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ORIGINAL ARTICLE

Prostate Disease

Indirect comparison between abiraterone acetate and enzalutamide for the treatment of metastatic castration-resistant prostate cancer: a systematic review

Wei Zhang[1,*], Teng-Yun Wu[2,*], Qi Chen[3], Xiao-Lei Shi[1], Guang-An Xiao[1], Lin Zhao[1], Chuan-Liang Xu[1], Tie Zhou[1], Ying-Hao Sun[1]

This study was designed to evaluate the efficacy, tolerability, and sequential administration of abiraterone acetate (AA) and enzalutamide (Enz) for metastatic castration-resistant prostate cancer (mCRPC). A literature search was performed with PubMed, Embase, and Web of Science databases to identify relevant studies. Reviewed literature included published phase III trials of AA or Enz in mCRPC and studies regarding their sequential administration. Given the difference in control arms in AA (active comparator) and Enz (true placebo) randomized phase III studies, indirect comparisons between AA and Enz in mCRPC showed no statistically significant difference in overall survival in prechemotherapy and postchemotherapy settings (HR: 0.90, 95% CI, 0.73–1.11; HR: 0.85, 95% CI, 0.68–1.07). Compared with AA, Enz may better outperform control arms in treating mCRPC both before and after chemotherapy regarding secondary endpoints based on indirect comparisons: time to prostate-specific antigen (PSA) progression (HR: 0.34, 95% CI, 0.28–0.42; HR: 0.40, 95% CI, 0.30–0.53), radiographic progression-free survival (HR: 0.37, 95% CI, 0.28–0.48; HR: 0.61, 95% CI, 0.50–0.74), and PSA response rate (OR: 18.29, 95% CI, 11.20–29.88; OR: 10.69, 95% CI, 3.92–29.20). With regard to the effectiveness of Enz following AA or AA following Enz, recent retrospective case series reported overall survival and secondary endpoints for patients with mCRPC progression after chemotherapy. However, confirmatory head-to-head trials are necessary to determine the optimal sequencing of these agents.

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Keywords: abiraterone acetate; enzalutamide; indirect comparison; metastatic castration-resistant prostate cancer; sequential therapy

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer and the sixth leading cause of cancer mortality in men worldwide.[1] Although most patients initially respond to androgen-deprivation therapy, prostate cancer eventually progresses to castration-resistant prostate cancer (CRPC).[2] Metastatic CRPC (mCRPC) is the typical cause of prostate cancer-related death; effective treatment options for mCRPC are lacking, and the median survival for men with mCRPC is <2 years.[3]

Docetaxel (Doc) chemotherapy has been established as the standard treatment approach for patients with mCRPC progression, and this regimen has a survival benefit.[4] However, it is now clear that this agent cannot be used universally because of its side effects. Even if Doc is initially active, patients inevitably progress at some point.[5] Since 2010, five novel agents have been specifically directed against CRPC with definite survival benefits, including abiraterone acetate (AA), enzalutamide (Enz), sipuleucel-T, radium-223, and cabazitaxel.[6] Among these five therapies with diverse mechanisms of action, AA and Enz are two new agents that block androgen synthesis by inhibiting CYP17 or the androgen receptor (AR), respectively. Recent studies have demonstrated that tumor progression after androgen-deprivation therapy commonly remains hormone driven;[7,8] thus, therapies targeting residual androgen production will be promising and well-tolerated alternatives to standard chemotherapy.[9]

The published clinical trials have only compared AA or Enz versus placebo in patients with mCRPC, and these trials demonstrated superiority in multiple outcomes, including overall survival (OS), time to PSA progression, radiographic progression-free survival (PFS), and PSA response rate.[10,11] Unfortunately, there is no currently available head-to-head comparison of these two agents. Furthermore, the optimal sequencing of therapies in terms of efficacy and tolerability and the potential for cross-resistance between the two agents remain uncertain. Physicians have to make difficult choices with limited substantial evidence when individualized treatment is widely advocated. Hence, we performed a literature-based systematic review and meta-analysis to evaluate the efficacy, tolerability, and sequential administration of AA and Enz for the management of mCRPC.

[1]Department of Urology, Changhai Hospital, Second Military Medical University, Shanghai, China; [2]Air Force General Hospital of Chinese People's Liberation Army, Beijing, China; [3]Department of Health Statistics, Faculty of Health Service, Second Military Medical University, Shanghai, China.
*These authors contributed equally to this work.
Correspondence: Prof. YH Sun (sunyh@medmail.com.cn) or Prof. T Zhou (wenzhoutie@163.com)
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MATERIALS AND METHODS

Literature search and article selection

A literature search was performed in April 30, 2015, of the PubMed, Embase, and Web of Science databases to identify relevant studies. The following search terms were utilized in the search: (*abiraterone/Zytiga* OR *enzalutamide/Xtandi/MDV3100*) AND *prostate cancer*. The search criteria were limited to the English language and human species. The retrieved articles were independently reviewed by WZ and TYW, and all disagreements were resolved by consensus. Reference lists of the retrieved articles as well as relevant review articles were also studied. In addition, clinicaltrials.gov was searched for any registered trials of either AA or Enz with accessible results to avoid the risk of publication bias (**Supplementary Figure 1**).

Inclusion and exclusion criteria

The double-blinded, randomized, placebo-controlled phase III trials with AA or Enz as a comparator in patients with mCRPC were included for indirect comparisons of each outcome. Furthermore, studies on Enz following AA and Doc or AA following Enz and Doc were included to evaluate the sequential use of these two agents in mCRPC. If more than one published manuscript was identified for the same trial, the most recent publication was considered for analysis, and the others were excluded.

Evaluation of study quality

The levels of evidence were estimated for all included studies with the Oxford Centre for Evidence-Based Medicine criteria.[12] The methodological quality assessment of the randomized controlled trials (RCTs) was conducted independently by WZ and TZ using the Jadad Scale.

