



## Original Article

# Differences in clinical outcome between docetaxel and abiraterone acetate as the first-line treatment in chemo-naïve metastatic castration-resistant prostate cancer patients with or without the ineligible clinical factors of the COU-AA-302 study



Darren M.C. Poon <sup>a,\*</sup>, Kuen Chan <sup>b</sup>, Siu H. Lee <sup>c</sup>, Tim W. Chan <sup>d</sup>, Henry Sze <sup>b</sup>, Eric K.C. Lee <sup>e</sup>, Daisy Lam <sup>a</sup>, Michelle F.T. Chan <sup>f</sup>, on behalf of the Hong Kong Society of Uro-Oncology (HKSUO)

<sup>a</sup> Department of Clinical Oncology, State Key Laboratory in Oncology in South China, Sir YK Pao Centre for Cancer, Hong Kong Cancer Institute and Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

<sup>b</sup> Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong

<sup>c</sup> Department of Oncology, Princess Margaret Hospital, Hong Kong

<sup>d</sup> Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong

<sup>e</sup> Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong

<sup>f</sup> Department of Clinical Oncology, Queen Mary Hospital, Hong Kong

## ARTICLE INFO

## Article history:

Received 7 June 2017

Received in revised form

26 June 2017

Accepted 14 August 2017

Available online 18 August 2017

## Keywords:

Abiraterone Acetate

Castration-Resistant Prostate Cancer

Chemo-Naïve

Chemotherapy

Metastasis

## ABSTRACT

**Background:** This study aimed to compare the efficacy of abiraterone acetate (AA) versus docetaxel (T) as first-line treatment in chemo-naïve metastatic castration-resistant prostate cancer (mCRPC) patients with or without the ineligible factors of the COU-AA-302 study (presence of visceral metastases, symptomatic disease, and/or Eastern Cooperative Oncology Group performance status  $\geq 2$ ).

**Materials and methods:** The clinical records of chemo-naïve mCRPC patients who received AA in six public oncology centers or T in two of these centers between 2003 and 2014 were reviewed. The survival time was compared among four subgroups of patients: those with ineligible factors administered AA (Group Ineligible-AA) or T (Group Ineligible-T), and those without ineligible factors and administered AA (Group Eligible-AA) or T (Group Eligible-T).

**Results:** During the study period, we identified 115 mCRPC patients who received AA or T, among whom 29, 36, 29, and 21 patients were classified as Groups Ineligible-AA, Ineligible-T, Eligible-AA, and Eligible-T, respectively. Both Group Ineligible-AA and Group Eligible-AA had significantly longer progression-free survival (PFS) and similar overall survival (OS) as Group Ineligible-T and Group Eligible-T (Ineligible, PFS: 6.3 vs. 5.9 months,  $P=0.0234$ , OS: 7.8 vs. 15.7 months,  $P=0.1601$ ; Eligible, PFS: 9.8 vs. 5.6 months,  $P=0.0437$ , OS: 20.5 vs. 18.2 months,  $P=0.7820$ ).

**Conclusions:** Compared to T, AA treatment resulted in longer PFS and similar OS in chemo-naïve mCRPC patients, irrespective of the presence of ineligible factors, suggesting that the initial treatment by AA may still be beneficial to those with the aforementioned ineligible factors.

© 2017 Asian Pacific Prostate Society, Published by Elsevier Korea LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

The majority of metastatic prostate cancer patients show an initial favorable response with androgen-deprivation therapy.<sup>1</sup>

However, castration-resistance inevitably develops in most of these patients.<sup>2</sup> Metastatic castration-resistant prostate cancer (mCRPC) is associated with a high mortality rate, accounting for approximately 30,000 deaths in the USA in 2015.<sup>3</sup>

With the recent emergence of novel androgen-receptor (AR) signaling pathway inhibitors, such as abiraterone acetate (AA) and enzalutamide, as well as the long-existing docetaxel (T), the landscape of management for mCRPC has been evolving rapidly in the

\* Corresponding author. Department of Clinical Oncology, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong.

E-mail address: [mc\\_poon@clo.cuhk.edu.hk](mailto:mc_poon@clo.cuhk.edu.hk) (DMC Poon).

past decade.<sup>4</sup> Notably, the roles of T and AA in chemo-naïve mCRPC patients were established in the TAX 327 and SWOG 9916 studies and in the COU-AA-302 study, respectively.<sup>5–7</sup>

However, the clinical question remains as to the optimal sequence of the two therapies, as there has been no direct comparative study for the two agents in chemo-naïve mCRPC patients in the first-line setting. Moreover, the patient groups treated in the three above-mentioned studies were not identical, with a subgroup of patients with less favorable prognosis, characterized by visceral metastases, symptomatic disease, and/or poor performance status [Eastern Cooperative Oncology Group (ECOG) performance status score  $\geq 2$ ], being excluded from the COU-AA-302 study. Thus, whether this particular subgroup of patients would benefit more from treatment by T or AA is uncertain.

