CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Androgen Receptor Targeted Agents for Castration Resistant Prostate Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	June 6, 2019
Report Length:	30 Pages

CADTH

Authors: Khai Tran, Suzanne McCormack

Cite As: Androgen Receptor Targeted Agents for Castration Resistant Prostate Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness. Ottawa: CADTH; 2019 Jun. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

AA	Abiraterone acetate
ADT	Androgen deprivation therapy
AEs	Adverse events
ALT	Alanine amino transferase
AST	Aspartate amino transferase
ARTA	Androgen receptor targeting agent
BPI-SF	Brief Pain Inventory-Short Form
CI	Confidence interval
CTX	Cabazitaxel
CRPC	Castrate resistant prostate cancer
DTX	Docetaxel
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EOD	Extent of disease
ENZ	Enzalutamide
FACT-P	Functional Assessment of Cancer Therapy-Prostate
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	Hazard ratio
HTA	Health technology assessment
JBI	Joanna Briggs Institute
LDH	Lactate dehydrogenase
MA	Meta-analysis
mCRPC	Metastatic castration-resistant prostate cancer
NA	Not applicable
NR	Not reported
OR	Odds ratio
OS	Overall survival
P	Prednisone
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Prostate-specific antigen
QoL	Quality of life
RCT	Randomized controlled trial
SR	Systematic review

Context and Policy Issues

Prostate cancer is the most common cancer in men and is the fourth most common cancer in Canada.[1] Approximately 1 in 7 men will be diagnosed with prostate cancer in their lifetime, and 1 in 27 will die from the disease.[1,2] However, the age-standardized mortality rate for all stages of prostate cancer have decreased by an average of 2.9% per year, or 41.0% from 1995 to 2012.[3,4] The majority (75%) of diagnosed prostate cancer are stage I or stage II (localized), and the age-standardized incidence rate of these cancer stages have decreased by 3.2% per year from 2005 to 2015.[4] The age-standardized incidence rate of stage III and IV cancers have remained relatively unchanged.[4]

Androgen deprivation therapy (ADT) has been the mainstay treatment for metastatic prostate cancer.[5] Current ADT approaches include surgical castration or medical castration using a gonadotropin releasing hormone agonist with or without an anti-androgen drug.[6] Although over 80% of patients respond to ADT initially, nearly all eventually develop progressive disease following castration, a lethal stage known as metastatic castration-resistant prostate cancer (mCRPC).[7] In 2004, docetaxel (DTX) was the first chemotherapy approved by the US Food and Drug Administration for treatment of mCRPC.[8,9] Since then, five newly developed agents were approved including a second generation taxane cabazitaxel (CTX),[10] cellular immunotherapy sipuleucel-T,[11] radiopharmaceutical radium-223,[12] and two androgen receptor-targeted agents (ARTA) abiraterone acetate (AA)[13-15] and enzalutamide (ENZ).[16,17]

Since ARTA have been demonstrated by recent studies in improving overall survival (OS) in both chemotherapy-pretreated and chemotherapy-naïve patients with mCRPC, both AA and ENZ have been approved as first-line treatment, instead of DTX.[13-17] However, some patients have rapidly progressed on ARTA treatments despite the initial clinical effectiveness.[18] After progression on first-line ARTA, it was unclear which subsequent therapy, such as second-line chemotherapy, an alternative ARTA, or an alternative ARTA with chemotherapy in between, would improve clinical outcomes.

The aim of this report is to review the comparative clinical effectiveness and cost-effectiveness of varying treatment sequences of ARTA in patients with CRPC.

Research Questions

1. What is the comparative clinical effectiveness of varying treatment sequences of androgen receptor targeted agents in patients with castrate-resistant prostate cancer?
2. What is the comparative cost-effectiveness of varying treatment sequences of androgen receptor targeted agents in patients with castrate-resistant prostate cancer?

Key Findings

Based on a single well conducted randomized controlled trial, patients who failed on first-line treatment with enzalutamide, subsequent treatment with abiraterone had low response rates, and the combination of enzalutamide and abiraterone was not indicated, owing to observed adverse effects. Likewise, evidence from very low quality non-randomized studies suggests that treatment sequence of enzalutamide-to-abiraterone is less favorable than abiraterone-to- enzalutamide sequence. Also, from very low quality non-randomized studies, subsequent chemotherapy with taxanes appeared to be more effective than alternative second-line androgen receptor targeting agents in treatment of chemotherapy-naïve metastatic castrate-resistant prostate cancer patients who progressed on first-line androgen receptor targeting agents. Due to substantial limitations of the non-randomized studies, these findings should be considered as preliminary and hypothesis generating. No comparative cost-effectiveness studies were identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Androgen Receptor Targeted Agents (ARTA) (including berdazimer sodium, ralaniten acetate, enzalutamide, apalutamide, abiraterone, darolutamide, proxalutamide, and seviteronel) and castration resistant prostate cancer (mCRPC). Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials, controlled clinical trials, or any other type of clinical trial, and economic studies. The search was also limited to English language documents published between January 1, 2014 and May 10, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with castrate-resistant prostate cancer (non-metastatic or metastatic)
Intervention	Treatment sequences of at least two androgen receptor targeted agents (e.g., enzalutamide, apalutamide, or abiraterone combined with prednisone, darolutamide), with or without chemotherapy
Comparator	Other androgen receptor targeted agent sequences (e.g., ARTA to another ARTA, ARTA to chemotherapy to ARTA), sequences with only one ARTA (e.g., ARTA then chemotherapy), chemotherapy alone (e.g., docetaxel, cabazitaxel), or radioisotope alone (e.g., radium-223)
Outcomes	Q1: Clinical effectiveness (e.g., progression-free survival, overall survival, response rate, quality of life, time to prostate-specific antigen progression); adverse events; discontinuation Q2: Cost-effectiveness (e.g., QALY, ICER)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-randomized studies, and economic evaluations

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2014.

Critical Appraisal of Individual Studies

The critical appraisal checklists of the Joanna Briggs Institute were used to assess the quality of the included RCTs[19] and non-randomized studies.[20] Summary scores were not

calculated for the included studies; rather, a review of the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 561 citations were identified in the literature search. Following screening of titles and abstracts, 536 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of the 26 potentially relevant articles, 13 publications were excluded for various reasons, while 13 publications including one RCT and 12 non-randomized studies met the inclusion criteria and were included in this report. No economic studies were identified. Appendix 1 presents the PRISMA flowchart[21] of the study selection.

