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

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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.

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 thus, therapies targeting residual androgen production will be promising and well-tolerated alternatives to standard chemotherapy.⁸

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.⁹ 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.

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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.13 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. The double-blinded, randomized, placebo-controlled phase III trials 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 I² statistics: homogeneity was rejected when the Q statistic P < 0.10 or the I² > 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 trials10,11,13–20 were ultimately utilized for the indirect comparisons between AA and Enz as treatments for mCRPC, and 8 case series studies21–28 and 1 case-control study29 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 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 without visceral disease (HR: 0.81; 95% CI, 0.62–1.06) and in those aged ≥75 years (HR: 0.95; 95% CI, 0.61–1.49) (Supplementary Table 2).

| Clinical trial | Subgroup | Study | Hazard ratio | 95%CI | Hazard ratio (95%CI) |
|---------------|----------|-------|--------------|------|---------------------|
| COU-AA-301    | All subjects | Fizazi 2012 | 0.74 | 0.64–0.86 |
|               |          | Scher 2012 | 0.63 | 0.53–0.75 |
|               | Enz vs. AA |          | 0.85 | 0.65–1.07 |
| COU-AA-301    | Visceral disease | Goodman 2014 | 0.79 | 0.69–0.90 |
|               |          | Scher 2012 | 0.78 | 0.59–0.98 |
|               | Enz vs. AA |          | 0.99 | 0.64–1.53 |
| COU-AA-301    | Non-visceral disease | Goodman 2014 | 0.69 | 0.58–0.83 |
|               |          | Scher 2012 | 0.56 | 0.40–0.80 |
|               | Enz vs. AA |          | 0.81 | 0.62–1.06 |
| COU-AA-301    | Age ≥75 yr | Mulders 2014 | 0.64 | 0.48–0.85 |
|               |          | Sternberg 2014 | 0.61 | 0.43–0.86 |
|               | Enz vs. AA |          | 0.95 | 0.61–1.49 |
| COU-AA-301    | Age <75 yr | Mulders 2014 | 0.78 | 0.65–0.93 |
|               |          | Sternberg 2014 | 0.63 | 0.50–0.79 |
|               | Enz vs. AA |          | 0.81 | 0.62–1.06 |
| COU-AA-302    | All subjects | Rinklopf 2014 | 0.61 | 0.70–0.90 |
|               |          | PREVAIL | 0.70 | 0.53–0.95 |
|               | Enz vs. AA |          | 0.90 | 0.67–1.11 |

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, 0.40–11.28) and 5.38 (95% CI, 4.15–6.97), while those for Enz versus placebo in the AFFIRM and PREVAIL trials were 7.64 (95% CI, 3.12–18.70) 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 (37.9%–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).

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**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. | 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. | Aged ≥75 years (218) |                          | 218 (100) | 132 (60.4) | 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. | 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. | 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. | All subjects (542) |                          | 541 (99.8) | 290 (53.5) | 215 (39.7) | 60–65 | 126 (23.2) | 129 (23.8) | 167 (30.8) | 101 (18.6) | - |
|               | Rathkopf et al. | PREVAIL |                          | 587 (97.7) | 261 (43.4) | 190 (31.6) | 75 (12.5) | - | - | 3 (0.5) |
| PREVAIL       | Beer et al. | 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).

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. 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. 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 reported an EC$_{50}$ of 25.1 nmol 1$^{-1}$ 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 1$^{-1}$) measured.
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Pooled estimate 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.\textsuperscript{46} 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.\textsuperscript{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.\textsuperscript{7} 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 tissue.\textsuperscript{41} Table 1 shows that 11.3–12.0% of patients treated with AA had liver function abnormalities, compared with 9.9%–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.\textsuperscript{10} More seriously, the mineralocorticoid excess may contribute to more cardiac disorders, namely arrhythmias, ischemic heart disease, or fatal cardiac events.\textsuperscript{38} 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,\textsuperscript{34} 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.\textsuperscript{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.\textsuperscript{7} Recently, the survival benefit and PSA response were reported in patients treated with AA post-Doc and Enz\textsuperscript{22,23} and in those treated with Enz post-Doc and AA.\textsuperscript{23–26} 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