The present retrospective study aimed to provide data on the efficacy of AA compared to T as first-line treatment in chemo-naïve mCRPC patients with or without the ineligible clinical factors of the COU-AA-302 study.

## 2. Methods

### 2.1. Patients

The present retrospective study was conducted using the databases of two previously reported studies from our group on mCRPC patients treated with AA and T, respectively.<sup>8,9</sup> Patient records were retrieved through the interhospital electronic record system. The AA-treated group comprised all mCRPC patients started on AA between August 2011 and December 2014 in six oncology centers in Hong Kong. These six centers represent all public oncology centers in Hong Kong. The comparison group of T-treated patients comprised all mCRPC patients started on T between 2003 and 2012 in two of the six oncology centers. Castration resistance was defined as disease progression despite a castration-level of testosterone being achieved. Symptomatic disease was defined as requirement of Step 2 or 3 analgesics in the World Health Organization analgesics ladder before treatment initiation. Patients with visceral disease who were medically unfit for, or who declined, chemotherapy, and those treated with AA outside the licensed indication within the period were also included.

The patients were categorized into four subgroups for clinical outcome analysis, according to the treatment by AA or T, and by the presence of visceral metastasis, symptomatic disease, and/or poor performance status (ECOG  $\geq 2$ ), i.e., characteristics corresponding to the exclusion criteria of the COU-AA-302 study, as follows: (1) those ineligible for the COU-AA-302 study and administered AA (Group Ineligible-AA); (2) those ineligible for the COU-AA 302 study and administered T (Group Ineligible-T); (3) those who met the inclusion criteria of COU-AA-302 and were administered AA (Group Eligible-AA); and (4) those who met the inclusion criteria of COU-AA-302 and were administered T (Group Eligible-T).

### 2.2. Treatment and follow-up details

AA treatment consisted of AA 1 g once daily in combination with prednisone 5 mg twice a day. Docetaxel treatment consisted of either a weekly (35 mg/m<sup>2</sup>) or 3-weekly (52.5–75 mg/m<sup>2</sup>) T regimen, with 5 mg prednisone twice per day. For both agents, treatment was discontinued upon disease progression, unacceptable toxicity, or death. The follow-up assessments comprised clinical assessment, serum prostate-specific antigen (PSA) analysis, blood counts, and liver and renal profiles. Regular imaging assessment was not mandatory unless progression was suspected clinically or was evident biochemically. The post-AA or post-T

treatments were decided at the discretion of the individual oncologists based on several factors, including the patient's preference, medical condition, physician's preference, affordability, and availability of alternative treatment options. Enzalutamide, another AR pathway-targeted agent, was not accessible during the study period.<sup>10</sup>

### 2.3. Endpoints and statistical analysis

The endpoints were progression-free survival (PFS), defined as the time from the first dose of AA or T to the diagnosis of clinical, radiological, or PSA progression, or death; and overall survival (OS), defined as the time from the first dose of AA or T to death of any cause. Clinical, biochemical, and radiological progressive disease were defined according to the Prostate Cancer Clinical Trials Working Group criteria.<sup>11</sup> The patient follow-up status as of 30 January 2016 was used for the analyses.

The baseline characteristics of patient subgroups were compared and the differences were analyzed by Fisher exact test. Kaplan–Meier plots of PFS and OS were obtained for the four subgroups, and any differences in PFS and OS among the subgroups were compared by the log-rank test. Multivariate analyses using a Cox proportional hazards regression model was performed for PFS using the following variables: treatment by AA or T, presence of ineligible clinical factors of the COU-AA-302 study (presence of visceral metastases, symptomatic disease, or poor performance status of ECOG  $\geq 2$ ), pretreatment hemoglobin (Hb), alkaline phosphatase and PSA levels, age, Gleason score, PSA doubling time, time to androgen deprivation therapy failure. For OS, analysis was repeated using the same variables along with the use of post-AA or T treatment. Hazard ratios and their 95% confidence intervals were computed. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows, version 17.0.1.80 (SPSS Inc., Chicago, IL, USA). For all analyses, *P* values  $\leq 0.05$  were considered significant.

