Ther Adv Urol
2018, Vol. 10(10) 305–315
DOI: 10.1177/1756287218786160

Abiraterone in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: a systematic review of 'real-life' studies

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Abstract

Background: To assess the efficacy and safety of treatment with abiraterone acetate (AA) in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (mCRPC) in the 'real-life' setting.

Methods: Data acquisition on the outcomes of the use of AA in chemotherapy-naive patients with mCRPC was performed by a MEDLINE comprehensive systematic literature search using combinations of the following key words: 'prostate cancer', 'metastatic', 'castration resistant', 'abiraterone', 'real life', and excluding controlled clinical trials (phase II and III studies). Identification and selection of the studies was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria. Outcomes of interest were overall survival (OS), progression-free survival (PFS), 12-week 50% reduction in prostate-specific antigen (PSA), and grade 3 and higher adverse events. Data were narratively synthesized in light of methodological and clinical heterogeneity.

Results: Within the eight identified studies that fulfilled the criteria, a total of 801 patients were included in the meta-analysis. Baseline PSA ranged between 9.5 and 212.0 ng/ml. Most of the patients had bone metastases. Duration of treatment with AA was longer in the studies with lower baseline PSA levels. The median OS ranged between 14 and 36.4 months. The PFS, assessed according to different definitions, ranged from 3.9 to 18.5 months. A 50% PSA reduction at 12 weeks was reached by a variable percentage of patients ranging from 36.0% to 62.1%. Finally, the rate of grade 3 and higher adverse events was reported in three studies and ranged from 4.4% to 15.5%.

Conclusions: Despite the high grade of heterogeneity among studies, treatment with AA seems to ensure good survival outcomes in the 'real-life' setting. However, prospective studies based on patients' characteristics being more similar to 'real-life' patients are necessary.

Keywords: abiraterone acetate, chemotherapy, metastatic castration-resistant prostate cancer, real-life studies

Received: 22 April 2018; accepted in revised form: 6 June 2018.

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Introduction

Prostate cancer is the second most common cancer in men, estimated to account for almost one in five new cancer diagnoses in 2018.[1] PC screening has been associated with an increase in the detection of localized, low-risk disease and a significant decrease in the detection of upfront metastatic disease.[2]

Patients with a new diagnosis of metastatic prostate cancer (mPC) have a median survival of 42 months.[3] In mPC, continuous androgen deprivation therapy (ADT) had been the standard of care from 1941 until recently, when two studies showed that combining ADT with six courses of docetaxel improves survival.[4,5] The duration of response to ADT is variable, with one third of patients progressing to metastatic castration-resistant prostate cancer (mCRPC) within 1–2 years of starting ADT.[6] The mCRPC state is defined by castrate serum testosterone (<50 ng/dl or 1.7 nmol/liter) while on ADT plus either biochemical or radiological progression.[7,8]

Since 2004, docetaxel chemotherapy had been the standard of care for patients with mCRPC.[9] Current treatment of mCRPC is based on several target drugs: none of these are curative, but have been shown to increase survival and delay tumour progression when used before or after docetaxel.[10,11] Abiraterone acetate (AA) is a potent and irreversible selective inhibitor of cytochrome P (CYP-17), which is a key enzyme in androgen synthesis. The resulting blockage in androgen production from the testicles, adrenals and the tumour itself increases the production of mineralocorticoids which may result in hypokalaemia, hypertension, fluid retention and oedema. For this reason, supplementary prednisone is recommended.[12] COU-AA-302 was the approval trial of AA in chemotherapy-naïve patients with mCRPC, showing an improved overall survival (OS).[13]

Little is known though about the efficacy of AA in the real-life scenario, considering the differences in patient selection, patient comorbidities, and other factors. The aim of this study was to review the current literature looking for 'real-life' studies on the use of AA in chemotherapy-naïve patients with mCRPC to evaluate its efficacy and safety. Furthermore, we compared the clinical setting studies with those of the COU-AA-302 trial. Finally, we aimed to summarize the possible reasons and confounders that could be addressed as causes of differences between the register of randomized clinical trials and 'real-life' studies.