Summary of Study Characteristics

The characteristics of the identified RCT[22] and non-randomized studies[23-34] are presented in Appendix 2.

Study Design, Country of Origin, and Year of Publication

The RCT (PLATO study)[22] was conducted by authors from North America, Europe and Australia, and was published in 2018. The 12 non-randomized studies[23-34] were all retrospective chart reviews, which were conducted by authors from Japan[23,24,26,28-30] and USA,[25,27,31-34] and were published in 2018, [23-25] 2017,[26-32] 2015[33] and 2014.[34]

Population

Ten studies[22-26,28,29,31,32,34] included patients with chemotherapy-naïve mCRPC and three studies[27,30,33] included mCRPC patients previously treated with or without chemotherapy. All patients progressed after first line ARTA and received subsequent treatments (e.g., alternative ARTA, taxane, or taxane followed by alternative ARTA). In all studies, patients had median age of approximately 70 years. Except the RCT, not all patient characteristics in the non-randomized studies were balanced between groups.

Interventions and Comparators

The sequences of treatment in the intervention groups were ENZ-to-ENZ + AA, AA-to-ENZ, and ARTA-to-ARTA. On the Sequence ARTA-to-ARTA, patients who progressed on first-line (i.e., AA or ENZ) received alternative ARTA (i.e., ENZ or AA).

The sequences of treatment in the comparator groups were ENZ-to-AA, ARTA-to-taxane (CTX or DTX), or ARTA-to-taxane-to-ARTA.

Outcomes

The main outcomes evaluated in the included studies were combined progression-free survival (PFS), prostate-specific antigen (PSA) response, time to PSA progression or PSA-PFS, and overall survival (OS).

Combined PFS was defined as the time from the start date of first-line treatment to the date on which disease progression (clinical or radiographic) after treatment with a second-line therapy was observed.

PSA response was defined as the proportion of patients achieved a decline of PSA by ≥ 30% or ≥ 50% from baseline from each line therapy.

Time to PSA progression (also referred as total PSA-PFS) was the sum of time from initiation of each line therapy to PSA progression (defined as a 25% increase in PSA from baseline or nadir PSA).

OS was defined as the time from initiation of the first-line therapy to all-caused death.

Data Analysis and Synthesis

The RCT[22] applied sample size calculation and analyzed data using the intention-to-treat approach. All non-randomized studies[23-34] performed appropriate statistical analyses for comparisons among treatment groups.

Funding

Two studies[22,31] were financially supported by pharmaceutical companies, two studies[27,33] received support from public funding, and nine studies.[23-26,28-30,32,34] did not report the source of funding.

Summary of Critical Appraisal

Quality assessments of the RCT[22] (Table 3) and of the non-randomized studies[23-34] (Table 4 and Table 5) are presented in Appendix 3.

In the RCT,[22] participants were truly randomized to treatment groups, treatment groups were similar at baseline, participants and treatment providers were blinded to treatment assignment, study groups were treated identically other than the intervention of interest, intention-to-treat analysis was applied, outcomes were measured in the same way for both groups using reliable methods, and appropriate statistical analyses were used. It was unclear if allocation to treatment was properly concealed, and whether or not outcomes assessors were blinded to treatment assignment. The quality of this RCT was considered as high.

All non-randomized studies[23-34] provided appropriate research questions and objectives, had at least one control group, measured the outcomes of participants in the same and reliable way, and used appropriate statistical analysis. In all studies, [23-34] there were some differences in certain patient characteristics among treatment groups, and it was unclear if participants received similar treatment and care other than the exposure or intervention of interest. Hence, it is possible, that the effect may be explained by the differences between participants or by other exposures or treatments, rather than the intervention of interest. The quality of all included non-randomized studies was considered as very low.

Summary of Findings

Clinical Effectiveness and Safety

The main findings and conclusions of the included studies[22-34] (Table 6) are presented in Appendix 4.

Comparison 1: ENZ-to-ENZ + AA versus ENZ-to-AA

In the RCT,[22] patients with chemotherapy-naïve mCRPC who progressed on first-line ENZ were randomly assigned to receive a combination of ENZ and AA or AA alone as second-line therapy.

Combined PFS

The median of combined PFS was 5.7 months in the ENZ-to-ENZ + AA and 5.6 months in the ENZ-to-AA sequence of treatment groups. No statistically significant difference between groups was observed.

Time to PSA progression

Both groups had similar median time to PSA progression (P = 0.45).

PSA response

During the second-line therapy, 1% of the ENZ-to-ENZ + AA group and 2% of the ENZ-to-AA group had a confirmed decline of ≥ 50% in baseline PSA.

Other outcomes

There were no significant differences between groups for other outcomes such as rate of pain progression, objective response rate, time to first use of subsequent antineoplastic therapy, and time to degradation of FACT-P score.

Safety

Patients in the ENZ-to-ENZ + AA group had higher incidence of grade 3 hypertension and elevated liver enzymes (alanine amino transferase, aspartate amino transferase) than those in the ENZ-to-AA group.

Comparison 2: AA-to-ENZ versus ENZ-to-AA

Six retrospective chart review studies[23,27,29,30,32,34] compared the clinical outcomes between AA-to-ENZ and ENZ-to-AA sequential treatment in mCRPC patients. In these studies, patients who failed on first-line ARTA (AA or ENZ) received alternative second-line ARTA (ENZ or AA).

Combined PFS

The median combined PFS was significantly longer in the AA-to-ENZ compared to ENZ-to-AA sequence of treatment as shown in three studies.[27,29,30] Two studies[23,34] found no significant difference in median combined PFS between groups.

Time to PSA progression

In three studies,[27,30,32] the sum of time from initiation of each ARAT agent to PSA progression was significantly longer in the in the AA-to-ENZ compared to ENZ-to-AA sequence of treatment. One study[34] found no significant difference in time to PSA progression between groups.

PSA response

Four studies[23,27,29,32] found that PSA response rate was not significantly different between AA and ENZ in the first-line therapy, but significant differences were observed to second-

line treatment (i.e., higher for ENZ compared to AA). Total PSA response rate was significantly higher in the in the AA-to-ENZ compared to ENZ-to-AA sequence of treatment. One study[34] found no significant difference in PSA response between groups.

Overall Survival

Five studies[23,27,29,30,32] found no significant difference in OS between AA-to-ENZ and ENZ-to-AA sequence groups.

Safety

One study[30] reported adverse events and found no differences in safety profiles between treatment sequences.