## 3. Results

### 3.1. Patient characteristics and treatment details

The merged database included 115 patients. Table 1 summarizes the baseline patient characteristics of the four subgroups. The median follow-up times for patients initially treated by T and AA were 17.15 (range 4.3–49.8) and 10.75 (range 1.2–34.0) months, respectively. Docetaxel-treated patients had a lower median age than those who received AA, while the ineligible patients had higher alkaline phosphatase and lower Hb levels than the eligible patients.

The treatment details of both the T and AA cohorts have been reported previously.<sup>8,9</sup> The median durations of AA treatment were 9.0 (range, 1.0–33.9) and 6.8 (range, 1.0–27.5) months in Group Eligible-AA and Group Ineligible-AA, respectively. The median numbers of cycles of T were six (range, 1–10) and six (range, 1–12) in Group Eligible-T and Group Ineligible-T, respectively. Post-T or post-AA treatments were delivered to 35.7% of all patients upon disease progression, with significantly more patients in the T groups receiving subsequent treatment compared to in the AA groups (*P* < 0.001).

### 3.2. Comparison of clinical efficacy between AA and T

#### 3.2.1. Progression-free survival

Group Ineligible-AA had significantly longer PFS than Group Ineligible-T (6.3 vs. 5.9 months, *P* = 0.0234). Similarly, for the

**Table 1**  
Baseline patient characteristics

Characteristics	Docetaxel (n = 57)				AA (n = 58)				P
	Ineligible (n = 36)		Eligible (n = 21)		Ineligible (n = 29)		Eligible (n = 29)		
	No. of patients	%	No. of patients	%	No. of patients	No. of patients	%		
Follow-up time (mo)	15.4 (4.3–42.6)				17.5 (6.9–49.8)				0.001
Median (range)					7.6 (1.2–32.6)				
ECOG performance status									<0.001
0–1	31	86.1	21	100.0	7	24.1	29	100.0	
≥2	5	13.9	0	0	22	75.9	0	0	
Presence of visceral metastasis									0.007
No	28	77.8	21	100.0	26	89.7	29	100.0	
Yes	8	22.2	0	0	3	10.3	0	0	
Presence of symptomatic disease <sup>a)</sup>									<0.001
No	2	5.6	21	100.0	10	34.5	29	100.0	
Yes	34	94.4	0	0	19	65.5	0	0	
Age (y)									<0.001
Mean (SD)	64.4 (8.9)				67.6 (8.0)				
Median (range)	69.0 (53–76)				69.0 (51–82)				
Gleason score									0.003
<8	18	50.0	12	57.1	13	44.8	17	58.6	
8–10	12	33.3	8	38.1	2	6.9	8	27.6	
Unknown	6	16.7	1	4.8	14	48.3	4	13.8	
PSA, µg/L									0.122
Mean (SD)	639.0 (689.0)				322.2 (380.4)				
Median (range)	160.0 (2.2–4046)				113.5 (1.4–1458)				
ALP, IU/L									<0.001
Mean (SD)	464.0 (415.1)				103.0 (415.1)				
Median (range)	334.5 (49–1564)				88.0 (50–259)				
Hb, g/dl									0.006
Mean (SD)	10.8 (1.9)				12.1 (1.5)				
Median (range)	10.5 (6.6–14)				12.3 (9.5–14.2)				
PSADT/mo									0.955
Mean (SD)	2.85 (2.0)				2.97 (1.7)				
Median (range)	2.3 (0.6–7.4)				2.3 (0.9–6.9)				
Time to ADT failure									0.64
<1 yr	18	50.0	10	47.6	13	44.8	10	34.5	
≥1 yr	18	50.0	11	52.4	16	55.2	19	65.5	
Subsequent therapies									<0.001
No treatment	16	44.4	10	47.6	26	89.7	22	75.9	
Potential life-prolonging therapy <sup>b)</sup>	9	25.0	4	19.0	2	6.9	7	24.1	
Others <sup>c)</sup>	11	30.6	7	33.3	1	3.4	0	0	

AA, abiraterone acetate; ADT, androgen deprivation therapy; ALP, pretreatment alkaline phosphatase level; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Hb, pretreatment hemoglobin level; HR, hazard ratio; IU, international units; PSA, prostate-specific antigen; PSADT, PSA doubling time; SD, standard deviation.

<sup>a)</sup> Presence of pain prior to AA treatment requiring World Health Organization level II or above analgesics.

<sup>b)</sup> Including AA, enzalutamide, cabazitaxel, and docetaxel.

<sup>c)</sup> Including flutamide, bicalutamide, and ketoconazole.