Material and methods

Searching strategy and studies selection

Three independent researchers (MB, LC, MM) performed a search as of January 2018 using several online search engines such as PubMed (MEDLINE), Ovid, Scopus, Cochrane Libraries and GoogleScholar. Different combinations of keywords were used according to a free text protocol: 'prostate cancer', 'metastatic', 'castration resistant', 'abiraterone', 'real life'. Authors also looked at references listed in the selected manuscripts or in review articles and meta-analyses. Moreover, authors expert in the field of prostate cancer (CDN, LS, PS and LC) were asked about their familiarity and opinion on certain articles on the specific topic. Date of publication was not used as an exclusion criterion. Conversely, the research was limited to manuscripts written in English. Controlled clinical trials (phase II and III studies) were excluded. We considered as 'real-life' studies all the observational studies outside the controlled clinical trial setting.

Selection criteria and study protocol were established prior to conducting the systematic review. The identification and selection of the studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria[14,15] (www.prisma-statement.org). PICO were defined as follows: population (P) of interest consisted of patients with mCRPC with no previous systemic therapies other than standard-of-care ADT, treated with AA 1000 mg once daily plus prednisone 5 mg twice a day until progression, death or unacceptable toxicity (I). Patients should have been treated in 'real-life' observational studies. 'Real-life' patients were compared (C) to those treated within the pivotal registration trial COU-AA-302. Outcomes (O) of interest were OS, progression-free survival (PFS), 12-week 50% prostate-specific antigen (PSA) decline rates and proportion of grade 3 and higher adverse events.

First, two independent authors (MB, FRT) reviewed article titles to ascertain if they met inclusion criteria. Then, abstracts and full-text articles underwent a more exhaustive assessment. Studies without primary data (i.e. reviews, commentaries and letters) were excluded, however references were screened for relevant cited manuscripts. A third author (LC) resolved discrepancies between the two authors who performed the literature research.

Data extraction

In an Excel (Microsoft, Redmond, WA, United States) spreadsheet the following items for each included study were recorded: first author's