Comparison 3: ARTA-to-ARTA versus ARTA-to-Taxane (DTX or CTX)

Four retrospective chart review studies[24-26,31] compared the clinical outcomes between ARTA-to-ARTA and ARTA-to-Taxane sequential treatment in patients with chemotherapy-naïve mCRPC. In the ARTA-to-ARTA sequence of treatment, patients who progressed on first-line ARTA (AA or ENZ) were treated with alternative second-line ARTA (ENZ or AA). In the ARTA-to-Taxane sequence, patients who progressed on first-line ARTA (AA or ENZ) were put on second-line chemotherapy with DTX or CTX. One study[33] with small sample size (n = 9 in AA-to-ENZ; n = 13 in AA-to-DTX) compared the clinical outcomes between AA-to ENZ and AA-to-DTX without using statistical analysis for comparisons.

Combined PFS

One study[26] reported combined PFS as an outcome, and found that ARTA-to-DTX had significantly longer combined PSF compared to the ARTA-to-ARTA sequence of treatment. One study,[33] without statistical comparison, also reported a longer combined PFS in the AA-to-DTX group compared to AA-to-ENZ group.

Time to PSA progression

The time to PSA progression was reported in two studies[24,25] and was significantly longer in the ARTA-to-Taxane (DTX or CTX) compared to ARTA-to-ARTA sequence of treatment. One study,[33] without statistical comparison, also reported a longer time to PSA progression in the AA-to-DTX group compared to AA-to-ENZ group.

PSA response

Three studies[24,25,31] found that PSA response rate to the second-line therapy was significantly higher with DTX or CTX compared to ARTA, after failure of initial ARTA. One study[26] showed that the combined PSA response rate to both lines of treatment was significantly higher in the ARTA-to-DTX compared to ARTA-to-ARTA sequence of treatment. One study,[33] without statistical comparison, also reported a higher PSA response rate in the AA-to-DTX group compared to AA-to-ENZ group.

Overall Survival

The median OS duration was shown to be significantly higher in the ARTA-to-DTX group than the ARTA-to-ARTA group in one study, [24] but not significantly different between groups in three studies.[25,26,31] One study,[33] without statistical comparison, reported a longer OS duration in the AA-to-DTX group compared to AA-to-ENZ group. Two studies[25,31] performed subgroup analyses and found that patients with poor prognosis (e.g., low

hemoglobin, high lactate dehydrogenase, and intermediate-to-high Halabi risk scores) receiving second-line chemotherapy had significantly longer OS compared to those receiving second-line ARTA.

Comparison 4: ARTA-to-ARTA versus ARTA-to-Taxane-to-ARTA

One retrospective chart review study[28], with an imbalanced number of patients in each group (n = 173 in ARTA; n = 102 in ARTA-to-ARTA; n = 27 in ARTA-to-Taxane-to-ARTA), investigated whether the use first-line ARTA with or without subsequent chemotherapy could affect the efficacy of the second-line ARTA. Between ARTA-to-ARTA and ARTA-to-Taxane-to-ARTA, there were no significant differences between groups with respect to PSA response rate and time to PSA progression. However, patients receiving subsequent ARTA with or without taxane therapy in between had significantly less clinical benefit than those in the ARTA only group, suggesting cross-resistance between ARTA.

Cost-Effectiveness

No comparative cost-effectiveness studies of different treatment sequences of ARTA in patients with mCRPC were identified; therefore, no summary can be provided.

Limitations

Except the well-conducted RCT, the quality of clinical evidence derived from non-randomized studies, which are of retrospective design, was considered as very low as the studies may have been subjected to multiple biases, including selection bias and information bias. Some patient characteristics (e.g., age, baseline PSA, blood test parameters, time from CRPC to first-line treatment with ARTA, baseline EOD score, time to second line therapy) were significantly different between groups in most studies, together with significant imbalance with respect to sample size in each group in four studies,[26-28,31] which might result in heterogeneous baseline measurements. The cohorts were relatively small, with no sample size calculation; therefore, the analyses might be underpowered to detect true differences, if any difference existed. The observation period might be too short to detect if there was any difference in terms of OS. It was unclear how first-line therapy was chosen that would impact subsequent therapy. Some factors, including disease severity and rate of disease progression, might have biased the physician in choosing sequential treatment regimens. As therapy information was not reported, administration doses of ARTA and taxanes might vary between groups and among studies, which could have affected the clinical outcomes. Due to limited data availability in retrospective design, not all potential confounding variables could be properly controlled in data analysis. Treatment-related adverse events were not reported in most studies, therefore the comparative safety among treatment sequences was unclear. The findings might not be generalizable to the Canadian context as no identified studies were conducted in Canada.

Conclusions and Implications for Decision or Policy Making

For comparative clinical effectiveness, one RCT[22] and 12 non-randomized studies[23-34] (all of retrospective design) were identified. No comparative cost-effectiveness studies were identified.

Four sets of comparative sequences of ARTA in the treatment of patients with mCRPC were identified and comprised: 1) ENZ-to-ENZ + AA versus ENZ-to-AA; 2) AA-to-ENZ

versus ENZ-to-AA; 3) ARTA-to-ARTA versus ARTA-to-Taxane (DTX or CTX); 4) ARTA-to-ARTA versus ARTA-to-Taxane-to-ARTA.