\begin{table}
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Clinical trial & Study & Events & Total & Rate (95% CI) & Weight & PSA decline (%) \\
\hline
AA post-Doc and Enz & Lohr 2013 & 38 & 0.06 (0.01-0.10) & 40.8% & 38 & 0.06 (0.01-0.10) & 10.0% & 41.0% & 10.0% & 0.451 \\
& Nicolson 2013 & 27 & 0.04 (0.03-0.11) & 52.5% & 27 & 0.04 (0.03-0.11) & 10.0% & 41.0% & 10.0% & 0.451 \\
& Subtotal & 65 & 0.06 (0.01-0.10) & 100.0% & 65 & 0.06 (0.01-0.10) & 100.0% & 65 & 0.06 (0.01-0.10) & 100.0% \\
& Heretogeneity = I² = 0.0%, P = 0.451 & & & & & & & & & \\
\hline
Enz post-Doc and AA & Schrader 2014 & 10 & 0.29 (0.14-0.44) & 9.1% & 10 & 0.29 (0.14-0.44) & 9.1% & 10 & 0.29 (0.14-0.44) & 9.1% & 0.0% \\
& Banchero 2014 & 30 & 0.13 (0.02-0.25) & 15.3% & 30 & 0.13 (0.02-0.25) & 15.3% & 30 & 0.13 (0.02-0.25) & 15.3% & 0.0% \\
& Brasser 2014 & 22 & 0.18 (0.13-0.25) & 31.9% & 22 & 0.18 (0.13-0.25) & 31.9% & 22 & 0.18 (0.13-0.25) & 31.9% & 0.0% \\
& Schmid 2014 & 20 & 0.10 (0.03-0.21) & 12.1% & 20 & 0.10 (0.03-0.21) & 12.1% & 20 & 0.10 (0.03-0.21) & 12.1% & 0.0% \\
& Thomsen 2014 & 4 & 0.17 (0.03-0.32) & 6.7% & 4 & 0.17 (0.03-0.32) & 6.7% & 4 & 0.17 (0.03-0.32) & 6.7% & 0.0% \\
& Badrigia 2014 & 61 & 0.21 (0.13-0.32) & 14.0% & 61 & 0.21 (0.13-0.32) & 14.0% & 61 & 0.21 (0.13-0.32) & 14.0% & 0.0% \\
& Axel 2015 & 15 & 0.88 (0.43-0.67) & 15.3% & 15 & 0.88 (0.43-0.67) & 15.3% & 15 & 0.88 (0.43-0.67) & 15.3% & 0.0% \\
& Subtotal & 72 & 0.18 (0.04-0.22) & 100.0% & 72 & 0.18 (0.04-0.22) & 100.0% & 72 & 0.18 (0.04-0.22) & 100.0% & 0.0% \\
& Heretogeneity = I² = 0.0%, P = 0.450 & & & & & & & & & \\
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\caption{Table 1}
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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).
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. Miyamoto et al. 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. 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. 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. 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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REFERENCES