Eligible groups, Group Eligible–AA also had significantly longer PFS than Group Eligible–T (9.8 vs. 5.6 months,  $P=0.0437$ ). Finally, comparing all eligible versus ineligible patients, the PFS was significantly longer (7.3 vs. 5.9 months,  $P=0.0141$ ) for the former (Fig. 1).

### 3.2.2. Overall survival

In contrast to the findings for PFS, there was no significant difference in OS between Group Ineligible–AA and Group Ineligible–T (7.8 vs. 15.7 months,  $P=0.1601$ ) or between Group Eligible–AA and Group Eligible–T (20.5 vs. 18.2 months,  $P=0.782$ ). Overall, as expected, the eligible patients had longer OS than the ineligible patients (19.1 vs. 10.7 months,  $P=0.0004$ ; Fig. 2).

## 3.3. Multivariate analyses

### 3.3.1. Progression-free survival

Treatment by AA, presence of ineligible factors, and the pretreatment Hb levels were found to be independent prognosticators for PFS (Table 2).

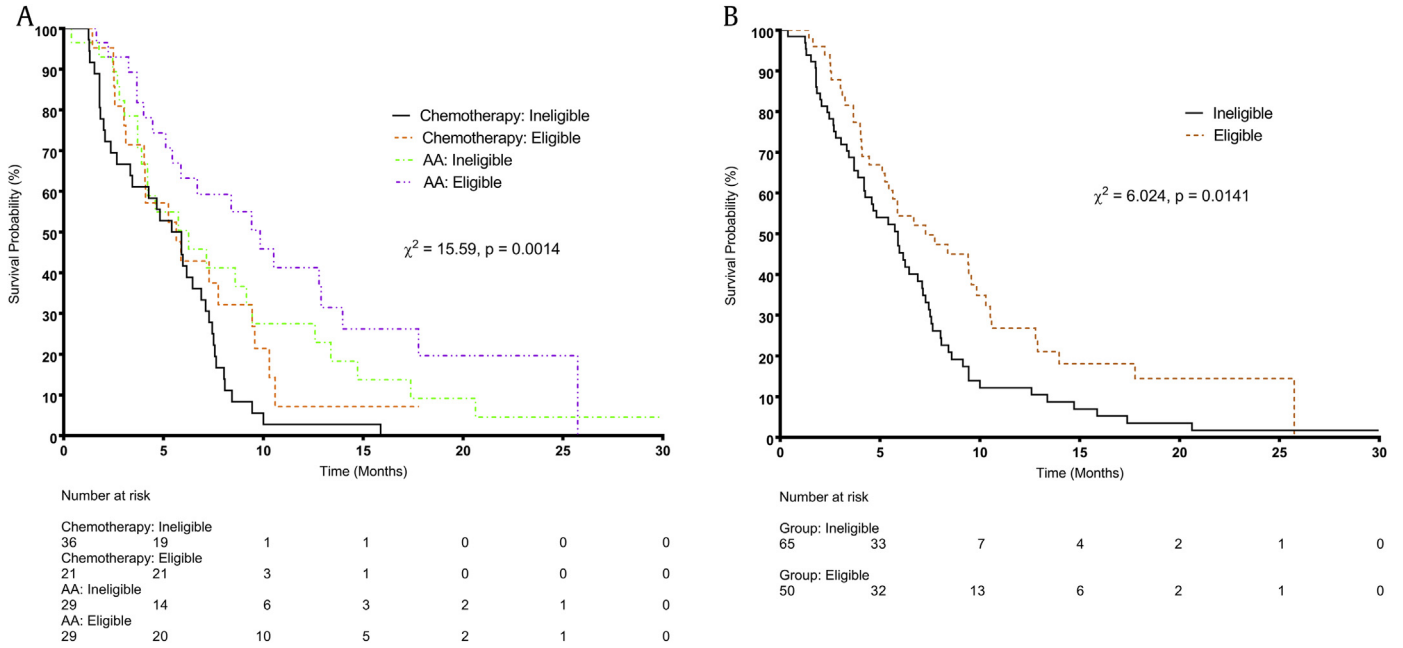
### 3.3.2. Overall survival

Significant prognostic variables for OS included the followings: the presence of ineligible factors, pretreatment Hb levels, and the use of subsequent therapies after failure of AA or docetaxel (Table 3).