Statistical analysis

Indirect comparisons of OS, time to PSA progression, radiographic PFS, and PSA response rate between AA and Enz as treatments for mCRPC were constructed according to the data from the AA versus placebo (COU-AA-301 and COU-AA-302) and Enz versus placebo (AFFIRM and PREVAIL) studies. Statistical analysis was performed using the pooled hazard ratio (HR) or odds ratio (OR) with 95% confidence intervals (CIs) as the summary statistics. The HR or RR indicated statistical superiority/inferiority between the groups if the 95% CI did not include 1, and relevant forest plots were also generated. To pool the data on AA and Enz sequential administration, the heterogeneity among studies was evaluated using the Q and I^2 statistics: homogeneity was rejected when the Q statistic $P < 0.10$ or the $I^2 > 50\%$. A fixed-effects model was used to estimate the weighted median values (or combined rates) and the 95% CIs if there was no evidence of heterogeneity; otherwise, a random-effects model was used. ITC version 1.0 software (Canadian Agency for Drugs and Technologies in Health, Ottawa, Ontario, Canada) and Stata version 12.0 software (StataCorp, College Station, TX, USA) were utilized for the analysis.

RESULTS

Study characteristics

Ten manuscripts on phase III trials[10,11,13–20] were ultimately utilized for the indirect comparisons between AA and Enz as treatments for mCRPC, and 8 case series studies[21–28] and 1 case–control study[29] were used to evaluate the optimal sequencing of these two agents (**Supplementary Table 1**). Because the clinicaltrials.gov search for registered trials with the same indication did not yield any additional relevant studies, the risk of publication bias was assessed as low. The methodological quality of the included RCTs was high for all the phase III trials (Jadad Scale: 5 of 5 points).

The COU-AA-301 and AFFIRM trials were indirectly compared based on all subjects and on subgroups with/without visceral disease or aged over/under 75 years, whereas the COU-AA-302 and PREVAIL trial comparison was confined to the entire cohorts. The definitions of the compared endpoints from these four trials are summarized in **Supplementary Table 2**. In regard to the non-RCTs, two studies evaluated the effectiveness of AA post-Doc and Enz and seven studies reported on Enz post-Doc and AA. The demographic characteristics of the participants in the RCTs and non-RCTs, including age, ECOG, extent of disease, diagnostic Gleason score, and baseline prostate-specific antigen (PSA), are presented in **Supplementary Tables 3** and **4**, respectively.

Indirect comparison outcomes

OS

The OS of patients who received AA or Enz was significantly better than that of those who received placebo in the COU-AA-301 (HR: 0.74; 95% CI, 0.64–0.86), COU-AA-302 (HR: 0.79; 95% CI, 0.66–0.95), AFFIRM (HR: 0.63; 95% CI, 0.53–0.75), and PREVAIL (HR: 0.73; 95% CI, 0.63–0.85) trials. The indirect estimate of the HR for Enz versus AA was 0.85 (95% CI, 0.68–1.07) for mCRPC progression after chemotherapy and 0.90 (95% CI, 0.73–1.11) for progression without previous chemotherapy. After the subgroup analysis, the OS was relatively, but not significantly, better for Enz compared with AA in patients without visceral disease (HR: 0.81; 95% CI, 0.62–1.06) and in those aged <75 years (HR: 0.81; 95% CI, 0.62–1.06), whereas the OS associated with the two agents was almost identical in patients with visceral disease (HR: 0.99; 95% CI, 0.64–1.53) and aged ≥75 years (HR: 0.95; 95% CI, 0.61–1.49) (**Figure 1**).

Time to PSA progression

The respective HRs for time to PSA progression for AA versus placebo in the COU-AA-301 and COU-AA-302 trials were 0.63 (95% CI, 0.52–0.78) and 0.50 (95% CI, 0.43–0.58), while those for Enz versus placebo in the AFFIRM and PREVAIL trials were 0.25 (95% CI, 0.20–0.30) and 0.17 (95% CI, 0.15–0.20). The indirect estimate of the HR showed that Enz provided a significantly longer time without PSA progression compared with AA in patients

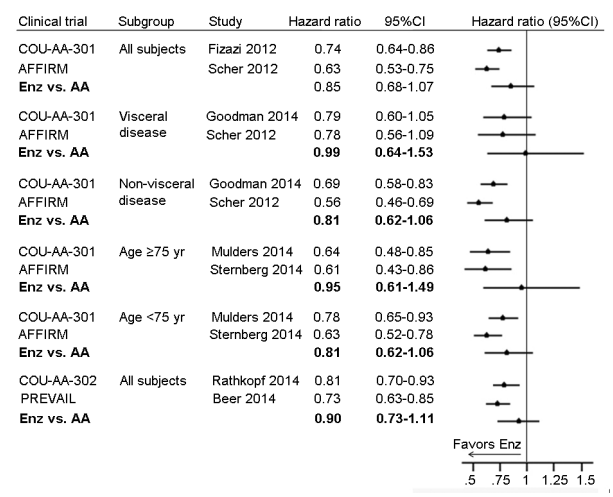

Figure 1: Individual study hazard ratio estimates and indirect comparison of overall survival between abiraterone acetate and enzalutamide.

with mCRPC progression after chemotherapy (HR: 0.40; 95% CI, 0.30–0.53) and in those without previous chemotherapy (HR: 0.34; 95% CI, 0.28–0.42). In addition, the HRs were significantly better for Enz compared with AA in the subgroups of patients aged ≥75 years (HR: 0.18; 95% CI, 0.10–0.34) and <75 years (HR: 0.48; 95% CI, 0.34–0.67) (**Figure 2a**).

Radiographic PFS

The respective HRs for radiographic PFS for AA versus placebo in the COU-AA-301 and COU-AA-302 trials were 0.66 (95% CI, 0.58–0.76) and 0.52 (95% CI, 0.45–0.61), while those for Enz versus placebo in the AFFIRM and PREVAIL trials were 0.40 (95% CI, 0.35–0.47) and 0.19 (95% CI, 0.15–0.23). The indirect estimate of the HR showed that Enz provided a significantly better radiographic PFS compared with AA in patients with mCRPC progression after chemotherapy (HR: 0.61; 95% CI, 0.50–0.74) and in those without previous chemotherapy (HR: 0.37; 95% CI, 0.28–0.48). Furthermore, the HRs were significantly better for Enz compared with AA in the subgroups of patients aged ≥75 years (HR: 0.41; 95% CI, 0.27–0.61) and <75 years (HR: 0.68; 95% CI, 0.54–0.86) (**Figure 2b**).