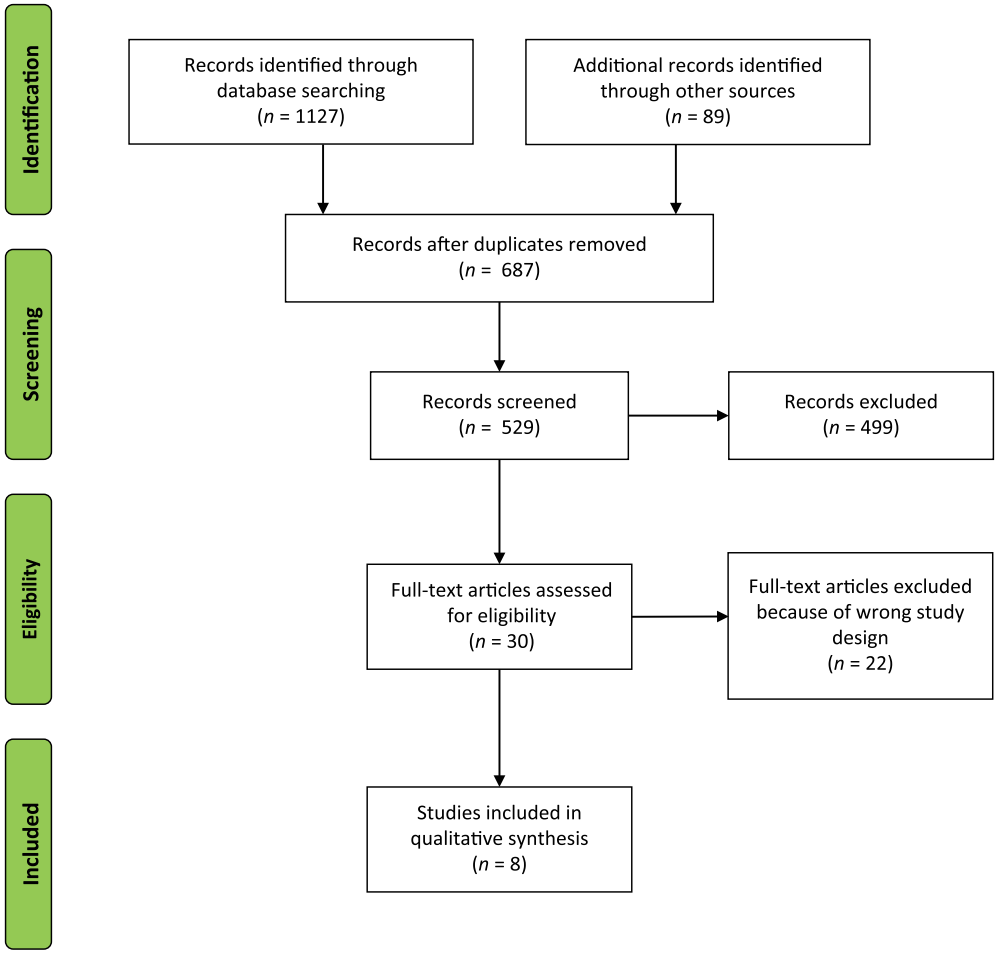

Figure 1. Preferred reporting items for systematic reviews and meta-analysis flow chart of study selection process.

name, year of publication and number of patients included. Baseline parameters of interest were total PSA, age at AA treatment initiation, Gleason score, duration of ADT before commencing AA, Eastern Cooperative Oncology Group (ECOG) performance status, presence and degree of pain and location of metastatic disease. Post-treatment characteristics of interest were the duration of AA treatment, total follow-up time, OS, 12-week 50% PSA decline, PFS duration and proportion of grade and higher 3 adverse events. Those variables were chosen according to the pivotal registration trial, as clinically meaningful indicators of treatment success and safety.

Level of evidence assessment

The authors systematically explored the overall quality of included studies. Two independent reviewers (MB, SR) assessed the level of evidence according to the Oxford Centre of Evidence Based Medicine.[16] Discrepancies were solved by a third reviewer (LC).

Data synthesis

Methodological and clinical heterogeneity of the included studies prevented us from performing a meta-analysis. Thus, we performed a narrative synthesis focusing on the outcomes of interest listed above.

Results

Studies characteristics

According to the aforementioned strategy, a total of eight studies were included (Figure 1) and compared with the COU-AA-302 trial (Tables 1–3).[17–24] The majority of the included studies (seven out

Table 1. Main characteristics of included real-life studies.

Investigator (year of publication)	Study period	Country	Study design	Number of patients
Rescigno et al.[18]	2006–2014	United Kingdom	Single centre	117
Thortzen et al.[19]	2012–2014	Denmark	Single centre	45
Rocha et al.[17]	2012–2013	Quebec (Canada)	Population based	204
Miyake et al.[20]	2014–2015	Japan	Multicentre	113
Poon et al.[21]	2011–2014	Hong Kong	Multicentre	58
McKay et al.[22]	2009–2013	United States of America	Multicentre	108
Cindolo et al.[23,25]	2013–2016	Italy	Multicentre	145
Manokumar et al.[24]	2012–2014	Ontario (Canada)	Single centre	11

of eight) were retrospective.[17–23] Out of all the studies, three were single centre,[18,19,24] four were multicentre,[20–23] and one study was based on administrative data[17] (Table 1). Most of the included studies were performed in western countries, specifically three in European countries,[18,19,23] three in North American countries,[17,22,24] and two of the included studies were carried out in Asian countries[20,21] (Table 1). Most of the studies were designed to compare the use of AA before *versus* after chemotherapy,[17,18,21,22] three studies were case series,[19,23,24] and only one study compared the efficacy of AA with enzalutamide.[20] The absence of a placebo arm, the differences in data collection and outcomes reporting reflect a low level of evidence (level of evidence 4).