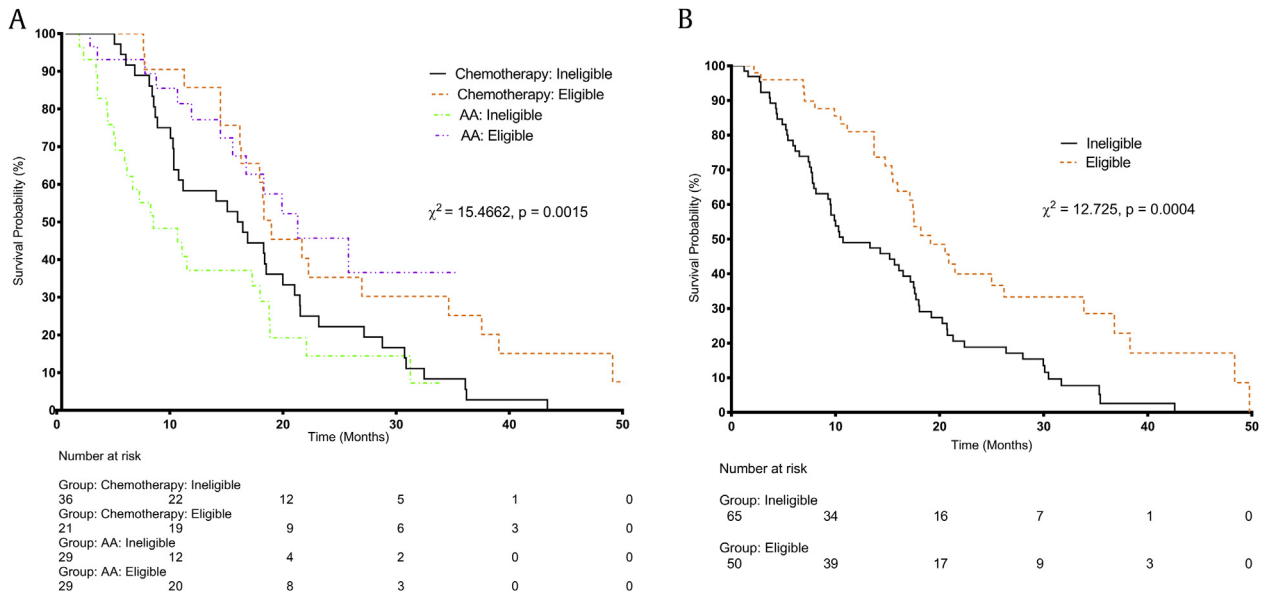
## 4. Discussion

At present, it remains unclear whether the clinical efficacy of AA in chemo-naïve mCRPC patients could be generalized to include patients with visceral metastases, symptomatic disease, and poor performance status, as this patient subgroup was excluded from the COU-AA-302 study. In contrast, patients with these unfavorable factors were included in the pivotal trial for T and, although the prognosis was less favorable, the survival benefit with T remained among these subgroups.<sup>12</sup> To our knowledge, the present study is the first to show that these patients had comparable OS and longer PFS when treated with AA, as compared to T, suggesting that they may still achieve clinical benefit from receiving initial treatment by AA.

Similarly, treatment by AA resulted in comparable OS and better PFS compared to T in the patients eligible for the COU-AA-302



**Fig. 1.** Kaplan–Meier curves for progression-free survival for the subgroups stratified by (A) treatment type and eligibility, and (B) eligibility irrespective of the treatment. AA, abiraterone acetate.



**Fig. 2.** Kaplan–Meier curves for overall survival for the subgroups stratified by (A) treatment type and eligibility, and (B) eligibility irrespective of the treatment. AA, abiraterone acetate.

study. To date, there has been no direct comparative prospective study between T, the *standard of care* for mCRPC patients since 2004 in the pre-AR signaling pathway inhibitor era, and novel therapies such as AA and enzalutamide. Recently, studies focusing on identifying predictive biomarkers, e.g. the detection of androgen receptor splice variant 7 in circulating tumor cells, for assisting the selection of the appropriate treatment for mCRPC patients, have been reported.<sup>13,14</sup> Nonetheless, until these potential predictive biomarkers have been validated in a large-scale prospective study and become commercially and widely applied, the appropriate selection of first-line treatment in chemo-naïve mCRPC patients remains uncertain. The results of the present study, conducted in the real-life setting, suggest that both T and AA, which did not show clear survival advantages over one another, are promising and

sensible treatment options for chemo-naïve mCRPC patients who are clinically permissible for these two therapies.

The possible explanation for the better PFS in the AA-treated patients could be attributed by the longer median duration of treatment with AA compared to T. Further, a higher proportion of patients treated by T received subsequent therapies. In the AA group patients, the more advanced age in both the Ineligible and Eligible groups and the higher proportion of patients with poor performance status in the Ineligible group may explain the less frequent employment of second-line treatment. Indeed, it was noted that the use of subsequent lines of potential life-prolonging therapy was a favorable determinant for OS in the multivariate analysis. Taken together, these are likely to be the reasons for the superior PFS but similar OS after initial AA treatment compared to T.