PSA response rate

The respective ORs for the PSA response rate for AA versus placebo in the COU-AA-301 and COU-AA-302 trials were 7.15 (95% CI, 4.53–11.28) and 5.38 (95% CI, 4.15–6.97), while those for Enz versus placebo in the AFFIRM and PREVAIL trials were 76.41 (95% CI, 31.22–187.04) and 98.40 (95% CI, 64.87–149.27). The indirect estimate of the OR showed that Enz provided a better PSA response compared with AA in patients with mCRPC progression after chemotherapy (OR: 10.69; 95% CI, 3.92–29.20) and in those without previous chemotherapy (OR: 18.29; 95% CI, 11.20–29.88). Furthermore, the ORs were better for Enz compared with AA in the subgroups of patients aged ≥75 years (OR: 27.84; 95% CI, 3.34–232.37) and <75 years (OR: 8.15; 95% CI, 2.82–23.57) (**Figure 3**).

Detailed adverse events

Adverse events happened in almost all the patients (98.1%–99.3%), and those Grade 3 or above made up 43.1%–60.4% of all events. One of the most common adverse events reported in trials for mCRPC, fatigue, was relatively more common among patients who received AA (39.7%–47.0%) compared to Enz (33.6%–35.6%). Adverse events of special interest included liver function abnormalities, cardiac disorders, hypertension, fluid retention, hypokalemia, and seizures. Among these, mineralocorticoid-related adverse events (fluid retention, hypertension, and hypokalemia) associated with elevated mineralocorticoid levels were more common in the AA group than in the Enz group. However, 6 of the 1672 patients treated with Enz had seizures, while no patients in the AA group had a seizure (**Table 1**).

Other endpoints

Other secondary endpoints such as time to pain progression (HR: 0.78; 95% CI, 0.52–1.18) and time to first skeletal-related event (HR: 1.12; 95% CI, 0.82–1.54) were indirectly compared between the COU-AA-301 and AFFIRM trials. There was no significant difference between Enz and AA in either endpoint (**Supplementary**

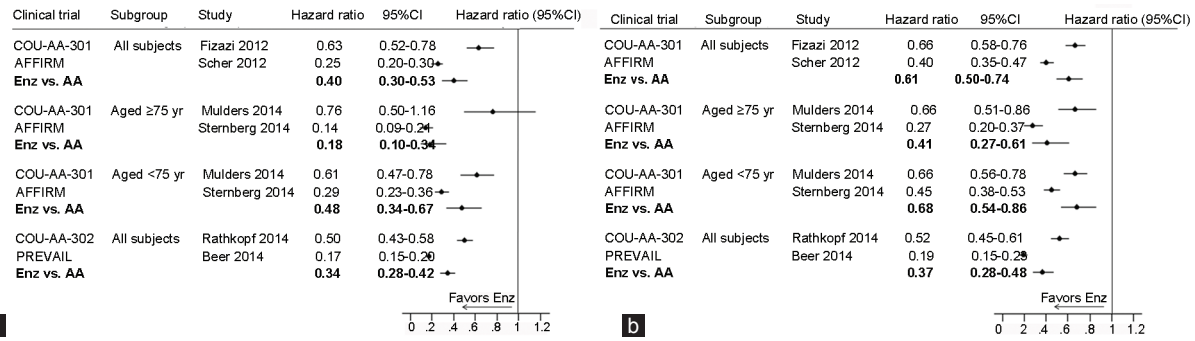

Figure 2: Individual study hazard ratio estimates and indirect comparison of time to PSA progression (**a**) and radiographic progression-free survival (**b**) between abiraterone acetate and enzalutamide.

Table 1: Summary of adverse events of RCTs

Clinical trial	*Study*	*Subgroup, n*	*Adverse events, n (%)*								
			All grades	*Grade 3/4*	*Fatigue*	*Liver function abnormalities*	*Cardiac disorders*	*Hypertension*	*Fluid retention*	*Hypokalemia*	*Seizures*
COU-AA-301	Fizazi *et al.*[10]	All subjects (791)	784 (99.1)	478 (60.4)	372 (47.0)	89 (11.3)	126 (15.9)	88 (11.1)	261 (33.0)	143 (18.1)	-
	Mulders *et al.*[16]	Aged ≥75 years (218)	218 (100)	132 (60.6)	104 (47.7)	-	43 (19.7)	20 (9.2)	77 (35.3)	39 (17.9)	-
		Aged <75 years (573)	566 (98.8)	346 (60.4)	268 (46.8)	-	63 (11.0)	56 (9.8)	135 (23.6)	104 (18.2)	-
AFFIRM	Scher *et al.*[11]	All subjects (800)	785 (98.1)	362 (45.3)	269 (33.6)	8 (1.0)	49 (6.1)	53 (6.6)	-	-	5 (0.6)
	Sternberg *et al.*[17]	Aged ≥75 years (199)	198 (99.5)	101 (50.8)	79 (39.7)	-	-	-	44 (22.1)	-	2 (1.0)
		Aged <75 years (601)	587 (97.7)	261 (43.4)	190 (31.6)	-	-	-	75 (12.5)	-	3 (0.5)
COU-AA-302	Ryan *et al.*[18] Rathkopf *et al.*[19]	All subjects (542)	541 (99.8)	290 (53.5)	215 (39.7)	60–65 (11.1–12.0)	126 (23.2)	129 (23.8)	167 (30.8)	101 (18.6)	-
PREVAIL	Beer *et al.*[20]	All subjects (871)	-	375 (43.1)	310 (35.6)	8 (0.9)	88 (10.1)	117 (13.4)	92 (10.6)	-	1 (0.1)

RCTs: randomized controlled trials

Figure 2a and **2b**). The time to health-related quality-of-life (HRQoL) deterioration and time to initiation of chemotherapy were also indirectly compared between the COU-AA-302 and PREVAIL trials. The HR for Enz was relatively superior to that for AA in time to HRQoL deterioration (HR: 0.80; 95% CI, 0.64–0.99), as measured using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale (**Supplementary Figure 2c**), whereas Enz had a significantly better HR for time to initiation of chemotherapy compared to AA (HR: 0.57; 95% CI, 0.46–0.72) in chemotherapy-naive patients (**Supplementary Figure 2d**).