Baseline patient's characteristics

Overall, 801 patients were treated in the included studies. The largest study included 204 patients,[17] while the smallest study included only 11 patients.[24] Age of patients at AA treatment initiation spanned between 71.3 and 80.0 years across the different studies. Across the studies, there were some differences in units of measurement of PSA[21,24] (Table 2). After conversion of these values, the baseline PSA level ranged between 9.5 and 212.0 ng/ml.

The initial Gleason score, reported in five of eight studies,[19–23] was at least 8 in a proportion of patients ranging from 27.6% to 84.1%, nevertheless in three studies the Gleason score was not reported (Table 2).[19–23]

The duration of ADT treatment before the mCRPC status, reported in four of eight studies,[19,20,22,23] ranged from 18.0 to 45.6 months. However, Cindolo and colleagues reported ADT duration as the proportion of patients with ADT therapy lasting over 12 months (77.9% of patients) (Table 2).[23]

With regards to the clinical status of patients starting AA, only six studies reported the performance status.[18–21,23,24] Performance status of 0–1 was reported in four studies[18,20,21,23] in a proportion of patients ranging from 62.1% to 96.6%. Moreover, Manokumar reported the ECOG scale score as a median value of 1 (range 1–2) (Table 2).[24]

As far as pain or symptoms assessment is concerned, only four of eight studies reported the proportion of patients with painful symptoms (from 12.8% to 38.6%).[18,20,21,23] Furthermore, most of the patients had bone metastases (from 43.6% to 79.6%).[17,18,20–23] Since an extreme variability in metastatic sites was recorded, we reported patients with metastases other than bone disease. Patients who had other sites of metastases with or without bone metastasis ranged between 46.5% and 66.0% (Table 2).

Outcomes description

The follow-up period of the selected studies ranged from 7.5 to 14.6 months, whereas the AA duration ranged from 5.3 to 16.0 months (Table 3). Treatment with AA was longer in the studies with lower baseline PSA levels. Indeed, Cindolo and

Table 2. Main baseline patient characteristics of included studies compared with pivotal randomized clinical trial.

Clinical characteristics	COU-AA 302	Rescigno	Thortzen	Rocha	Miyake	Poon	McKay	Cindolo	Manokumar
Number of patients	546	117	45	204	113	58	108	145	11
Median age	71.0 (5.0–77.0)	NA	71.3 (56.6–90.7)*	80.0 (IQR 76.0–84.0)	76.4$ (58.0–96.0)*	77.0 (56.0–92.0)*	60.0 (IQR 56.0–65.0)	76.5$ (SD 7.0)	78.6$ (SD 8.0)
Median baseline PSA (ng/ml)	42.0 (16.1–116.0)	61.0 (IQR 25.0–194.0)	156 (3–1672)*	NA	24.3$ (1.1–3402.7)*	212 (6.22–3095.0)*	9.5 (IQR 5.3–34.1)	17.4 (0.4–2100.0)*	23.9° (IQR 5.9–51.9)
Gleason score		NA		NA					NA
⩽7	46.0%		40.0%		15.9%	41.4%	55.0%		
⩾8	54.0%		60.0%		84.1%	27.6%	42.0%	57.5%	
Unknown						31.0%	4.0%	2.8%	
Duration of ADT (months)	40.4 (1.6–225.6)$	NA	45.6 (7.2–177.6)*	NA	18$ (0.8–185.2)*	NA	28 (IQR 15–49)	>12, *n* = 113 (77.9%)	NA
ECOG	NA		100% 1–2‡	NA			NA		Median
0–1		113 (96.6%)			88 (77.9%)	36 (62.1%)		125 (95%)	1 (1–2)*
⩾2		2 (1.7%)			25 (22.1%)	22 (37.9%)		6 (5%)	
Pain or symptoms			NA	NA			NA		NA
Yes	⩾2 34%	15 (12.8%)			20 (17.1%)	19 (32.8%)		56 (38.6%)	
No		90 (76.9%)			93 (82.3%)				
Metastases sites			NA						NA
Overall		105 (89.8%)		169 (82.8%)			97 (90%)		
Bone	51%	51 (43.6%)			90 (79.6%)	35 (60.3%)	71 (66%)	75 (53.5%)	
Other sites ± bones	49%	54 (46.2%)			54 (47.9%)	27 (46.5%)	72 (66%)	65 (44.8%)	

