Abstract]) OR "nonsteroidal anti androgens"[Title/Abstract]
#21	(#19) OR (#20)
#22	(((((#6) OR (#9)) OR (#12)) OR (#15)) OR (#18)) OR (#21)
#23	((#3) AND (#22)) Filters: Randomized Controlled Trial, Humans, English
	EMBASE
#1	'prostate cancer'/exp
#2	'prostat* neoplasm*':ti,ab,kw OR 'prostat* cancer*':ti,ab,kw OR 'prostat* tumor*':ti,ab,kw
#3	#1 OR #2

Contd...

Supplementary Table 1: Contd...

Search	*Search query*
	EMBASE
#4	'docetaxel'/exp
#5	docetaxel:ti,ab,kw OR docetaxol:ti,ab,kw OR taxoltere:ti,ab,kw OR 'rp 56976':ti,ab,kw OR 'nsc 628503':ti,ab,kw
#6	#4 OR #5
#7	'enzalutamide'/exp
#8	enzalutamide:ti,ab,kw OR 'hc 1119':ti,ab,kw OR xtandi:ti,ab,kw OR 'mdv 3100':ti,ab,kw
#9	#7 OR #8
#10	'abiraterone acetate'/exp OR 'abiraterone'/exp
#11	abiraterone:ti,ab,kw OR zytiga:ti,ab,kw OR 'cb 7630':ti,ab,kw OR 'cb 7598':ti,ab,kw
#12	#10 OR #11
#13	'darolutamide'/exp
#14	darolutamide:ti,ab,kw OR nubeqa:ti,ab,kw OR 'odm 201':ti,ab,kw
#15	#13 OR #14
#16	'apalutamide'/exp
#17	apalutamide:ti,ab,kw OR 'arn 509':ti,ab,kw OR erleada:ti,ab,kw
#18	#16 OR #17
#19	'antiandrogen'/exp
#20	'nonsteroidal anti-androgen*':ti,ab,kw OR antiandrogen*:ti,ab,kw
#21	#19 OR #20
#22	#6 OR #9 OR #12 OR #15 OR #18 OR #21
#23	#3 AND #22
#24	#3 AND #22 AND [randomized controlled trial]/lim AND [english]/lim
	Cochrane Library
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	(prostat* neoplasm*):ti,ab,kw OR (prostat* cancer*):ti,ab,kw OR (prostat* tumor*):ti,ab,kw (Word variations have been searched)
#3	#1 OR #2
#4	MeSH descriptor: [Docetaxel] explode all trees
#5	(Docetaxel):ti,ab,kw OR (Docetaxol):ti,ab,kw OR (taxoltere):ti,ab,kw OR (RP-56976):ti,ab,kw OR (nsc 628503):ti,ab,kw
#6	#4 OR #5
#7	(enzalutamide):ti,ab,kw OR (HC-1119):ti,ab,kw OR (Xtandi):ti,ab,kw OR (MDV-3100):ti,ab,kw
#8	MeSH descriptor: [Abiraterone Acetate] explode all trees
#9	(Abiraterone Acetate):ti,ab,kw OR (abiraterone):ti,ab,kw OR (Zytiga):ti,ab,kw OR (CB-7630):ti,ab,kw OR (CB-7598):ti,ab,kw
#10	#8 OR #9
#11	(darolutamide):ti,ab,kw OR (Nubeqa):ti,ab,kw OR (ODM-201):ti,ab,kw
#12	(apalutamide):ti,ab,kw OR (ARN-509):ti,ab,kw OR (Erleada):ti,ab,kw
#13	MeSH descriptor: [Nonsteroidal Anti-Androgens] explode all trees
#14	(nonsteroidal anti-androgen*):ti,ab,kw OR (Nonsteroidal Anti Androgen*):ti,ab,kw OR (Nonsteroidal Antiandrogen*):ti,ab,kw
#15	#13 OR #14
#16	#6 OR #7 OR #10 OR #11 OR #12 OR #15
#17	(random*):ti,ab,kw OR (RCT):ti,ab,kw
#18	#3 AND #16 AND #17 [Trials]