Optimal sequencing evaluation

OS

A total of seven manuscripts reported the OS from the time of AA or Enz treatment initiation to death for patients with mCRPC progression after chemotherapy; two on AA following Enz and five on Enz following AA. After the pooled estimate, the median OS of patients with mCRPC was 9.7 months (95% CI, 6.0–13.4) or 7.4 months (95% CI, 6.8–8.1) when they were treated with AA after Enz or with Enz after AA, respectively (**Figure 4a**).

PFS

Overall, four manuscripts reported the PFS for patients with mCRPC progression after chemotherapy, defined as the time without PSA, radiographic and symptomatic progression. Two studies on AA following Enz and two on Enz following AA were included in the analysis. After the pooled estimate, the median PFS of patients with mCRPC was 3.2 months (95% CI, 2.1–4.3) or 2.9 months (95% CI, 2.4–3.4) when they were treated with AA after Enz or with Enz after AA, respectively (**Figure 4b**).

PSA response rate

The ≥30%, ≥50%, and ≥90% PSA response rates for patients with mCRPC progression after chemotherapy were calculated based on pooled estimates of the data from two studies on AA following Enz and seven studies on Enz following AA. In total, the ≥50% PSA response rate was 5% (95% CI, 0%–11%) for patients treated with AA following Enz and 18% (95% CI, 14%–22%) for those treated with Enz following AA (**Figure 5a**). In the initially AA/Enz-sensitive subgroups, the ≥50% PSA response rates were 29% (95% CI, 8%–50%) with subsequent Enz treatment and 3% (95% CI, −6%–11%) with subsequent AA treatment. In the initially AA/Enz-insensitive subgroups, the ≥50% PSA response rate was 9% (95% CI, 2%–17%) and 7% (95% CI, −2%–16%) for subsequent Enz treatment and AA treatment, respectively (**Figure 5b**). Furthermore, a ≥30% PSA decline was observed in 15% (95% CI, 6%–23%) of the patients treated with AA following Enz and in 36% (95% CI, 28%–44%) of those treated with Enz following AA (**Supplementary Figure 3a**). However, neither AA after Enz (0%; 95% CI, −1%–1%) nor Enz after AA (1%; 95% CI, 0%–1%) achieved a satisfactory ≥90% PSA response (**Supplementary Figure 3b**).

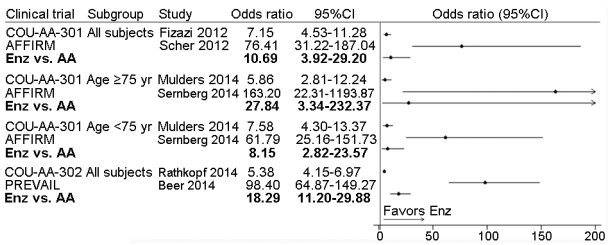

Figure 3: Individual study odds ratio estimates and indirect comparison of PSA response rate between abiraterone acetate and enzalutamide.

DISCUSSION

AR signaling in mCRPC cells remains active even under castration-induced levels of serum testosterone and is considered to play a significant role in the progression from androgen-sensitive prostate cancer to CRPC.[30] These data suggest that AR remains a key target in novel mCRPC therapies. AA and Enz, which both target the AR signaling pathway, have been approved by the FDA for use in both prechemotherapy and postchemotherapy settings and have shown satisfactory efficacy and tolerability in mCRPC patients. However, several issues remain unsolved: the most suitable patient population, potential cross-resistance mechanisms, optimal sequential dosing, and possible combination strategies.

The improvement in OS was not significantly different between AA and Enz according to our indirect comparisons. However, our literature review suggested a potential advantage of Enz over AA in most secondary endpoints, including time to PSA progression, radiographic PFS, PSA response rate, time to HRQoL deterioration, and time to initiation of chemotherapy (chemotherapy-naive patients), but there has been no head-to-head comparison. To avoid or alleviate the mineralocorticoid-related adverse events associated with AA, all the patients in the COU-AA-301 and COU-AA-302 trials were assigned to compulsory use of prednisone. In contrast, Enz was administered without the need for concomitant prednisone in the AFFIRM and PREVAIL trials. Recently, Richards *et al.*[31] reported that prostate cancer progression might occur secondary to glucocorticoid-induced activation of AR signaling through mutated AR. This may be a possible explanation for the superiority of Enz over AA in most secondary endpoints. Nevertheless, the above notion remains controversial. Richards and colleagues[31] reported an EC_{50} of 25.1 μmol l^{-1} for prednisolone-mediated activation of AR in cells transfected with the T877A AR mutant; this concentration is much higher than the plasma concentrations of prednisolone (4–305 nmol l^{-1}) measured

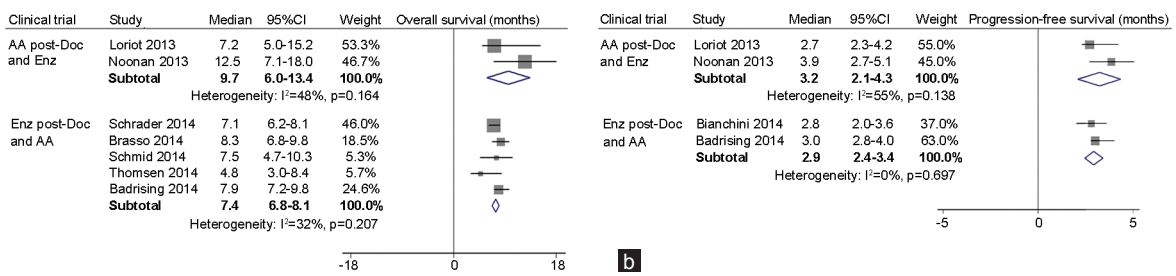

Figure 4: Pooled estimate of overall survival (**a**) and progression-free survival (**b**) for two different sequential treatments.