**Table 2**  
Univariate and multivariate analyses for progression-free survival

	Univariate analysis		Multivariate analysis	
	HR <sup>a)</sup> (95% CI)	P	HR <sup>a)</sup> (95% CI)	P
Primary treatment				
Chemotherapy	1.00		1.00	
AA	0.50 (0.33–0.76)	0.001	0.38 (0.19–0.76)	0.01
Presence of ineligible factors <sup>b)</sup>				
Yes	1.00		1.00	
No	0.60 (0.40–0.91)	0.02	0.48 (0.25–0.91)	0.03
Time to ADT failure				
≥1 yr	1.00		1.00	
<1 yr	1.92 (1.27–2.90)	0.002	1.16 (0.68–1.96)	0.59
Gleason score				
<8	1.00		1.00	
8–10	1.42 (0.88–2.27)	0.15	0.93 (0.56–1.53)	0.77
Unknown	1.06 (0.63–1.77)	0.82	1.24 (0.69–2.22)	0.47
Pretreatment PSA level, µg/L				
≤198	1.00		1.00	
>198	1.78 (1.18–2.67)	0.006	1.23 (0.76–2.01)	0.40
Pretreatment ALP level, IU/L				
≤123	1.00		1.00	
>123	1.86 (1.23–2.81)	0.003	0.73 (0.37–1.45)	0.37
Pretreatment Hb level, g/dL				
≤11	1.00		1.00	
>11	0.42 (0.27–0.65)	<0.0001	0.47 (0.27–0.82)	0.01
Age	0.97 (0.95–0.99)	0.01	1.00 (0.97–1.04)	0.93
PSADT	0.96 (0.85–1.09)	0.53	0.99 (0.87–1.12)	0.83

AA, abiraterone acetate; ADT, androgen deprivation therapy; ALP, pretreatment alkaline phosphatase level; CI, confidence interval; Hb, pretreatment hemoglobin level; HR, hazard ratio; IU, international units; PSA, prostate-specific antigen; PSADT, PSA doubling time.

<sup>a)</sup> HR <1 indicates better progression-free survival.

<sup>b)</sup> Presence of ineligible factors included visceral metastasis, symptomatic disease, and/or poor performance status.

As both initial first-line treatment options, irrespective of the presence of unfavorable characteristics, provided comparable OS outcomes in our cohort, the treatment-related toxicities and quality of life (QOL) are pertinent in choosing the therapy. This is in line with the recommendations of the US Food and Drug Administration and other organizations, which state that the patient-reported outcomes along with the survival outcome are indispensable in evaluating the overall benefit of a therapy.<sup>15,16</sup> Generally, cytotoxic chemotherapy is considered to have more toxic side effects, such as neutropenic sepsis, than noncytotoxic AR-signaling pathway inhibitors. These toxic complications could potentially affect the QOL. In this regard, the TAX-327 study showed that 29.1% of patients randomized to the 3-weekly T arm had experienced QOL deterioration during the treatments, despite only 22% of patients allocated to this treatment arm having reported subsequent QOL responses.<sup>17</sup> In contrast, in the COU-AA-302 study, AA was found to be able to preserve the functional status, as indicated by the lack of deterioration in the health-related QOL, for a median duration of 12.7 months.<sup>18</sup> However, owing to the retrospective nature of the present study, although valuable, the QOL data were not of adequate quality to allow for further analysis. It is noteworthy that the dose intensity of T in our cohort was lower than that usually recommended (75 mg/m<sup>2</sup>), with 25% of patients receiving a nonstandard dose at a 3-weekly schedule, and the survival time for our patients who received AA may have become more advantageous as a result.<sup>8</sup> By contrast, it is also possible that this observation may merely reflect the patients' suboptimal tolerance towards cytotoxic chemotherapy in the real-life setting, which would corroborate the former remark that both the survival outcomes and patients' reported outcomes are equally imperative to measure the overall efficacy of a therapeutic intervention.