1. All Cancers (Excluding Non-melanoma Skin Cancer) Estimated Incidence, Mortality and Prevalence Worldwide in 2012. World Health Organization; 2012. Available from: http://www.globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. [Last accessed on 2015 May 15]
2. Lam JS, Leppert JT, Vemulaapalli SN, Shwarts O, Belideagrun AS. Secondary hormonal therapy for advanced prostate cancer. J Urol 2006; 175: 27–34
3. Cookson MS, Lowrance WT, Murad MH, Kibel AS. Castration-resistant prostate cancer: AUA guideline amendment. J Urol 2015; 193: 491–9.
4. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol: official J Am Soc Clin Oncol 2008; 26: 242–5.
5. Italiano A, Ortholan C, Oudard S, Poussel D, Gravis G, et al. Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration-resistant prostate cancer. Eur Urol 2009; 55: 1368–75.
6. Zhang T, Zhu J, George DJ, Armstrong AJ. Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistant prostate cancer. Exp Opin Pharmacother 2015; 16: 473–85.
7. Attar RM, Takimoto CH, Gottardis MM. Castration-resistant prostate cancer: locking up the molecular escape routes. Clin Cancer Res: official J Am Assoc Cancer Res 2009; 15: 3251–5.
8. Massard C, Fizazi K. Targeting continued androgen receptor signaling in prostate cancer. Clin Cancer Res: official J Am Assoc Cancer Res 2011; 17: 3876–83.
9. Agarwal N, Sonpavde G, Sternberg CN. Novel molecular targets for the therapy of castration-resistant prostate cancer. Eur Urol 2012; 61: 950–60.
10. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012; 13: 983–92.
11. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367; 1187–97.
12. Phillips B, Ball C, Sackett D, Badenoch D, Straus S, et al. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). Centre for Evidence-Based Medicine; 2009. Available from: http://www.cebm.net/index.aspx?o=1025. [Last accessed on 2015 May 15]
13. Logothetis CJ, Basch E, Molina A, Fizazi K, North SA, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer. Lancet Oncol 2012; 13: 1210–7.
14. Ferris K, Scher HI, Miller K, Basch E, Sternberg CN, et al. Effect of enzalutamide...
on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer; results from the randomised, phase 3 AFFIRM trial. Lancet Oncol 2014; 15: 1147–56.

Goodman DB Jr, Flag TW, Molina A, Mulders PF, Fizazi K, et al. Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 2014; 17: 34–9.

Mulders PF, Molina A, Marberger M, Saad F, Higano CS, et al. Efficacy and safety of abiraterone acetate in an elderly patient subgroup (aged 75 and older) with metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy. Eur Urol 2014; 65: 875–83.

Stember CN, de Bono JS, Chi KN, Fizazi K, Mulders P, et al. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. Ann Oncol: official J Eur Soc Med Oncol 2014; 25: 429–34.

Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015; 16: 152–60.

Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol 2014; 66: 815–25.

Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Stember CN, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–33.

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol: official J Eur Soc Med Oncol 2013; 24: 1802–7.

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, et al. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol: official J Eur Soc Med Oncol 2013; 24: 1802–7.

Schradaj AJ, Boegemann M, Ohlmann CH, Sneloer TJ, Krabbe LM, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. Eur Urol 2014; 65: 30–6.

Bianchini D, Lorente D, Rodriguez-Vida A, Omlin A, Pezaro C, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. Eur J Cancer 2014; 50: 78–84.

Brasso K, Thomsen FB, Schradaj AJ, Schmid SC, Lorente D, et al. Enzalutamide antitumour activity against metastatic castration-resistant prostate cancer previously treated with docetaxel and abiraterone: a multicentre analysis. Eur Urol 2016; 68: 317–24.

Schmid SC, Geitl A, Bokar A, Tauber R, Seitz AK, et al. Enzalutamide after docetaxel and abiraterone therapy in metastatic castration-resistant prostate cancer. Adv Ther 2014; 31: 234–41.

Thomsen FB, Roder MA, Ratnaborg P, Brasso K, Borre M, et al. Enzalutamide treatment in patients with metastatic castration-resistant prostate cancer progressing after chemotherapy and abiraterone acetate. Scand J Urol 2014; 48: 268–75.

Badrising S, van der Noort V, van Oort IM, van den Berg HP, Los M, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. Cancer 2014; 120: 968–75.

Azad AA, Eigt BJ, Murray RN, Kolminnamonberger C, Chi KN. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer patients. Eur Urol 2015; 67: 23–9.

Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. Nat Rev Cancer 2001; 1: 34–45.

Richards J, Lim AC, Hay CW, Taylor AE, Wingate A, et al. Interactions of abiraterone, eplerenone, and prednisolone with wild-type and mutant androgen receptor; a rationale for increasing abiraterone exposure or combining with MDV3100. Cancer Res 2012; 72: 2176–82.

End D, Molina A, Todd M, Meyers ML. Interactions of abiraterone, eplerenone, and prednisolone with wild-type and mutant androgen receptor: a rationale for increasing abiraterone exposure or combining with MDV3100. Cancer Res 2013; 73: 2926.