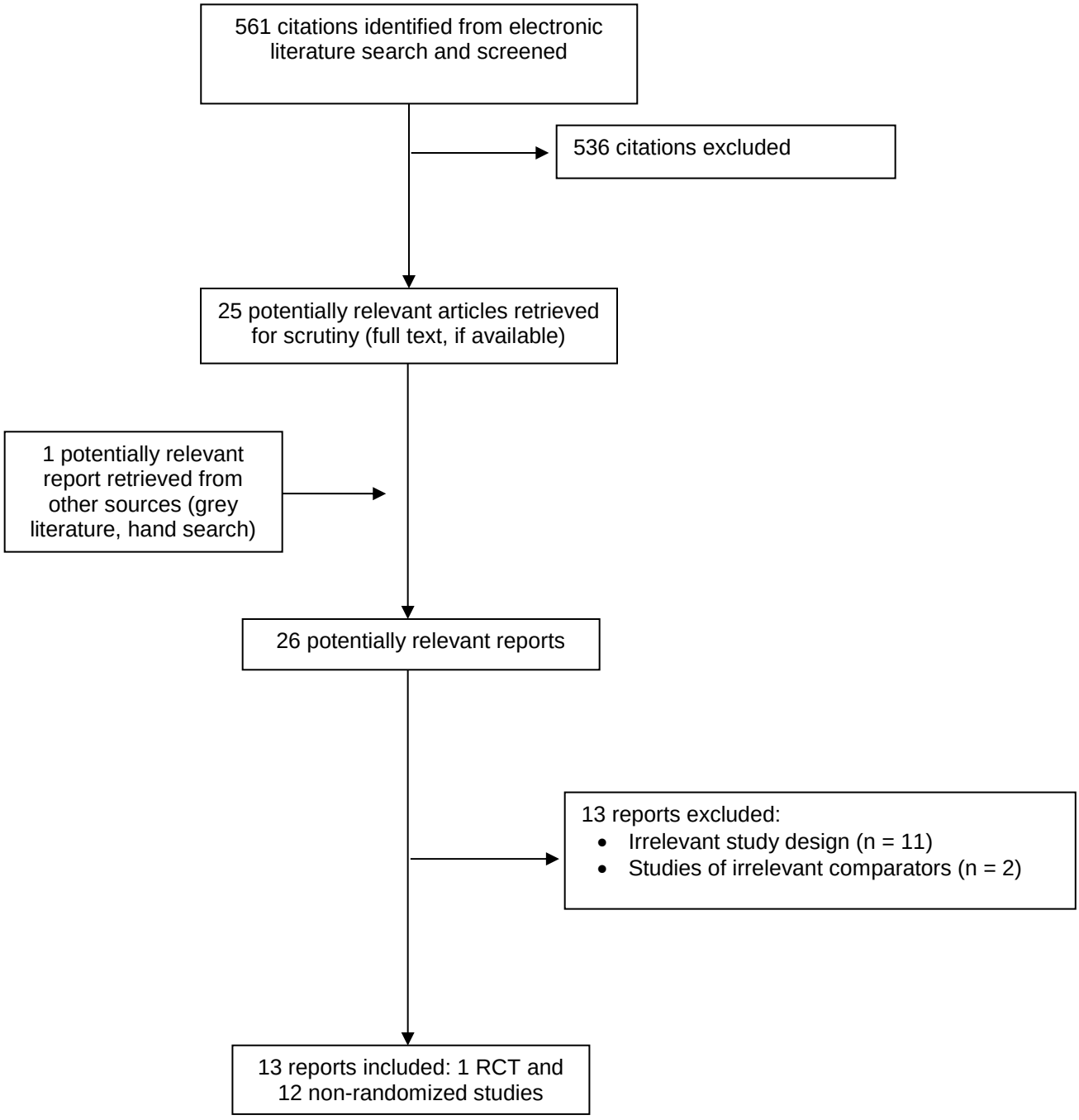
Results from an RCT suggest that AA and prednisone had low response rates in mCRPC patients who progressed after treatment with ENZ, and the combination of ENZ and AA given as second-line therapy resulted in a greater amount of patients experiencing hypertension and elevated liver enzymes. Retrospective studies provided very low quality evidence for the remaining comparative sequences. Between AA-to-ENZ and ENZ-to-AA sequence of treatment, AA-to-ENZ sequence appeared to be more favorable than ENZ-to-AA sequence in patients with mCRPC regarding the improved clinical outcomes such as combined PFS, time to PSA progression and PSA response rate, but not OS. Between ARTA-to-ARTA and ARTA-to-Taxane (DTX or CTX), ARTA-to-Taxane appeared to be more effective than ARTA-to-ARTA treatment sequence in patients with chemotherapy-naïve mCRPC regarding the improved clinical outcomes such as combined PFS, time to PSA progression and PSA response rate. Patients with poor prognosis receiving second-line chemotherapy might have improved OS compared to those receiving ARTA. One retrospective chart review did not find any differences between ARTA-to-ARTA and ARTA-to-Taxane-to-ARTA respect to PSA response rate and time to PSA progression. Given the aforementioned limitations of the retrospective studies, their findings should be considered as preliminary and hypothesis generating. Prospective controlled trials with high degree of internal validity and adequate power are required to draw definitive conclusions.