**Table 3**  
Univariate and multivariate analyses for overall survival

	Univariate analysis		Multivariate analysis	
	HR <sup>a)</sup> (95% CI)	P	HR <sup>a)</sup> (95% CI)	P
Primary treatment				
Chemotherapy	1.00		1	
AA	1.09 (0.71–1.68)	0.69	4.42 (0.02–807.93)	0.58
Presence of ineligible factors <sup>b)</sup>				
Yes	1.00		1	
No	0.46 (0.29–0.71)	0.001	0.55 (0.31–0.96)	0.04
Time to ADT failure				
≥1 yr	1.00		1	
<1 yr	1.99 (1.32–3.02)	0.001	0.90 (0.46–1.75)	0.75
Gleason score				
<8	1.00		1	
8–10	1.38 (0.86–2.23)	0.19	0.88 (0.48–1.63)	0.69
Unknown	1.18 (0.68–2.03)	0.56	0.54 (0.22–1.37)	0.19
Pretreatment PSA level, µg/L				
≤198	1.00		1	
>198	1.80 (1.18–2.73)	0.006	1.50 (0.91–2.46)	0.11
Pretreatment ALP level, IU/L				
≤123	1.00		1	
>123	2.36 (1.52–3.69)	<0.0001	1.49 (0.84–2.64)	0.18
Pretreatment Hb level, g/dL				
≤11	1.00		1	
>11	0.25 (0.16–0.39)	<0.0001	0.29 (0.16–0.53)	<0.001
Subsequent treatment				
No treatment	1.00		1	
Potential life-prolonging treatment <sup>c)</sup>	0.46 (0.25–0.86)	0.01	0.29 (0.14–0.62)	0.001
Other treatment <sup>d)</sup>	0.65 (0.40–1.08)	0.10	0.60 (0.34–1.06)	0.08
Age	1.00 (0.98–1.02)	0.96	1.02 (0.98–1.07)	0.33
PSADT	0.97 (0.86–1.09)	0.61	17.82 (0.1–3170.24)	0.28

AA, abiraterone acetate; ADT, androgen deprivation therapy; ALP, pretreatment alkaline phosphatase level; CI, confidence interval; Hb, pretreatment hemoglobin level; HR, hazard ratio; IU, international units; PSA, prostate-specific antigen; PSADT, PSA doubling time.

<sup>a)</sup> HR <1 indicates better overall survival.

<sup>b)</sup> Presence of ineligible factors included visceral metastasis, symptomatic disease, and/or poor performance status.

<sup>c)</sup> Including abiraterone acetate, enzalutamide, cabazitaxel, and docetaxel.

<sup>d)</sup> Including flutamide, bicalutamide, and ketoconazole.



As expected, the presence of ineligible clinical factors was adversely associated with both PFS and OS in our multivariate analyses. Meanwhile, the survival outcomes in both our Ineligible and Eligible groups were analogous (comparable OS and better PFS with AA vs. T). These findings suggest that the presence of adverse clinical factors, or *ineligible factors*, may only have prognostic, but not predictive, significance in the management of mCRPC. This postulation is supported by the findings of other studies that mCRPC patients with unfavorable factors have poorer prognosis but comparable magnitude of clinical benefit with the study treatments compared to those without these factors. In the TAX 327 study, despite the median OS for patients with visceral metastases, pain symptoms, and poor performance status being shorter compared to in those without these factors, the substantial OS benefit persevered in these subgroups treated with T when compared to the control arm.<sup>12</sup> Moreover, in the COU-AA-301 study, AA was associated with a significant benefit to the placebo in OS, as well as other secondary endpoints (e.g. the PFS and PSA response rate) in post-T mCRPC patients with or without visceral metastases.<sup>19</sup> In the PREVAIL study, enzalutamide improved the PFS and showed a trend towards better OS compared to the placebo for chemo-naïve mCRPC patients, regardless of the presence of visceral metastases, high-volume bone metastases, and nodal only disease.<sup>20</sup> Taken together with our results, it is suggested that mCRPC patients presenting with adverse prognostic clinical factors could be managed similarly to those without, while clinical studies on more efficacious treatment approaches for these patients are eagerly awaited.

We acknowledge that this study has several limitations owing to its retrospective design, including possible selection bias and incompleteness of data collection, among others. Meanwhile, being a retrospective nonrandomized study, the baseline disease and patient characteristics among the AA- and T-treated subgroups were not comparable entirely, and direct comparison of the survival outcome may then be difficult to interpret. However, we consider the result of significant association with better survival outcome with the use of AA in the multivariate analysis would be a trustworthy finding, and could alleviate the confounding impact of the unbalancing baseline factors. Moreover, the sample size of our study was limited, but we consider that the off-label use of AA in patients with ineligible factors would be limited under the existing licensed indication worldwide. Furthermore, the date of disease progression for the patients in our cohort may not have been determined accurately, owing to the different follow-up protocols among the different centers, which may have resulted in the assessment of PFS being less precise. However, we consider this limitation unlikely to affect the ability to assess the OS. Finally, despite all patients in our study being assessed and managed by qualified practicing oncologists, the determination of the ECOG score for each patient and their need for analgesics are subjective in nature, and may hence have affected the stratification of the patients among the four prespecified subgroups.