*Range.
$Mean.
‡All the patients had a performance status of 1 or 2; derived from the original article after measure unit conversion.
AA, abiraterone acetate; ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group Scale of Performance Status; IQR, interquartile range; NA, not assessed; PSA, prostate-specific antigen; SD, standard deviation.

Table 3. Main results of included studies compared with pivotal randomized clinical trial.

	COU-AA 302	Rescigno	Thortzen	Rocha	Miyake	Poon	McKay	Cindolo	Manokumar
Follow-up duration	49.2 (IQR 47.0–51.8)	14.6* (IQR 9.0–20.6)	9.9 (0.9–23.4)[$]	NA	8.6 (1.0–16.8)[$]	7.5 (1.0–24.6)[$]	NA	13.6 IQR (7.0–16.0)	NA
Time on AA	13.8 (IQR 8.3–27.4)	NA	5.3 (0.5–17.9)[$]	5.9	NA	6.8 (0.6–21.5)[$]	16.0	10.0 (1.0–35.0)[$]	NA
Median OS (95% CI)	34.7 (32.7–36.8)	36.4 (24.3–48.5)	16.6 (12.8–18.2)	14.0 (11–20)	Not reached	18.1 (9.9–25.0)	NA	26.5 (21.0–32.0)	NA
Median biochemical PFS (95% CI)	11.1	NA	3.9 (0.5–18.2)[$]	NA	9.0	NA	NA	NA	NA
Median radiological PFS (95% CI)	16.5	NA	7.1 (0.8–12.6)[$]	NA	NA	NA	NA	NA	NA
Median clinical PFS (95% CI)	33.4	NA	NA	NA	NA	6.7[‡] (4.5–14.7)	NA	18.5 (16.0–20.0)	NA
12-week 50% PSA decline	68.0%	47.9%	36.0%	NA	53.1%	62.1%	NA	49.5%	NA
Grade ⩾3 adverse events	290 (54%)	NA	0%	NA	5 (4.4%)	9 (15.5%)	NA	17 (11.7%)	NA

Time is expressed in months when not indicated otherwise.
*Range.
[$]Median follow up was calculated on both pre- and post-chemotherapy populations.
[‡]Median PFS was evaluated according to Prostate Cancer Clinical Trials Working Group (PCWG-2) criteria, including biochemical, radiological, and clinical progression.
AA, abiraterone acetate; CI, confidence interval; IQR, interquartile range; NA, not assessed; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.