References

1. Prostate cancer in Canada. Ottawa (ON): Public Health Agency of Canada; 2017: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/cancer/prostatecancer-eng.pdf. Accessed 2019 Jun 3.
2. Fradet Y, Klotz L, Trachtenberg J, Zlotta A. The burden of prostate cancer in Canada. Can Urol Assoc J. 2009;3(3 Suppl 2):S92-s100.
3. Ellison L. Prostate cancer trends in Canada, 1995 to 2012. Health at a Glance. 2016. https://www150.statcan.gc.ca/n1/en/pub/82-624-x/2016001/article/14548-eng.pdf?st=FtULtfam. Accessed 2019 Jun 3.
4. LeBlanc AG, Demers A, Shaw A. Recent trends in prostate cancer in Canada. Health Rep. 2019;30(4):12-17.
5. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972;22(4):232-240.
6. Komura K, Sweeney CJ, Inamoto T, Ibuki N, Azuma H, Kantoff PW. Current treatment strategies for advanced prostate cancer. Int J Urol. 2018;25(3):220-231.
7. Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nat Clin Pract Urol. 2009;6(2):76-85.
8. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-1512.
9. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513-1520.
10. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-1154.
11. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411-422.
12. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-223.
13. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005.
14. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138-148.
15. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive 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(2):152-160.
16. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-1197.
17. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424-433.
18. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med. 2014;371(11):1028-1038.
19. JBI Checklist for Randomized Controlled Trials. Adelaide (AU): The Joanna Briggs Institute; 2017: https://www.joannabriggs.org/sites/default/files/2019-05/JBI_RCTs_Appraisal_tool2017_0.pdf. Accessed 2019 Jun 3.
20. JBI Checklist for Quasi-Experimental Studies (non-randomized experimental studies). Adelaide (AU): The Joanna Briggs Institute; 2017: https://www.joannabriggs.org/sites/default/files/2019-05/JBI_Quasi-Experimental_Appraisal_Tool2017_0.pdf. Accessed 2019 Jun 3.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-e34.
22. Attard G, Borre M, Gurney H, et al. Abiraterone Alone or in Combination With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer With Rising Prostate-Specific Antigen During Enzalutamide Treatment. J Clin Oncol. 2018;36(25):2639-2646.
23. Matsubara N, Yamada Y, Tabata KI, et al. Abiraterone Followed by Enzalutamide Versus Enzalutamide Followed by Abiraterone in Chemotherapy-naive Patients With Metastatic Castration-resistant Prostate Cancer. Clin Genitourin Cancer. 2018;16(2):142-148.
24. Miyake H, Sugiyama T, Aki R, et al. Comparison of Alternative Androgen Receptor-axis-targeted Agent (ARATA) and Docetaxel as Second-line Therapy for Patients With Metastatic Castration-resistant Prostate Cancer With Progression After Initial ARATA in Real-world Clinical Practice in Japan. Clin Genitourin Cancer. 2018;16(3):219-225.
25. Oh WK, Cheng WY, Miao R, et al. Real-world outcomes in patients with metastatic castration-resistant prostate cancer receiving second-line chemotherapy versus an alternative androgen receptor-targeted agent (ARTA) following early progression on a first-line ARTA in a US community oncology setting. Urol Oncol. 2018;36(11):500.e501-500.e509.
26. Matsubara N, Yamada Y, Tabata KI, et al. Comparison of Sequential Treatment With Androgen Receptor-Targeted Agent Followed by Another Androgen Receptor-Targeted Agent Versus Androgen Receptor-Targeted Agent Followed by Docetaxel in Chemotherapy-Naive Patients With Metastatic Castration-Resistant Prostate Cancer. Clin Genitourin Cancer. 2017;15(6):e1073-e1080.
27. Maughan BL, Luber B, Nadal R, Antonarakis ES. Comparing Sequencing of Abiraterone and Enzalutamide in Men With Metastatic Castration-Resistant Prostate Cancer: A Retrospective Study. Prostate. 2017;77(1):33-40.
28. Miyake H, Hara T, Ozono S, Fujisawa M. Impact of Prior Use of an Androgen Receptor-Axis-Targeted (ARAT) Agent With or Without Subsequent Taxane Therapy on the Efficacy of Another ARAT Agent in Patients With Metastatic Castration-Resistant Prostate Cancer. Clin Genitourin Cancer. 2017;15(2):e217-e222.
29. Miyake H, Hara T, Tamura K, et al. Comparative Assessment of Efficacies Between 2 Alternative Therapeutic Sequences With Novel Androgen Receptor-Axis-Targeted Agents in Patients With Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer. Clin Genitourin Cancer. 2017;15(4):e591-e597.
30. Mori K, Kimura T, Onuma H, et al. Lactate dehydrogenase predicts combined progression-free survival after sequential therapy with abiraterone and enzalutamide for patients with castration-resistant prostate cancer. Prostate. 2017;77(10):1144-1150.
31. Oh WK, Miao R, Vekeman F, et al. Real-world Characteristics and Outcomes of Patients With Metastatic Castration-resistant Prostate Cancer Receiving Chemotherapy Versus Androgen Receptor-targeted Therapy After Failure of First-line Androgen Receptor-targeted Therapy in the Community Setting. Clin Genitourin Cancer. 2017;19:19.
32. Terada N, Maughan BL, Akamatsu S, et al. Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naive castration-resistant prostate cancer: The Kyoto-Baltimore collaboration. Int J Urol. 2017;24(6):441-448.

33. Zhang T, Dhawan MS, Healy P, et al. Exploring the Clinical Benefit of Docetaxel or Enzalutamide After Disease Progression During Abiraterone Acetate and Prednisone Treatment in Men With Metastatic Castration-Resistant Prostate Cancer. Clin Genitourin Cancer. 2015;13(4):392-399.
34. Suzman DL, Luber B, Schweizer MT, Nadal R, Antonarakis ES. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. Prostate. 2014;74(13):1278-1285.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Attard et al., 2018[22] PLATO North America, Europe and Australia Funding: Pharmaceutical companies	Multisite, double-blinded, parallel, 1:1, RCT Intention-to-treat analysis: Yes Sample size calculation: Yes	Men with chemotherapy-naïve mCRPC who progressed on ENZ Median age (years): – ENZ→ENZ + AA/P: 72 – ENZ→Placebo + AA/P: 71 Median PSA (µg/L): – ENZ→ENZ + AA/P: 14.4 – ENZ→Placebo + AA/P: 11.0 Median testosterone (nmol/L): – ENZ→ENZ + AA/P: 1.2 – ENZ→Placebo + AA/P: 1.2 Median LDH (U/L): – ENZ→ENZ + AA/P: 180.5 – ENZ→Placebo + AA/P: 176.0 No significant difference between groups in metastatic site, ECOF performance status, and BPI-SF	ENZ→ENZ + AA/P (n = 126) After developing PSA progression on ENZ (160 mg orally once daily), patients were assigned to ENZ (160 mg daily) + AA (1,000 mg orally once daily) and P (5 mg orally twice daily)	ENZ→Placebo + AA/P (n = 125) After developing PSA progression on ENZ (160 mg orally once daily), patients were assigned to placebo + AA (1,000 mg orally once daily) and P (5 mg orally twice daily)	Primary: – PFS[a] (combined PFS [clinical or radiographic]) Secondary: – Time to PSA progression (a 25% increase in PSA from baseline or nadir, also called PSA-PFS) – PSA response of ≥ 50% – PSA response of ≥ 30% – Rate of pain progression – Objective response rate – Time to first use of subsequent antineoplastic therapy – Time to degradation of FACT-P score – Safety (AEs, clinical laboratory tests, physical examinations, vital signs, 12 lead ECGs)
Matsubara et al., 2018[23] Japan Funding: NR	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with chemotherapy-naïve mCRPC who progressed on AA or ENZ, then were treated with alternative ARTA (AA or ENZ) Median age (years): – AA→ENZ: 73.5 – ENZ→AA: 76.0 Median time to CRPC (month) – AA→ENZ: 13.2	AA→ENZ (n = 50) Dosage: NR	ENZ→AA (n = 47) Dosage: NR	– Combined PFS[c] (clinical or radiographic) – PSA response (a decline of ≥ 50% from baseline) – OS[e]

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
		– ENZ→AA: 8.9 Median time from CRPC to AA or ENZ (months) – AA→ENZ: 8.9 – ENZ→AA: 12.5 No significant difference between groups in median age, prior radical local treatment, Gleason score, median time from CRPC to AA or ENZ, median number of previous treatment lines with vintage hormonal agents, ECOG performance status, metastatic site, and clinical laboratory tests, excluding PSA. Significant difference between groups in median time to CRPC, and median PSA.			
Miyake et al., 2018[24] Japan Funding: NR	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with chemotherapy-naïve mCRPC who progressed after first-line ARTA (AA or ENZ) received second-line chemotherapy (DTX or alternative ARTA Mean age (years): – ARTA→ARTA: 75.6 – ARTA→DTX: 74.4 Mean ADT duration (months): – ARTA→ARTA: 18.2 – ARTA→DTX: 18.6 Mean baseline PSA (mg/mL): – ARTA→ARTA: 23.36 – ARTA→DTX: 28.9	ARTA→ARTA (n = 108) Dosage: NR	ARTA→DTX (n = 114) Dosage: NR	– PSA response (a decline of >0, ≥ 30%, ≥ 50% from baseline) – Time to PSA progression (PSA-PFS) – OS