## 5. Conclusions

This multicenter retrospective study is the first study to compare the efficacy between T and AA as first-line treatment in chemo-naïve mCRPC patients. In particular, those who were ineligible for the COU-AA-302 study due to the presence of unfavorable clinical factors, including visceral metastases, symptomatic disease, and/or poor performance status, were included and analyzed. In this study, AA treatment in mCRPC patients resulted in improved PFS and comparable OS as compared to docetaxel, in both ineligible, who are currently not indicated for AA therapy, and eligible patients. Despite having a less favorable prognosis to those eligible

for the COU-AA-302 study, our data suggest that initial treatment by AA may still be beneficial to patients with the aforementioned adverse clinical factors.

## Conflicts of interest

The authors declare that they have no conflict of interest.

## Authors' contributions

DMP contributed to conception, analysis and interpretation of data. DMP was also involved in drafting and revising the manuscript. DMP, KC, SHL, TWC, HS, EKL, DL, and MFC contributed to acquisition of data. DMP, KC, SHL, TWC, HS, EKL, DL, and MFC read and approved the final version of the manuscript as well as the order of presentation of the authors.

## Availability of data and materials

All data and materials can be obtained by contacting the corresponding author.

## Compliance with ethical standards

The study was approved by the institutional review board of the authors' institutions (Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee/Ref no: CRE-2015.481). Permission to access the medical records through the inter-hospital computer network was granted by the aforementioned review board. The principles of the Helsinki Declaration were followed. Informed consent has been exempted by the review board as most of the patients in this study were dead when the data were collected.

## Acknowledgements

The authors wish to thank Mr. Jimmy Yu and Dr. Leung-Sing Fai for their input and contributions to the study.

## References

- Schroder F, Crawford ED, Axcrone K, Payne H, Keane TE. Androgen deprivation therapy: past, present and future. *BJU Int* 2012;109(Suppl 6):1–12.
- Donkena KV, Yuan H, Young CY. Recent advances in understanding hormonal therapy resistant prostate cancer. *Curr Cancer Drug Targets* 2010;10:402–10.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;(65):5–29.
- Crawford ED, Higano CS, Shore ND, Hussain M, Petrylak DP. Treating patients with metastatic castration resistant prostate cancer: a comprehensive review of available therapies. *J Urol* 2015;194:1537–47.
- Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chin KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *New Engl J Med* 2004;351:1502–12.
- Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *New Engl J Med* 2013;368:138–48.
- Petrylak DP, Tangen CM, Hussain MH, Lara Jr PN, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *New Engl J Med* 2004;351:1513–20.
- Poon DM, Ng J, Chan K. Importance of cycles of chemotherapy and post-docetaxel novel therapies in metastatic castration-resistant prostate cancer. *Prostate Int* 2015;3:51–5.
- Poon DM, Chan K, Lee SH, Chan TW, Sze H, Lee EK, et al. Abiraterone acetate in metastatic castration-resistant prostate cancer—the unanticipated real-world clinical experience. *BMC Urol* 2016;16:12.
- Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *New Engl J Med* 2014;371:424–33.
- Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;26:1148–59.

12. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol* 2008;26:242–5.
13. Scher HI, Lu D, Schreiber NA, Louw J, Graf RP, Johnson A, et al. Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer. *JAMA Oncol* 2016;2:1441–9.
14. Antonarakis ES, Lu C, Wang H, Lubner B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *New Engl J Med* 2014;371:1028–38.
15. U.S. Department of Health and Human Services. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Available at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf> (accessed on 16 June 2015).
16. Basch E, Abernethy AP, Mullins CD, Reeve BB, Smith ML, Coons SJ, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. *J Clin Oncol* 2012;30:4249–55.
17. Berthold DR, Pond GR, Roessner M, de Wit R, Eisenberger M, Tannock IF, et al. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. *Clin Cancer Res* 2008;14:2763–7.
18. Basch E, Autio K, Ryan CJ, Mulders P, Shore N, Khoeh T, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol* 2013;14:1193–9.
19. Goodman Jr OB, Flaig TW, Molina A, Mulders PF, Fizazi K, Logothetis CJ, 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.
20. Evans CP, Higano CS, Keane T, Andriole G, Saad F, Iversen P, et al. The PREVAIL Study: primary outcomes by site and extent of baseline disease for enzalutamide-treated men with chemotherapy-naïve metastatic castration-resistant prostate cancer. *Eur Urol* 2016;70:675–83.