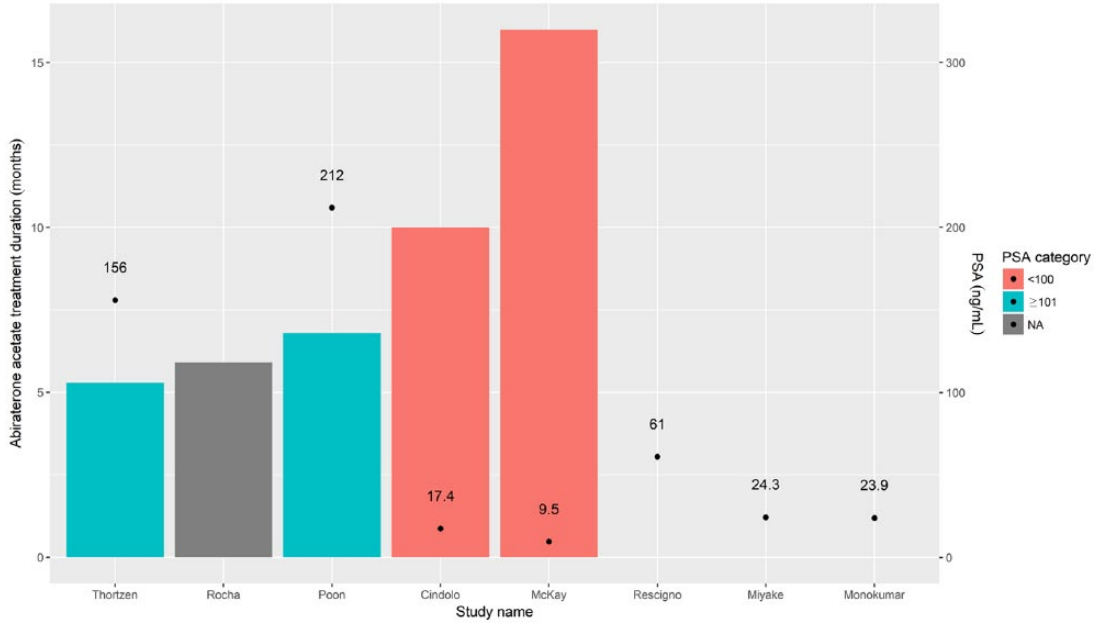

Figure 2. Bar graph showing the abiraterone acetate treatment duration in each study as a bar. Three studies do not report data about abiraterone acetate treatment duration. Dots represent the baseline prostate-specific antigen (PSA) levels. Blue bars represent the abiraterone acetate treatment duration in those studies with baseline PSA level ⩾100 ng/ml, while red bars represent the abiraterone acetate treatment duration in those studies with baseline PSA level <100 ng/ml. The grey bar represents the only study that reported the abiraterone acetate treatment duration but not the baseline PSA level. Studies with longer abiraterone acetate treatment duration had lower baseline PSA level. NA, not assessed.

colleagues as well as McKay and colleagues reported AA exposure length of 10.0 and 16.0 months, with baseline PSAs of 17.4 and 9.5 ng/ml, respectively.[22,23] Conversely, Thortzen and colleagues and Poon and colleagues reported AA treatment length of 5.3 and 6.8 months, with baseline PSA of 156 and 212 ng/ml, respectively[19,21] (Figure 2).

OS varied across different studies. Miyake reported that 76.5% reached the 2-year OS and that the median OS was not reached; in the other studies the median OS ranged between 14 and 36.4 months[17–23] (Table 3). The PFS was assessed using different definitions (e.g. radiological, biochemical, clinical); independently from the definitions the PFS ranged from 3.9 to 18.5 months. However, four studies did not report any PFS assessment[17,18,22,24] (Table 3).

Overall five studies reported rates of 50% PSA decline at 12 weeks.[18–21,23] At 12 weeks a more than 50% PSA decline was reached in a variable percentage of patients ranging from 36% to 62.1%. Finally, the percentage of grade 3 and higher adverse events was reported in three studies[20,21,23] and ranged between 4.4% and 15.5%. Thortzen and colleagues reported that no patient stopped the treatment due to side effects.[19]

Discussion

One of the main aims of clinical research is to assess the effectiveness of a treatment outside the context of clinical trials. In other words, clinical researchers attempt to test if the findings of a clinical trial could be generalized in the 'real-life' setting.[26] The aim of our study was to summarize the evidence from 'real-life' studies regarding the efficacy and safety of AA in patients with mCRPC before chemotherapy and to highlight the main differences with the registration trial. The COU-AA-302 trial was the approved study of AA in chemotherapy-naïve patients: 1088 men with mCRPC were randomized to AA or placebo plus 5 mg prednisone. Within a median follow up of 49.2 months the median OS was longer for the AA group compared with the placebo group by 4.4 months (34.7 *versus* 30.3 months), with a hazard ratio of 0.81 in favour of AA.[13]