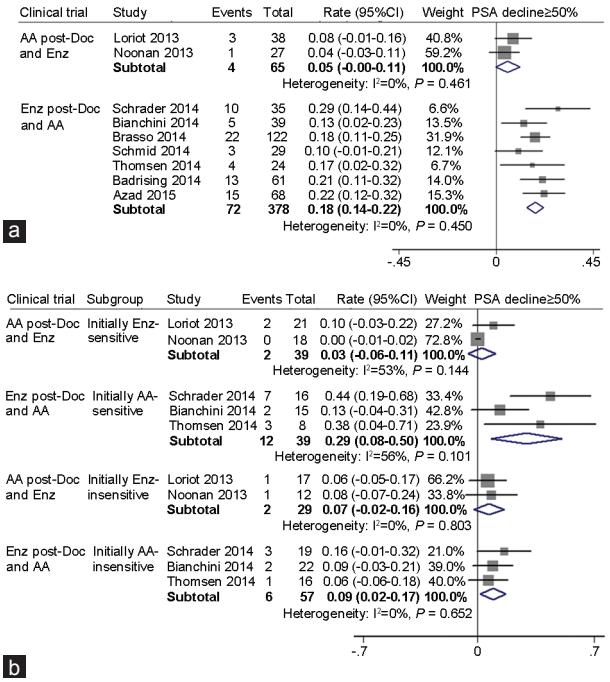

Figure 5: Pooled estimate of ≥50% PSA decline for two different sequential treatments in all patients (**a**) and in initial sensitive and insensitive subgroups (**b**).

in patients who received AA plus prednisolone.[32] Furthermore, a retrospective analysis of the COU-AA-301 trial did not show that baseline glucocorticoid would adversely affect the clinical benefit of AA in patients with mCRPC.[33] In our indirect comparisons, the median follow-up durations were somewhat different between the included trials (COU-AA-301: 20.2 months; AFFIRM: 14.4 months; COU-AA-302: 27.1 months; and PREVAIL: 22.0 months) because of the limited number of available published manuscripts. Tan *et al.*[34] indirectly compared the COU-AA-301 and AFFIRM trials based on the interim analyses with comparable median durations of follow-up (12.8 and 14.4 months). They suggested that Enz might have better efficacy in terms of secondary outcomes than AA, but no significant difference in OS.

Remarkably, visceral disease is common in patients with advanced prostate cancer, with reported rates of 25% for liver metastasis and 46% for lung involvement.[35] Recent clinical trials have identified visceral disease as a negative prognostic factor for mCRPC: those with visceral disease at baseline often had a particular poor prognosis regardless of treatment regimen.[36,37] The OS benefit associated with AA and Enz compared with placebo was inferior in patients with visceral disease compared with those without visceral disease. The indirect comparison also confirmed the similar inability of AA and Enz to improve OS when administered in the subset of patients with visceral disease.

According to the US Surveillance Epidemiology and End Results database, older patients (aged ≥75 years) are more likely to present with very advanced prostate cancer and account for over half of the deaths from prostate cancer, which is greater than the proportion caused by any other type of cancer.[38] Elderly patients with mCRPC usually do not receive curative chemotherapy-based treatment; instead, they undergo disease surveillance and receive supportive care, as they are physically frail with greater comorbidities.[39] The subgroup analysis showed that both AA and Enz achieved a comparable improvement of OS and were well tolerated in elderly patients with mCRPC, thus providing treatment options with definite efficacy for those who might not tolerate more toxic therapies. Moreover, compared to their respective control arms, the significant improvements in secondary endpoints, including time to PSA progression, radiographic PFS, and PSA response rate, were also achieved by AA and Enz in the subgroup of patients aged ≥75 years.

Although chemotherapy provides a survival benefit for patients with mCRPC, many of these patients are initially asymptomatic or mildly symptomatic or they have existing comorbidities and thus may not be eligible for chemotherapy.[40] Recently, Enz and AA demonstrated superiority in prolonging the time to initiation of chemotherapy and in OS compared to placebo in chemotherapy-naive patients in the COU-AA-302 and PREVAIL trials, respectively.[19,20] Our indirect comparisons showed that Enz provided significantly better HRs (ORs) for all secondary endpoints compared to AA, while no difference existed in the HR for OS between the two agents.

The adverse events associated with AA and Enz were generally less severe and allowed for treatment continuation without interruption or dose modification.[9] Although the incidence of all adverse events or high-grade ones for AA and Enz were quite similar, each agent has its own adverse events of special interest. The most commonly reported adverse event for both AA and Enz was fatigue, stemming from the castration-induced level of circulating testosterone and the inhibition of AR signaling in noncancerous tissues.[41] **Table 1** shows that 11.3%–12.0% of patients treated with AA had liver function abnormalities, compared with 0.9%–1.0% of those treated with Enz, indicating that unlike other anti-androgen agents, Enz was not associated with hepatotoxicity. Mineralocorticoid-related adverse events, including fluid retention, hypertension, and hypokalemia, occurred more frequently in the AA group than in the Enz group, as did cardiac disorders. AA inhibits the steroidogenic pathway to elevate mineralocorticoid levels; hence, it should be used cautiously in patients with metabolite disturbances, renal failure, or congestive heart failure.[10] More seriously, the mineralocorticoid excess may contribute to more cardiac disorders, namely arrhythmias, ischemic heart disease, or fatal cardiac events.[16] Therefore, AA treatment should also be restricted among elderly patients with coexisting cardiac conditions. On the other hand, Enz is known to have off-target actions on GABA receptors that lower seizure thresholds,[42] and seizures occurred in 6 of the 1672 patients in our analysis. These data indicate that patients with predisposing conditions such as known seizure disorder, brain metastasis, and brain injury should be closely monitored while taking Enz. The data from Tan *et al.*[34] who compared data from the interim analyses of the AA and Enz trials showed no significant differences in liver function abnormalities with AA versus Enz, but more cardiac disorders with AA. Furthermore, fluid retention and seizures were the specific adverse events related to AA and Enz, respectively.

Although the individual efficacy of AA and Enz in patients with mCRPC before and after chemotherapy has been well established, physicians still face multiple unresolved dilemmas regarding optimal sequencing and timing, possible combinations, cross-resistance mechanisms, and cost.[43] Recently, the survival benefit and PSA response were reported in patients treated with AA post-Doc and Enz[21,22] and in those treated with Enz post-Doc and AA.[23–29] However, most of the publications were retrospective case series with few patients, thus necessitating a pooled analysis of these studies.