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
		Significant difference between groups in mean baseline PSA No significant difference between groups in age, mean ADT duration, ECOG performance status, and metastatic site			
Oh et al., 2018[25] USA Funding: Pharmaceutical companies	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with chemotherapy-naïve mCRPC who progressed after first-line ARTA (AA or ENZ) received second-line chemotherapy (DTX or CTX) or alternative ARTA Mean age (years): – ARTA→ARTA: 77.7 – ARTA→DTX or CTX: 72.7 Significant difference between groups in most patient characteristics	ARTA→ARTA (n = 198) Dosage: NR	ARTA→DTX or CTX (n = 147) Dosage: NR	– PSA response (a decline of ≥ 50% from baseline) – Time to PSA progression (a 25% increase in PSA from baseline or nadir, also called PSA-PFS) – OS – Clinical response[f] – Time to next therapy[g] – Pain – Symptomatic skeletal events
Matsubara et al., 2017[26] Japan Funding: NR	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with chemotherapy-naïve mCRPC who progressed on first-line ARTA (AA or ENZ) received second-line ARTA or DTX Median age (years): – ARTA→ARTA: 75 – ARTA→DTX: 68 Median time to CRPC (month) – ARTA→ARTA: 12.4 – ARTA→DTX: 11.3	ARTA (AA or ENZ)→ARTA (AA or ENZ) (n = 97) Dosage: NR	ARTA (AA or ENZ)→DTX (n = 42) Dosage: NR	Primary: – Combined PFS[c] (clinical or radiographic) Secondary: – PSA response (a decline of ≥ 50% from baseline) – OS[e]

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
		Median time from CRPC to AA or ENZ (months) – ARTA→ARTA: 3.0 – ARTA→DTX: 2.0 Significant difference between groups in terms of age, median time from CRPC to AA or ENZ, median number of previous treatment lines with vintage hormonal agents, EOD score, lymph node metastasis, and median albumin concentration.			
Maughan et al., 2017[27] USA Funding: National Institute of Health	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with mCRPC with or without chemotherapy received sequential treatment with AA followed by ENZ or vice versa Median age (years): – AA→ENZ: 63 – ENZ→AA: 62 Median PSA at diagnosis (mg/mL): – AA→ENZ: 18.9 – ENZ→AA: 11.3 Median PSA prior to first agent in sequence (ng/mL): – AA→ENZ: 33.0 – ENZ→AA: 29.8 No significant difference between groups in reported patient characteristics including ECOG performance status, symptom, Gleason score, and metastatic site.	AA→ENZ (n = 65) Dosage: NR	ENZ→AA (n = 16) Dosage: NR	– Combined PFS (clinical or radiographic) – OS – Time to PSA progression (a 25% increase in PSA from baseline or nadir, also called PSA-PFS) – PSA response (a decline of ≥ 50% from baseline)

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Miyake et al., 2017[28] Japan Funding: NR	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with chemotherapy-naïve mCRPC who were treated with a single ARTA (AA or ENZ), or were sequentially treated with ARATs with or without taxane (chemo) therapy in between. Mean age (years): 77.1 Mean duration of primary ADT (days): 558 Mean PSA (ng/mL): 22.4 Not reported on characteristics among groups	ARTA (AA or ENZ)→ARTA (AA or ENZ) (n = 102) Dosage: NR	ARTA (AA or ENZ)→Taxane→ARTA (AA or ENZ) (n = 27) ARAT as first-line (n = 173) Dosage: NR	– PSA response (a decline of ≥ 50% from baseline) – Time to PSA progression (a 25% increase in PSA from baseline or nadir, also called PSA-PFS)
Miyake et al., 2017[29] Japan Funding: NR	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with chemotherapy-naïve mCRPC who progressed on first-line ARTA (AA or ENZ) received second-line alternative ARTA Mean age (years) – AA→ENZ: 75.2 – ENZ→AA: 76.0 Mean duration of ADT (months) – AA→ENZ: 18.0 – ENZ→AA: 18.3 Mean baseline PSA (ng/mL) – AA→ENZ: 23.2 – ENZ→AA: 23.4 No significant difference between groups in reported patient characteristics including ECOG performance status, symptom, Gleason score, and metastatic site.	AA→ENZ (n = 49) Dosage: NR	ENZ→AA (n = 59) Dosage: NR	– PSA response (a decline of ≥ 50% from baseline) – Combined PFS (clinical or radiographic) – OS

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Mori et al., 2017[30] Japan Funding: NR	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with mCRPC with or without chemothrapy received sequential treatment with AA followed by ENZ or vice versa Median age (years): – AA→ENZ: 75 – ENZ→AA: 75 Median observation period (months): – AA→ENZ: 13.5 – ENZ→AA: 14 Baseline PSA (ng/mL): – AA→ENZ: 51.1 – ENZ→AA: 114.9 Median duration of primary ADT (months): – AA→ENZ: 21 – ENZ→AA: 15.5 No significant difference between groups in most patient characteristics, except hemoglobin level	AA→ENZ (n = 46) AA:1,000 mg/day + P (10 mg/day) ENZ: 160 mg/day	ENZ→AA (n = 23)	Primary: – Combined PFS (clinical or radiographic) Secondary: – PSA response (a decline of ≥ 50% from baseline) – Time to PSA progression (a 25% increase in PSA from baseline or nadir, also called PSA-PFS) – OS – AE
Oh et al., 2017[31] USA Funding: Pharmaceutical companies	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with chemotherapy-naïve mCRPC who progressed after first-line ARTA (AA or ENZ) received second-line chemotherapy (DTX or CTX) or alternative ARTA Mean age (years): – ARTA→ARTA: 73.3 – ARTA→DTX or CTX: 77.7 Significant difference between groups in most patient characteristics	ARTA→ARTA (n = 340) Dosage: NR	ARTA→DTX or CTX (n = 206) Dosage: NR	– OS – Clinical response[f] – PSA response (a decline of ≥ 50% from baseline)