Our systematic review of the literature showed several interesting findings and highlighted

several differences between the COU-AA-302 trial and the 'real-life' studies. First, the level of evidence derived from 'real-life' studies is of low grade. We would like to emphasize that this result was expected and it is not at all surprising. However, most of the included studies aimed to analyse aspects that were not taken into consideration in the registration study. Indeed, most of the studies were designed to compare the use of AA before *versus* after chemotherapy regimens,[17,18,21,22] three studies were just case series,[19,23,24] and one study compared the efficacy of AA with enzalutamide.[20] The main limitation of the included studies was the small number of patients, indeed the largest study managed to include less than half of the patients of the COU-AA-302 trial (204 *versus* 546 patients).[13,18]

It is also interesting to note that the enrolment of patients spanned from 2006 to 2016 across the different studies. In the COU-AA-302 trial the randomization of patients started as of April 2009 and the final results were published in 2015.[13] This may reflect the use of AA before its efficacy was proved from a pivotal study. Moreover, the use of AA outside of the clinical trial eligibility criteria (as for compassionate use, or in those patients unfit for chemotherapy) was reported.[23,25]

However, it is well known that the patient population in real-life studies can be more complex than that of clinical trials: this difference may result in an overestimation of endpoint outcomes.[27] Furthermore, the generalizability of clinical trial findings could be questioned based on the strict inclusion criteria of pivotal trials that may be difficult to meet in real life.[26,27]

Our review showed several differences in patient demographics. Specifically, most of the studies included patients significantly older than those included in the pivotal trial;[17,20,21,23,24] conversely one study included younger patients.[22] Similarly, several oncological baseline characteristics meaningfully differed between 'real-life' studies and the pivotal study. Indeed, baseline PSA was generally higher at the initiation of AA treatment in 'real-life' studies. Moreover, the proportion of patients with Gleason scores greater than eight was also more represented in 'real-life' studies than in the pivotal trial. Furthermore, differences in the length of ADT before starting AA therapy were also not negligible. Indeed the duration of ADT varied in a clinically meaningful fashion across the included studies. All these differences may have an impact on response to treatment with AA. McKay and colleagues showed that a lower PSA at AA initiation and a longer duration of ADT were associated with longer duration of treatment with AA in univariate analysis. After adjustment for all covariates, the duration of ADT was still associated with longer treatment with AA.[22] This is in agreement with our results that showed longer median AA duration in studies that included patients with lower baseline PSA.

In addition, in the 'real-life' setting the proportion of patients who reported pain or were symptomatic at diagnosis ranged between 12.8% and 38.6% within four studies that reported this information.[18,20,21,23] It is of note that in the pivotal trial only asymptomatic or mildly symptomatic patients were included. In the final population, 34% of patients reported Brief Pain Inventory Short Form scores of at least 2. A direct comparison between the pivotal study and the 'real-life' setting is not possible, since the assessment of pain or symptoms was not standardized in all the included studies.[18,20] However, it is of interest that across the different cohorts the proportion of symptomatic patients widely varies. The importance and the effect of pain was deeply explored by Cindolo and colleagues in two different analyses of the same database.[23,25] Initially the authors reported a correlation between the patient's satisfaction with treatment and the presence of pain, showing that the patient's treatment satisfaction was also related to PFS.[25] In a successive analysis, the authors also showed a direct correlation between pain and PFS as well as OS.[23]

The aforementioned differences between the pivotal trial and 'real-life' studies with regard to inclusion criteria invariably exert differences in terms of outcomes of interest. Indeed, generally shorter AA duration, OS and PFS were recorded in 'real-life' studies. Such observations could not be considered exclusive of AA treatment.[28] The efficacy–effectiveness gap is a well recognized entity, which describes the difference between outcomes in clinical trials and clinical practice.[28] This gap was described in the setting of prostate cancer,[28] as well as in the setting of other malignancies.[29] Such differences may explain the lower efficacy of AA treatment in the 'real-life' setting compared with pivotal trials. Previously, several authors have questioned the generalizability of results deriving from studies of highly selected populations to the average patient and even more