Because AA and Enz inhibit persistent AR signaling through different mechanisms, patients who are resistant to one agent may theoretically benefit from the other agent. Our data showed only a limited survival benefit and a modest PSA response of the sequential

AA-Enz or Enz-AA treatments, which were inferior to those expected from the COU-AA-301 and AFFIRM trials. These findings suggest that cross-resistance, or at least partial cross-resistance, exists between AA and Enz. Nevertheless, these differences might also be influenced by the more advanced disease stage in the included studies than in the phase III trials. Despite the low PSA response rate observed for both treatment sequences, our data showed that more patients who received Enz following AA achieved ≥30% and ≥50% declines in PSA than those who received the reverse sequential application. However, whether patients were treated with sequential AA-Enz or Enz-AA, a small but significant number obtained a significant benefit. Therefore, we need to identify predictive biomarkers that may help distinguish patients who will benefit from additional AR signaling-targeted therapy from those who may become resistant to this treatment strategy.[44] Miyamoto *et al.*[45] demonstrated that measuring treatment-induced AR signaling responses within circulating tumor cells might help guide therapy for CRPC patients. Unfortunately, there is currently no reliable biomarker that predicts the optimal sequencing of AA and Enz. Ultimately, based on the available evidence, AA and Enz can be considered for patients who experience disease progression on one of these agents.

Even though most patients with mCRPC respond to AA or Enz treatment, resistance to these agents inevitably develops. Recent studies focusing on resistance mechanisms have demonstrated that the AR signaling pathway still plays a central role. Potential mechanisms include AR amplification, splicing, missense or deletion variants, and mutation or overexpression of androgen biosynthetic enzymes or the glucocorticoid receptor.[46] Among these options, AR splice variants, particularly the variant 7 (AR-V7) isoform, have been implicated in resistance to AA and Enz by conferring ligand-independent AR transactivation in preclinical studies, and they cannot be targeted by currently available AR-targeted drugs.[47,48] The aforementioned mechanisms are also involved in the proposed cross-resistance between AA and Enz *in vitro* and *in vivo*.[49] Multiple mechanisms contribute to cross-resistance in different patients and perhaps coexist in the same patient due to the heterogeneity of disease clonal evolution induced by therapeutic selective pressure. Faced with this dilemma, Richards *et al.*[31] indicated that combination treatment, rather than sequential treatment, with AA and Enz might be more clinically useful to reverse some mechanisms of drug cross-resistance.

Our study has several limitations. The differences in baseline characteristics among the four trials subjected to indirect comparisons could not be completely avoided. First, patients with visceral disease were included in the PREVAIL trial, but excluded from the COU-AA-302 trial. Second, for the control groups, prednisone use was compulsory in the COU-AA-301 and COU-AA-302 trials, while the AFFIRM and PREVAIL trials had a true placebo group, but allowed concomitant corticosteroids when necessary. Third, the comparisons were generated between the full analyses of the COU-AA-301 and COU-AA-302 trials and the interim analyses of the AFFIRM and PREVAIL trials, which had different follow-up periods. Fourth, almost all the included studies evaluating optimal sequencing were case series studies, and their methodological quality was relative low.

CONCLUSIONS

AA and Enz have demonstrated similar survival benefits in patients with mCRPC before and after chemotherapy, whereas Enz may be advantageous for secondary endpoints including time to PSA progression, radiographic PFS, PSA response rate, time to HRQoL deterioration, and time to initiation of chemotherapy (chemotherapy-naive patients). Although recent retrospective case series have reported OS and secondary endpoints for patients with mCRPC progression after chemotherapy to access the effectiveness of Enz following AA or AA following Enz, the optimal sequencing of these agents and whether potential cross-resistance exists require confirmatory prospective combination or sequencing trials.

AUTHOR CONTRIBUTIONS

WZ and TYW conceived this study, conducted the searching, and drafted the manuscript. QC and XLS participated in article screening and performed the statistical analysis. GAX, LZ, and CLX checked the data. TZ and YHS contributed to the design of this study and provided proposals for the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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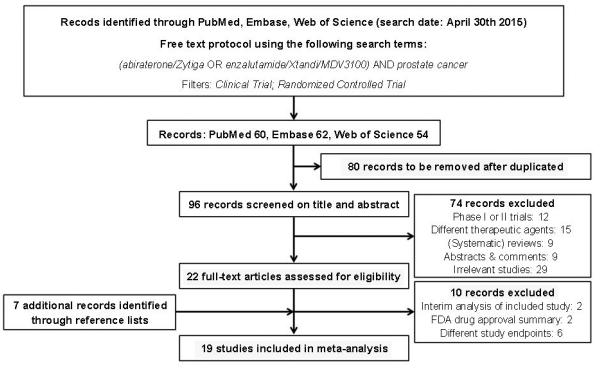
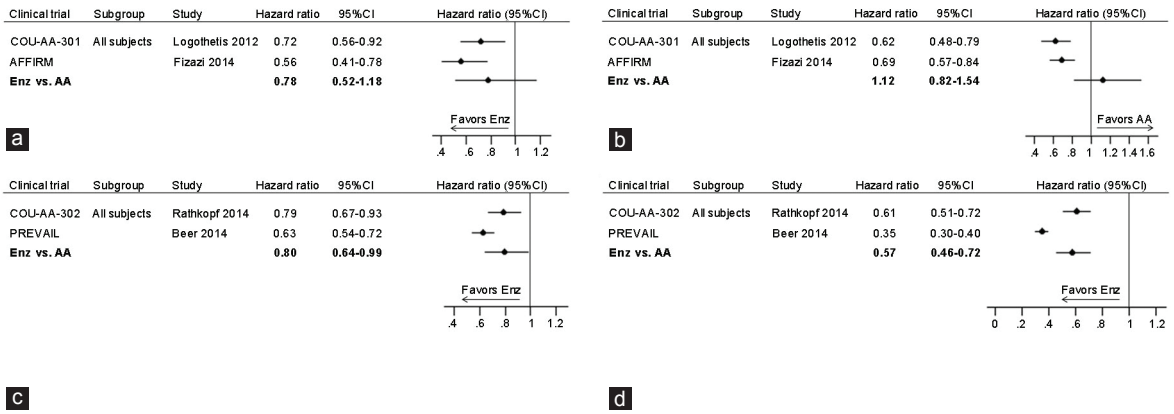
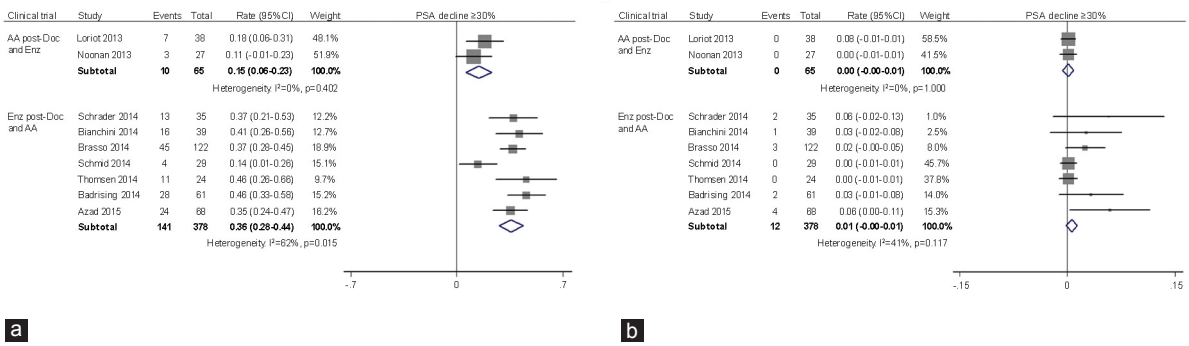