Supplementary Table 2: Adverse events

Event	*Grading*	*GETUG-AFU15, 2013*[1]		*CHAARTED, 2015*[2]		*STAMPEDE, 2016*[3]		*LATITUDE, 2017*[4]		*TITAN, 2019*[5]		*PEACE1, 2022*[6]	
		DOC+ADT	*ADT*	*DOC+ADT*	*ADT*	*DOC+ADT*	*ADT*	*ABI+ADT*	*ADT*	*APA+ADT*	*ADT*	*ABI+DOC+ADT*	*DOC+ADT*
AE (any grade)						550 (100%)	1213 (99%)	558 (93%)	557 (93%)	507 (96.8%)	509 (96.6%)	346 (100%)	349 (100%)
AE (grade ≥3)				115 (29.6%)		288 (52%)	399 (32%)	374 (63%)	287 (48%)	221 (42.2%)	215 (40.8%)	217 (63%)	181 (52%)
Completed 6 cycles		93 (48%)		335 (86.1%)		456 (77%)							
Discontinuation (AE)		39 (21%)	-			72 (13%)		73 (12%)	61 (10%)	42 (8.0%)	28 (5.3%)	32 (17%)	1 (<1%)
Falls	Any grade									39 (7.4%)	37 (7.0%)		
	Grade ≥3									4 (0.8%)	4 (0.8%)		
Fractures	Any grade									33 (6.3%)	24 (4.6%)		
	Grade ≥3									7 (1.3%)	4 (0.8%)		
Rash	Any grade									142 (27.1%)	45 (8.5%)		
	Grade ≥3									33 (6.3%)	3 (0.6%)		
Neuropathy	Any grade												
	Grade ≥3			47 (12.1%)									
Sensory neuropathy	Any grade	54 (29%)	7 (4%)										
	Grade ≥3	3 (2%)	0										
Nervous system other (including peripheral neuropathy)	Any grade												
	Grade ≥3					19 (3%)	20 (2%)						
Seizure	Any grade									3 (0.6)	2 (0.4%)		
	Grade ≥3									1 (0.2)	0		
Stroke	Any grade												
	Grade ≥3												
Nervous system disorders	Any grade												
	Grade ≥3												
Dysesthesia	Any grade												
	Grade ≥3												
Paresthesia	Any grade												
	Grade≥3												
Peripheral motor neuropathy	Any grade												
	Grade ≥3												
Peripheral sensory neuropathy	Any grade												
	Grade ≥3												
Peripheral neuropathy	Any grade												
	Grade ≥3											4 (1%)	6 (2%)
Cognitive/memory impairment	Any grade												
	Grade ≥3												
Loss of consciousness	Any grade												
	Grade ≥3												
Blood and lymphatic system disorders	Any grade												
	Grade ≥3												
Febrile neutropenia	Any grade	15 (8%)	0										
	Grade≥3	15 (8%)	0	24 (6.1%)		84 (15%)	15 (1%)					18 (5%)	32 (9%)

Contd...

Supplementary Table 2: Contd...

Event	*Grading*	*GETUG-AFU15, 2013*[1]		*CHAARTED, 2015*[2]		*STAMPEDE, 2016*[3]		*LATITUDE, 2017*[4]		*TITAN, 2019*[5]		*PEACE1, 2022*[6]	
		DOC+ADT	*ADT*	*DOC+ADT*	*ADT*	*DOC+ADT*	*ADT*	*ABI+ADT*	*ADT*	*APA+ADT*	*ADT*	*ABI+DOC+ADT*	*DOC+ADT*
Infections with neutropenia	Any grade	5 (3%)	0										
	Grade ≥3	5 (3%)	0	9 (2.3%)									
Neutropenia/neutrophils	Any grade	94 (50%)	5 (3%)										
	Grade ≥3	61 (32%)	0	47 (12.1%)		66 (12%)	6 (0.5%)					34 (10%)	32 (9%)
Anaemia	Any grade	136 (72%)	41 (22%)					54 (9%)	85 (14%)	48 (9.2%)	71 (13.5%)		
	Grade ≥3	4 (2%)	2 (1%)	5 (1.3%)				15 (2.5%)	27 (4.5%)	9 (1.7%)	17 (3.2%)		
Thrombocytopenia/decreased platelet count	Any grade	20 (11%)	9 (5%)										
	Grade ≥3	1 (<1%)	0	1 (0.3%)									
Bone marrow hypocellular	Any grade												
	Grade ≥3												
Leukocytosis	Any grade												
	Grade ≥3												
Thrombotic thrombocytopenic purpura	Any grade												
	Grade ≥3												