to clinically complex patient populations such as elderly patients or those with multiple comorbidities.[29] Our review also raised questions about the power of 'real-life' data analyses that could account for only a few hundred or even fewer patients. Moreover, data maturity should be acknowledged as a limitation of the included 'real-life' studies, with generally shorter follow up than the pivotal trial and with one study not even able to reach the median OS.[20] However, if 'real-life' studies show smaller effectiveness of treatment in small cohorts, such as those of included studies, population-based studies showed that the marginal survival advantage described in pivotal studies could be better represented in larger populations. Indeed, Bandini and colleagues relied on the Surveillance Epidemiology and End Results (SEER) registry to test the stage migration effect on oncological survival in the setting of mPC. The authors showed, after propensity score matching, an overall mortality-free survival advantage of 3 months in patients more recently studied (patients with *de novo* mPC diagnosed between 2009 and 2014 *versus* those diagnosed between 2004 and 2008).[30] The investigators concluded that the improved survival could be related to the introduction of several systemic agents for mCRPC.[30]

A similar consideration could also apply to the last two outcomes of interest in our review, specifically the 12-week 50% PSA decline and the proportion of grade 3 and higher adverse events. Our review showed a lower 12-week 50% PSA decline rate than the pivotal study, however lower rates of grade 3 and higher adverse events were also shown. The importance of this difference on survival outcomes could not be directly addressed in our analysis, however the effect of PSA response on OS was previously described.[18] The importance of symptoms and adverse events on PFS and OS has also been previously analysed.[23,25]

In summary, our analysis has shown clinically meaningful differences between randomized clinical trial and 'real-life' studies in the setting of AA treatment in chemotherapy-naïve patients with mCRPC. These differences were about inclusion criteria, outcome definition, and survival. Despite the low level of evidence obtained in the included studies, they brought information to the literature that was not included in the pivotal study. However, future prospective observational studies should aim to fill the efficacy–effectiveness gap and to give a deeper insight into patient selection treatment modality and timing. Such large prospective trials should include a broad spectrum of patients as in clinical practice and rely on well established criteria to define the outcomes of interest.[28,31] Moreover, the availability of extensive data, and the ease and low cost of performing observational studies, even retrospective, based on large populations, will in the future be one of the most important benchmarks to test the real efficacy of several treatment strategies, including the use of AA in mCRPC.[32]

In addition, future studies may compare the use of AA with other drugs such as enzalutamide.[33] Indeed, the only included study that tested the hypothesis of differences in terms of survival and tolerability after AA *versus* enzalutamide in chemotherapy-naïve patients with mCRPC concluded that both the medications were effective and tolerable, despite some statistically significant differences in terms of PSA response, PFS, and adverse events.[20]

Furthermore, when comparing the use of AA in the pre- *versus* post-chemotherapy setting, the results are contrasting. Indeed, a study showed statistically significant differences in terms of efficacy and survival when AA was administered in the pre- *versus* post-chemotherapy setting.[18] Otherwise, other studies showed no differences.[17,21] Interestingly, the use of chemotherapy prior to AA was inversely associated with AA therapy duration.[22]

Several limitations of our study should be acknowledged. First, most of included studies are based on retrospective analysis. Second, not all studies present in the literature about real-life management of AA are characterized by the same variables analysed and the same units of measurements. Third, the number and type of patients enrolled in these real-life studies are significantly and meaningfully different from those included in the COU-AA-302. However the study reflects the clinical situation in which patients with mCRPC are managed with AA. Nevertheless, the strength of our analysis is that this is the first literature review in which data from 'real-life' studies have been collected and summarized.

Conclusion

AA management in patients with mCRPC seems to ensure good survival outcomes. However,

several differences between the pivotal study and 'real-life' studies should be acknowledged. Such differences highlight the need for observational studies that include large numbers of patients and better reflect 'real-life' patients.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Cindolo L and De Nunzio C are consultant for Janssen Cilag.

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