Supplementary Figure 1: PRISMA flow diagram of the search strategy.



Supplementary Figure 2: Individual study hazard ratio estimates and indirect comparison of time to pain progression (**a**), first skeletal-related event (**b**), health-related quality-of-life deterioration (**c**), and initiation of chemotherapy (**d**) between abiraterone acetate and enzalutamide.



Supplementary Figure 3: Pooled estimate of ≥30% (**a**) and ≥90% (**b**) PSA declines for two different sequential treatments.

Supplementary Table 1: Summary of comparative studies

Study	Clinical trial	Study design	LE	Study quality	Follow-up duration, median (IQR)	Subgroup	Cases, n		
							AA	Enz	Placebo
Logothetis *et al.*[13]	COU-AA-301	RCT	1b	5	20.2 (18.4–22.1)	-	797	-	398
Fizazi *et al.*[10]	COU-AA-301	RCT	1b	5	20.2 (18.4–22.1)	-	797	-	398
Fizazi *et al.*[14]	AFFIRM	RCT	1b	5	14.4	-	-	800	399
Goodman *et al.*[15]	COU-AA-301	RCT	1b	5	-	Visceral and nonvisceral disease	797	-	398
Scher *et al.*[11]	AFFIRM	RCT	1b	5	14.4	Visceral and nonvisceral disease	-	800	399
Mulders *et al.*[16]	COU-AA-301	RCT	1b	5	20.2 (18.4–22.1)	Aged ≥75 years and <75 years	797	-	397
Sternberg *et al.*[17]	AFFIRM	RCT	1b	5	-	Aged ≥75 years and <75 years	-	800	399
Ryan *et al.*[18]	COU-AA-302	RCT	1b	5	49.2 (47.0–51.8)	-	546	-	542
Rathkopf *et al.*[19]	COU-AA-302	RCT	1b	5	27.1	-	546	-	542
Beer *et al.*[20]	PREVAIL	RCT	1b	5	22.0	-	-	872	845
Loriot *et al.*[21]	AA post-Doc and Enz	Retrospective case series	4	-	-	-	38	-	-
Noonan *et al.*[22]	AA post-Doc and Enz	Retrospective case series	4	-	-	-	27	-	-
Schrader *et al.*[23]	Enz post-Doc and AA	Prospective case series	4	-	-	-	-	35	-
Bianchini *et al.*[24]	Enz post-Doc and AA	Retrospective case series	4	-	4.3	-	-	39	-
Brasso *et al.*[25]	Enz post-Doc and AA	Retrospective case series	4	-	-	-	-	137	-
Schmid *et al.*[26]	Enz post-Doc and AA	Prospective case series	4	-	5.0	-	-	35	-
Thomsen *et al.*[27]	Enz post-Doc and AA	Retrospective case series	4	-	-	-	-	24	-
Badrising *et al.*[28]	Enz post-Doc and AA	Retrospective case series	4	-	4.1 (3.4–5.3)	-	-	61	-
Azad *et al.*[29]	Enz post-Doc and AA	Retrospective case control	3b	-	-	-	-	68	-

LE: level of evidence; IQR: interquartile range; RCT: randomized controlled trial; AA: abiraterone acetate; Enz: enzalutamide; Doc: docetaxel

Supplementary Table 2: Summary of compared endpoints definitions of RCTs

Clinical trial	OS	Time to PSA progression	Radiographic PFS	PSA response rate
COU-AA-301	Time from randomization to death from any cause	A 25% increase over the baseline/nadir and an increase in the absolute-value PSA level by at least 5 ng ml^{-1}, which was confirmed by a second value; a 50% increase above the nadir at a minimum of 5 ng ml^{-1} (if at least a 50% decrease in the PSA level had been achieved)	Freedom from soft-tissue disease progression according to modified RECIST (with a baseline lymph node of ≥2.0 cm considered to be a target lesion) or progression according to bone scans showing two or more new lesions not consistent with tumor flare	PSA decline of ≥50% confirmed by a second PSA decline at least 4 weeks later
AFFIRM	Time from randomization to death from any cause	A ≥25% increase and an absolute increase of ≥2 ng ml^{-1} above the nadir/baseline, which was confirmed by a second consecutive value obtained at least 3 weeks later	Time from randomization to the earliest objective evidence of radiographic progression or death due to any cause	≥50% and ≥90% reductions in PSA from baseline to lowest postbaseline PSA result as determined by the central laboratory were calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment
COU-AA-302	Time from randomization to death from any cause	Based on PCWG2 criteria	Freedom from death from any cause; freedom from progression in soft-tissue lesions according to modified RECIST or progression on bone scanning according to criteria adapted from the PCWG2	Proportion of patients achieving a PSA decline ≥50% according to PCWG2 criteria
PREVAIL	Time from randomization to death from any cause	A ≥25% increase and an absolute increase of ≥2 ng ml^{-1} above the nadir/baseline, which was confirmed by a second consecutive value obtained at least 3 weeks later	Time from randomization to the first objective evidence of radiographic disease progression assessed by the blinded independent central review facility or death due to any cause within 168 days after treatment discontinuation, whichever occurred first	≥50% and ≥90% reductions in PSA from baseline to the lowest postbaseline PSA result as determined by the local laboratory, were calculated by treatment group for patients with PSA values at the baseline assessment and at least 1 postbaseline assessment