Montgomery B, Kheosh T, Molina A, Li J, Bellumut J, et al. Impact of baseline corticosteroids on survival and steroid androgens in metastatic castration-resistant prostate cancer: exploratory analysis from COU-AA-301. Eur Urol 2015; 67: 866–73.

Tan PS, Haaland B, Montero AJ, Kyriakopoulou CE, Lopes G. Hormonal therapeutics enzalutamide and abiraterone acetate in the treatment of metastatic castration-resistant prostate cancer (mCRPC) post-docetaxel-an indirect comparison. Clin Med Insights Oncol 2014; 8: 29–36.

Bubendorf L, Schopfer A, Wagner U, Sauder G, Moch H, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol 2000; 31: 578–83.

Armsong AJ, Garrett-Mayer E, de Wit R, Tannock I, Eisenberger M. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clin Cancer Res: official J Am Assoc Cancer Res 2010; 16: 203–11.

Pond GR, Sonpavde G, de Wit R, Eisenberger MA, Tannock IF, et al. The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. Eur Urol 2014; 65: 3–6.

Scosyrev E, Messing EM, Mohile S, Golijanin D, Wu G. Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. Cancer 2012; 118: 3062–70.

Shelke AR, Mohile SG. Treating prostate cancer in elderly men: how does aging affect the outcome? Curr Treat Options Oncol 2011; 12: 263–75.

Harris V, Lloyd K, Forsey S, Rogers P, Roche M, et al. A population-based study of prostate cancer chemotherapy. Clin Oncol (R Coll Radiol) 2011; 23: 706–8.

Grossmann M, Zajic JD. Management of side effects of androgen deprivation therapy. Endocrinol Metab Clin North Am 2010; 40: 655–71, x.

Foster WR, Car BD, Shi H, Levesque PC, Obermeier MT, et al. Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. Prostate 2011; 71: 480–8.

Loriot Y, Fizazi K. Towards random sequencing or precision medicine in castration-resistant prostate cancer? Eur Urol 2012; 62: 480–9.

Armstrong AJ, Eisenberger MA, Halabi S, Oudard S, Nanas DM, et al. Biomarkers in the management and treatment of men with metastatic castration-resistant prostate cancer. Eur Urol 2012; 61: 549–59.

Miyamoto DT, Lee RJ, Stott SL, Ting DT, Wittner BS, et al. Androgen receptor signaling in circulating tumor cells as a marker of hormonally responsive malignancy. Cancer Discov 2012; 2: 995–1003.

Crona DJ, Milowsky MI, Whang YE. Androgen receptor targeting drugs in castration-resistant prostate cancer and mechanisms of resistance. Clin Pharmacol Ther 2015; 98: 582–9.

Nakazawa M, Antonarakis ES, Luo J. Androgen receptor splice variants in the era of enzalutamide and abiraterone. Horm Cancer 2014; 5: 265–73.

Hu R, Lu C, Mostaghel EA, Veynasubramanian S, Gurel M, et al. Distinct transcriptional programs meditated by the ligand-dependent full-length androgen receptor and its splice variants in castration-resistant prostate cancer. Cancer Res 2012; 72: 3457–62.

Ferraideschi R, Sharifi N, Aucus RJ, Attard G. Molecular pathways: inhibiting steroid biosynthesis in prostate cancer. Clin Cancer Res: official J Am Assoc Cancer Res 2013; 19: 3353–9.