Event	*ARASENS, 2022*[7]		*ARCHES, 2022*[8]		*ENZAMET, 2023*[9]		*STAMPEDE, 2023*[10]			
	DARO+DOC+ADT	*DOC+ADT*	*ENZA+ADT*	*ADT*	*ENZA+ADT±DOC*	*ADT±DOC*	*ADT+ABI*	*ADT*	*DOC±ADT+ABI+ENZA*	*DOC±ADT*
AE (any grade)	649 (99.5%)	643 (98.9%)	520 (90.9%)	504 (87.8)	563 (100%)	551 (99%)				
AE (grade ≥3)	458 (70.2%)	439 (67.5%)	224 (39.2%)	160 (27.9%)	388 (69%)	265 (47%)				
Completed 6 cycles	571 (87.6%)	556 (85.5%)	89 (15.5%)	91 (15.8%)						
Discontinuation (AE)	72/652 (11%)	53/650 (8%)			63/563 (11%)	25/558 (5%)				
Falls			58 (10.1%)	19 (3.3%)	89 (16%)	26 (5%)	19 (4%)	7 (1%)	43 (9%)	19 (4%)
			7 (1.2%)	3 (0.5%)	9 (2%)	2 (<1%)	4 (1%)	1 (<1%)	6 (1%)	4 (1%)
Fractures			77 (13.5%)	31 (5.4%)	44 (8%)	16 (3%)	9 (2%)	2 (<1%)	26 (6%)	11 (2%)
			20 (3.5%)	9 (1.6%)	21 (4%)	7 (1%)	3 (1%)	0	9 (2%)	6 (1%)
Rash			22 (3.8%)	10 (1.7%)			76 (15%)	39 (8%)	49 (11%)	47 (10%)
			0	0			2 (<1%)	0	0	0
Neuropathy										
Sensory neuropathy										
Nervous system other (including peripheral neuropathy)							92 (18%)	56 (11%)	122 (28%)	81 (18%)
							17 (3%)	14 (3%)	12 (3%)	12 (3%)
Seizure					7 (1%)	0	2 (<1%)	1 (<1%)	4 (1%)	1 (<1%)
					1 (<1%)	0	0	0	4 (1%)	0
Stroke							0	0	3 (<1%)	2 (<1%)
							0	0	3 (<1%)	1 (<1%)
Nervous system disorders							319 (64%)	180 (36%)	430 (97%)	231 (51%)
							28 (6%)	16 (3%)	30 (7%)	18 (4%)

Contd...

Supplementary Table 2: Contd...

Event	*ARASENS, 2022*[7]		*ARCHES, 2022*[8]		*ENZAMET, 2023*[9]		*STAMPEDE, 2023*[10]			
	DARO+DOC+ADT	*DOC+ADT*	*ENZA+ADT*	*ADT*	*ENZA+ADT±DOC*	*ADT±DOC*	*ADT+ABI*	*ADT*	*DOC±ADT+ABI+ENZA*	*DOC±ADT*
Dysesthesia										
Paresthesia										
Peripheral motor neuropathy										
Peripheral sensory neuropathy	65 (10.0%)	67 (10.3%)								
Peripheral neuropathy	76 (11.7%)	67 (10.3%)								
Cognitive/memory impairment			38 (6.6%)	15 (2.6%)	91 (16%)	29 (5%)	36 (8%)	19 (4%)	86 (19%)	24 (5%)
			4 (0.7%)	0	2 (<1%)	1 (<1%)	3 (1%)	1 (<1%)	3 (<1%)	2 (<1%)
Loss of consciousness			15 (2.6%)	2 (0.3%)						
			9 (1.6%)	1 (0.2%)						
Blood and lymphatic system disorders										
Febrile neutropenia					37 (6%)	33 (6%)	3 (1%)	2 (<1%)	5 (1%)	17 (4%)
	51 (7.8)	48 (7.4)			37 (6%)	33 (6%)	3 (1%)	2 (<1%)	5 (1%)	17 (4%)
Infections with neutropenia										
Neutropenia/neutrophils			8 (1.4%)	4 (0.7%)	50 (8%)	31 (5%)				
	220 (33.7%)	222 (34.2%)	4 (0.7%)	2 (0.3%)	31 (5%)	18 (3%)				
Anaemia							244 (49%)	186 (37%)	228 (52%)	212 (47%)
	31 (4.8)	33 (5.1)					6 (1%)	7 (1%)	7 (2%)	9 (2%)
Thrombocytopenia/decreased platelet count			3 (0.5%)	0			25 (5%)	19 (4%)	25 (6%)	33 (7%)
			3 (0.5%)	0			1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
Bone marrow hypocellular										
Leukocytosis										
Thrombotic thrombocytopenic purpura							0	3 (<1%)	1 (<1%)	4 (<1%)
							0	1 (<1%)	1 (<1%)	1 (<1%)

ABI: abiraterone; ENZA: enzalutamide; APA: apalutamide; DARO: darolutamide; ADT: androgen deprivation therapy; DOC: docetaxel; AE: adverse event