OS: overall survival; PFS: progression-free survival; RCTs: randomized controlled trials; PSA: prostate-specific antigen

Supplementary Table 3: Summary of baseline patient characteristics of RCTs

Clinical trial	*Study*	*Subgroup*	*Age (years), median (range)*	*ECOG PS, n (%)*		*Extent of disease, n (%)*			*Diagnostic Gleason score, n (%)*		*Baseline PSA (ng ml^{-1}), median (range)*
				0 or 1	*2*	*Bone*	*Node*	*Visceral*	*≤7*	*≥8*	
COU-AA-301	Logothetis *et al.*[13] Fizazi *et al.*[10]	All subjects	69 (42–95)	715 (89.7)	82 (10.3)	710 (89.1)	361 (45.3)	193 (24.2)	341 (42.8)	356 (44.7)	129 (0·4–9253)
	Goodman *et al.*[15]	Visceral disease	69 (42–88)	-	31 (12.3)	218 (86.2)	124 (49.0)	194 (76.7)	103 (40.7)	114 (45.1)	153 (0.7–9253)
		Nonvisceral disease	70 (45–95)	-	51 (9.4)	492 (90.4)	237 (43.6)	0 (0)	238 (43.8)	242 (44.5)	124 (0.4–5906)
	Mulders *et al.*[16]	Aged ≥75 years	78 (75–95)	182 (82.7)	38 (17.3)	195 (88.6)	98 (44.5)	53 (24.1)	100 (45.5)	76 (34.5)	133 (1.6–6092)
		Aged <75 years	66 (42–74)	533 (92.4)	44 (7.6)	515 (89.3)	263 (45.6)	141 (24.4)	241 (41.8)	280 (48.5)	127 (0.4–9253)
AFFIRM	Fizazi *et al.*[14] Scher *et al.*[11]	All subjects	69 (41–92)	730 (91.3)	70 (8.8)	735 (92.2)	442 (55.8)	214 (27.0)	360 (45.0)	366 (45.8)	108 (0.2–11794)
	Scher *et al.*[11]	Visceral disease	-	-	-	-	-	-	-	-	-
		Nonvisceral disease	-	-	-	-	-	-	-	-	-
	Sternberg *et al.*[17]	Aged ≥75 years	-	-	22 (11.1)	-	-	57 (28.6)	-	-	133
		Aged <75 years	-	-	48 (8.0)	-	-	159 (26.5)	-	-	99
COU-AA-302	Ryan *et al.*[18] Rathkopf *et al.*[19]	All subjects	71	-	-	452 (82.8)	267 (48.9)	0 (0)	-	263 (48.2)	42
PREVAIL	Beer *et al.*[20]	All subjects	72 (43–93)	872 (100)	0 (0)	741 (85.0)	437 (50.1)	104 (11.9)	414 (47.5)	424 (48.6)	54 (0.1–3182)

ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: prostate-specific antigen; RCTs: randomized controlled trials

Supplementary Table 4: Summary of baseline patient characteristics of non-RCTs

Clinical trial	*Study*	*Age (years), median (range)*	*ECOG PS, n (%)*		*Extent of disease, n (%)*			*Diagnostic gleason score, n (%)*		*Baseline PSA (ng ml^{-1}), median (range)*	*Time on prior Enz/ AA (months), median (range)*	*Time on AA/ Enz (months), median (range)*
			0 or 1	*2*	*Bone*	*Node*	*Visceral*	*≤7*	*≥8*			
AA post-Doc and Enz	Loriot *et al.*[21]	71 (52–84)	16 (42.1)	14 (36.8)	37 (97.4)	15 (39.5)	10 (26.3)	26 (68.4)	11 (28.9)	232 (2–3000)	8.0 (1–24)	3.0 (1–13)
AA post-Doc and Enz	Noonan *et al.*[22]	70 (56–84)	21 (70.0)	7 (23.3)	26 (86.7)	18 (60.0)	9 (30.0)	13 (43.3)	13 (43.3)	-	10.3 (1.5–23.8)	3.3 (0.25–13)
Enz post-Doc and AA	Schrader *et al.*[23]	70 (57–81)	-	-	-	-	-	10 (28.6)	19 (54.3)	-	9.0	4.9
Enz post-Doc and AA	Bianchini *et al.*[24]	70 (54–85)	25 (64.1)	14 (35.9)	33 (84.6)	21 (53.8)	6 (15.4)	17 (43.6)	21 (53.8)	500 (15–6357)	6.4	2.9 (0.6–7.2)
Enz post-Doc and AA	Brasso *et al.*[25]	71 (57–85)	68 (49.6)	28 (20.4)	-	-	-	41 (29.9)	65 (47.4)	348 (82–808)	7.0 (1.6–53.6)	3.2 (0.03–21.9)
Enz post-Doc and AA	Schmid *et al.*[26]	72 (60–83)	27 (77.1)	8 (22.9)	35 (100)	25 (71.4)	6 (17.1)	8 (22.9)	14 (40.0)	-	6.0 (2–20)	2.8 (0.1–9.5)
Enz post-Doc and AA	Thomsen *et al.*[27]	72 (57–82)	16 (66.7)	8 (33.3)	-	-	-	6 (25.0)	14 (58.3)	578 (44–5460)	6.0	4.0
Enz post-Doc and AA	Badrising *et al.*[28]	69	35 (57.4)	26 (42.6)	48 (78.7)	33 (54.1)	13 (21.3)	24 (39.3)	26 (42.6)	267 (79–687)	6.5	3.7
Enz post-Doc and AA	Azad *et al.*[29]	70	-	-	64 (94.1)	24 (35.3)	13 (19.1)	21 (30.9)	39 (57.4)	-	7.4	4.1

ECOG PS: Eastern Cooperative Oncology Group performance status; Doc: docetaxel; AA: abiraterone acetate; Enz: enzalutamide; PSA: prostate-specific antigen; RCTs: randomized controlled trials