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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 |
|----------------|------------------|--------------------------|-----|---------------|----------------------------------|-----------------------------------------|----------|
| Logothetis et al.  | COU-AA-301       | RCT                      | 1b  | 5             | 20.2 (18.4–22.1) –                | -                                       | 797      |
| Fizzi et al.      | COU-AA-301       | RCT                      | 1b  | 5             | 20.2 (18.4–22.1) –                | -                                       | 797      |
| Fizzi et al.      | AFFIRM           | RCT                      | 1b  | 5             | 14.4 –                            | -                                       | 800      |
| Goodman et al.    | COU-AA-301       | RCT                      | 1b  | 5             | - Viscerale and nonvisceral disease | 797 – 398                               | 398      |
| Scher et al.      | AFFIRM           | RCT                      | 1b  | 5             | 14.4 –                            | Viscerale and nonvisceral disease - 800 | 399      |
| Mulders et al.    | COU-AA-301       | RCT                      | 1b  | 5             | 20.2 (18.4–22.1) –                | Aged ≥75 years and <75 years            | 797      |
| Sternberg et al.  | AFFIRM           | RCT                      | 1b  | 5             | - Aged ≥75 years and <75 years    | - 800 – 399                            | 399      |
| Ryan et al.       | COU-AA-302       | RCT                      | 1b  | 5             | 49.2 (47.0–51.8) –                | -                                       | 546      |
| Rathkopf et al.   | COU-AA-302       | RCT                      | 1b  | 5             | 27.1 –                            | -                                       | 546      |
| Beer et al.       | PREVAIL          | RCT                      | 1b  | 5             | 22.0 –                            | -                                       | 872      |
| Loriot et al.     | AA post-Doc and Enz | Retrospective case series | 4   | -             | -                                 | -                                       | -        |
| Noonan et al.     | AA post-Doc and Enz | Retrospective case series | 4   | -             | -                                 | -                                       | -        |
| Schrader et al.   | Enz post-Doc and AA | Prospective case series  | 4   | -             | -                                 | -                                       | -        |
| Bianchini et al.  | Enz post-Doc and AA | Retrospective case series | 4   | -             | 4.3 –                             | -                                       | -        |
| Brasso et al.     | Enz post-Doc and AA | Retrospective case series | 4   | -             | -                                 | -                                       | -        |
| Schmid et al.     | Enz post-Doc and AA | Prospective case series  | 4   | -             | 5.0 –                             | -                                       | -        |
| Thomsen et al.    | Enz post-Doc and AA | Retrospective case series | 4   | -             | -                                 | -                                       | -        |
| Badrising et al.  | Enz post-Doc and AA | Retrospective case series | 4   | -             | 4.1 (3.4–5.3) –                   | -                                       | -        |
| Azad et al.       | Enz post-Doc and AA | Retrospective case control | 3b  | -             | -                                 | -                                       | -        |

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) |
|----------------|-------|----------|-----------------------------|----------------|-------------------------|---------------------------------|------------------------------------------|
| COU-AA-301     | Logothetis et al.\textsuperscript{13} | All subjects | 69 (42–95) | 715 (89.7) | 31 (12.3) | 218 (86.2) | 194 (76.7) | 103 (40.7) | 114 (45.1) | 153 (0.7–9253) | 341 (42.8) | 356 (44.7) | 129 (0.4–9253) |
|                | Fizazi et al.\textsuperscript{14} | Goodman et al.\textsuperscript{16} | Visceral disease | 69 (42–88) | 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.\textsuperscript{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 (94.4) | 44 (7.6) | 515 (89.3) | 263 (45.1) | 141 (24.4) | 241 (41.8) | 280 (48.5) | 127 (0.4–9253) |
| AFFIRM         | Fizazi et al.\textsuperscript{14} | Scher et al.\textsuperscript{11} | Visceral disease | 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) |
|                |       |       | Nonvisceral disease | - | - | - | - | - | - | - | - | - |
|                |       |       | 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.\textsuperscript{16} | Rathkopf et al.\textsuperscript{19} | All subjects | 71 | - | - | 452 (82.8) | 267 (48.9) | 0 (0) | 263 (48.2) | 42 |
| PREVAIL        | Beer et al.\textsuperscript{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) |
|----------------|-------|-----------------------------|----------------|-------------------------|---------------------------------|------------------------------------------|
| AA post-Doc and Enz | Loriot et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{23} | 70 (57–81) | - | - | - | - | 10 (28.6) | 19 (54.3) | - | - | 9.0 | 4.9 |
| Enz post-Doc and AA | Bianchini et al.\textsuperscript{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.\textsuperscript{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 (0.3–21.9) |
| Enz post-Doc and AA | Schmid et al.\textsuperscript{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.\textsuperscript{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 | Badrisning et al.\textsuperscript{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.\textsuperscript{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