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Terada et al., 2017[32] USA Funding: NR	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men with chemotherapy-naïve mCRPC who progressed on first-line ARTA (AA or ENZ), then were treated with second-line ARTA Age (years): NR Median PSA at start of first agent (ng/mL) – AA→ENZ: 24.1 – ENZ→AA: 17.0 No significant difference between groups in metastasis, ECOF performance status, Gleason score, median PSA at start of first agent, metastatic site Significant difference between groups in number of patients chosen from different institutions, and number of prior anti-androgen treatment	AA→ENZ (n = 113) Dosage: NR	ENZ→AA (n = 85) Dosage: NR	– Time to PSA progression (> 25% relative to baseline) – PSA response (a decline of ≥ 50% from baseline) – OS[e]
Zhang et al., 2015[33] USA Funding: Prostate Cancer Foundation and Department of Defense	Retrospective cohort Appropriate statistical methods used: Yes Sample size calculation: No	Men mCRPC with or without chemotherapy, who progressed on AA, received ENZ, DTX, or DTX then ENZ Age: NR Statistics were not provided for comparisons between groups in patient characteristics	AA→ENZ (n = 9) Dosage: NR	AA→DTX (n = 13) AA→DTX→ENZ (n = 19) Dosage: NR	– PSA response (a decline of ≥ 50% from baseline) – Time to PSA progression – OS – Combined PFS (clinical or radiographic)
Suzman et al., 2014[34] USA Funding: NR	Retrospective cohort Appropriate statistical methods	Men with chemotherapy-naïve mCRPC who progressed on AA received either ENZ or DTX Mean age (years):	AA→ENZ (n = 30) Dosage: NR	AA→DTX (n = 31) Dosage: NR	– PSA response (a decline of ≥ 30%, ≥ 50% from baseline) – Time to PSA progression (a 25% increase in PSA

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
	used: Yes Sample size calculation: No	– AA→ENZ: 70.6 – AA→DTX: 68.3 No significant difference between groups in age, Gleason score, and ECOG performance status Significant difference between groups in metastatic site, baseline PSA, and number of PSAs in 6 months after initiation of therapy			from baseline or nadir, also called PSA-PFS) – Combined PFS (clinical or radiographic)

AA = abiraterone acetate; ADT = androgen deprivation therapy; AEs = adverse events; ARTA = androgen receptor targeting agent; BPI-SF = Brief Pain Inventory-Short Form; CRPC = castrate resistant prostate cancer; CTX = cabazitaxel; DTX = docetaxel; ECG = electrocardiograms; ECOG = Eastern Cooperative Oncology Group; EOD = extent of disease; ENZ = enzalutamide; FACT-P = Functional Assessment of Cancer Therapy-Prostate; mCRPC = metastatic castration-resistant prostate cancer; NR = not reported; OS = overall survival; P = prednisone; PFS = progression-free survival; PSA = prostate-specific antigen; QoL = quality of life

[a] PSF = Time from random assignment to the first of the following events assessed by the investigator: radiographic progression, unequivocal clinical progression,[b] or death during study (i.e., death from random assignment to within 112 days [i.e., four cycles] of treatment discontinuation without objective evidence of radiographic progression)

[b] Unequivocal clinical progression = Any of the following: new onset of prostate cancer pain requiring chronic opiate use as defined previously, deterioration of ECOG performance status to ≥ 3 as a result of prostate cancer, initiation of cytotoxic chemotherapy for prostate cancer, or radiation therapy or surgical intervention because of complications of tumor progression

[c] Combined PSF = Time from the start date of the first-line treatment to the date on which disease progression[d] after treatment with a second-line therapy was observed

[d] Disease progression: increasing PSA and radiographic progression according to the Prostate Cancer Working Group 2 or 3 criteria at that time, and symptom deterioration caused by prostate cancer

[e] OS = Time from initiation of AA or ENZ treatment to death from any cause

[f] Clinical response = Improvement in clinical parameters reflecting QoL: a ≥ 1 point reduction in the ECOG performance score, a 5% increase in weight, or 2 g/dL increase in hemoglobin, over a course of ≥ 3 months

[g] Time to next therapy = Time from second-line therapy initiation to administration of a different therapy of interest

Appendix 3: Quality Assessment of Included Studies

Table 3: Quality Assessment of Randomized Controlled Trial

JBI Critical Appraisal Checklist for RCT[19]	Attard et al., 2018[22]
1. Was true randomization used for assignment of participants to treatment groups?	Yes
2. Was allocation to treatment groups concealed?	Unclear
3. Were treatment groups similar at the baseline?	Yes
4. Were participants blind to treatment assignment?	Yes
5. Were those delivering treatment blind to treatment assignment?	Yes
6. Were outcomes assessors blind to treatment assignment?	Unclear
7. Were treatment groups treated identically other than the intervention of interest?	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes
9. Were participants analyzed in the groups to which they were randomized?	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes
11. Were outcomes measured in a reliable way?	Yes
12. Was appropriate statistical analysis used?	Yes
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes

JBI = Joanna Briggs Institute; RCT = randomized controlled trial

Table 4: Quality Assessment of Non-Randomized Studies

JBI Critical Appraisal Checklist for Non-Randomized Studies[20]	Matsubara et al., 2018[23]	Miyake et al., 2018[24]	Oh et al., 2018[25]	Matsubara et al., 2017[26]	Maughan et al., 2017[27]	Miyake et al., 2017[28]
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes
2. Were the participants included in any comparisons similar?	No	No	No	No	No	No
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
4. Was there a control group?	Yes	Yes	Yes	Yes	Yes	Yes
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	NA	NA	NA	NA	NA	NA
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	NA	NA	NA	NA	NA	NA
7. Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes	Yes
8. Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes
9. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes

JBI = Joanna Briggs Institute; NA = not applicable

Table 5: Quality Assessment of Non-Randomized Studies (continued)

JBI Critical Appraisal Checklist for Non-Randomized Studies[20]	Miyake et al, 2017[29]	Mori et al., 2017[30]	Oh et al., 2017[31]	Teerada et al., 2017[32]	Zhang et al., 2015[33]	Suzman et al., 2014[34]
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes
2. Were the participants included in any comparisons similar?	Unclear	No	No	No	No	No
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
4. Was there a control group?	Yes	Yes	Yes	Yes	Yes	Yes
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	NA	NA	NA	NA	NA	NA
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes
7. Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes	Yes
8. Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes
9. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes

JBI = Joanna Briggs Institute; NA = not applicable

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Attard et al., 2018[22]	
ENZ→ENZ + AA/P (n = 126) versus ENZ→Placebo + AA/P (n = 125) **Treatment duration in period two (median, months)** – 5.6 versus 5.6 **Combined PFS (median, months); clinical or radiographic** – 5.7 versus 5.6 – HR (95% CI) = 0.83 (0.61 to 1.12); *P* = 0.22 **PSA response (%) to second line therapy; a decline of ≥ 50% from baseline** – 1% (1/124) versus 2% (3/122) **Time to PSA progression or PSA-PFS (median, months); a 25% increase in PSA from baseline or nadir** – 2.8 versus 2.8 – HR (95% CI) = 0.87 (0.62 to 1.24); *P* = 0.45 **Other secondary outcomes (i.e., rate of pain progression, objective response rate, time to first use of subsequent antineoplastic therapy, time to degradation of FACT-P score):** No significant difference between groups **Safety** – Grade 3 hypertension: 10% versus 2% – Increased ALT: 6% versus 2% – Increased AST: 2% versus 0%	*"Combining enzatulamide with abiraterone acetate and prednisone is not indicated after PSA progression during treatment with enzatulamide alone; hypertension and elevated liver enzymes are more frequent with combination therapy"*[22] p.2639
Matsubara et al., 2018[23]	
AA→ENZ (n = 50) versus ENZ→AA (n = 47) **Follow-up periods (median, months)** – 15.5 versus 19.0 **PSA response** – to first-line treatment: AA (48%) versus ENZ (51%); *P* = 0.840 – to second-line treatment: AA (6.4%) versus ENZ (30%); *P* = 0.004 – to both lines of treatment: 18% versus 2.1%; *P* = 0.016 **Combined PFS (median, months); clinical or radiographic** – 11.1 versus 9.04 – HR (95% CI) = 0.71 (0.46 to 1.08); *P* = 0.105 **OS (median; months)** – 25.4 versus 24.2 – HR (95% CI) = 0.98 (0.64 to 1.528); *P* = 0.834	*"In conclusion, this retrospective multi-center analysis revealed the cross-resistance between AA and ENZ, and no significant differences were observed in terms of the first-line and second line PFS, combined PFS, and OS between AA-AEZ and ENZ-AA sequences."*[23] p. 148
Miyake et al., 2018[24]	
ARTA (AA or ENZ)→ARTA (n = 108) versus ARTA→DTX (n= 114) **PSA response (%) to second-line therapy**	*"Favorable oncologic outcomes can be expected with DTX treatment, rather than with*

Main Study Findings	Author's Conclusions
– a decline of >0% from baseline: 50 versus 70.2; *P* = 0.021 – a decline of ≥ 30% from baseline: 33.3 versus 52.6; *P* = 0.0037 – a decline of ≥ 50% from baseline: 21.3 versus 42.1; *P* < 0.001 **Time to PSA progression or PSA-PFS (median, months)** – 4.2 versus 7.2; *P* < 0.001 **OS (median; months)** – 14.5 versus 17.5; *P* = 0.023	*alternative ARTA, for mCRPC patients after failure of an initial ARTA."*[24] p.219
Oh et al., 2018[25]	
ARTA (AA or ENZ)→ARTA (n = 198) versus ARTA→ DTX or CTX (n = 147) **PSA response (%) to second-line therapy; a decline of ≥ 50% from baseline** – 24.6 versus 40.9 – Adjusted OR = 2.27; *P* = 0.005 **Time to PSA progression or PSA-PFS (median, months)** – 4.2 versus 6.0 – Adjusted HR = 0.66; *P* = 0.010 **OS (median; months)** – 11.8 versus 13.1 – Adjusted HR = 0.81; *P* = 0.148 **OS (median; months) among poor prognosis patients** – low hemoglobin (< 11 g/dL): Adjusted HR = 0.41; *P* = 0.002 – high LDH (> upper limit of normal): Adjusted HR = 0.18; *P* = 0.014 – low albumin (< 1 x lower limit of normal): Adjusted HR = 0.42; *P* = 0.020 – intermediate-to-high Halabi risk scores: Adjusted HR = 0.55; *P* = 0.009 **Clinical response (%)** – 31.8% versus 50.7% – Adjusted OR = 1.78; *P* = 0.020 **Time to next therapy (months)** – 15.3 versus 9.3 **Opioid use for pain** – Adjusted OR = 1.35; *P* = 0.846 **Symptomatic skeletal events** – Adjusted OR = 0.33; *P* = 0.066	*"Following progression on first-line ARTA, second-line chemotherapy may be more beneficial in mCRPC compared with second-line ARTA in patients with poor prognosis."*[25] p.500e.1
Matsubara et al., 2017[26]	
ARTA (AA or ENZ)→ARTA (n = 97) versus ARTA→DTX (n = 42) **Combined PFS (median, months); clinical or radiographic** – 9.68 versus 12.42 – HR (95% CI) = 0.51 (0.33 to 0.80); *P* = 0.004 **PSA response (%) to both lines of treatment; a decline of ≥ 50% from baseline**	*"ARTA-DTX might improve clinical outcomes in terms of second-line PFS and combined PFS, compared with ARTA-ARTA sequence. However, this significance was not observed for OS."*[26] p.e1073

Main Study Findings	Author's Conclusions
– 10.3 versus 21.4; *P* = 0.080 **OS (median; months)** – 24.71 versus 27.93 – HR (95% CI) = 0.60 (0.34 to 1.09); *P* = 0.095	
Maughan et al., 2017[27]	
AA→ENZ (n = 65) versus ENZ→AA (n = 16) **Combined PFS (median, months); clinical or radiographic** – 19.5 versus 13.0 – Univariate analysis: HR (9% CI) = 0.58 (0.36 to 0.94); *P* = 0.03 – Multivariate analysis: HR (95% CI) = 0.37 (0.22 to 0.64); *P* < 0.001 **OS (median; months)** – 33.3 versus 29.9 – Univariate analysis: HR (9% CI) = 0.74 (0.40 to 1.38); *P* = 0.35 – Multivariate analysis: HR (95% CI) = 0.57 (0.29 to 1.11); *P* =0.98 **Time to PSA progression or PSA-PFS (median, months)** – 17.5 versus 12.3 – Univariate analysis: HR (95% CI) = 0.56 (0.35 to 0.90); *P* = 0.02 – Multivariate analysis: HR (95% CI) = 0.44 (0.26 to 0.74); *P* =0.002 **PSA response (%) to both lines of treatment; a decline of ≥ 50% from baseline** – 33.8 versus 6.3; *P* = 0.03	*"We observed differences suggesting improved outcomes favoring the abiraterone-to-enzalutamide sequence in men with mCRPC, with statistical confirmation in terms of PFS but not OS."*[27] p.33
Miyake et al., 2017[28]	
ARTA (n = 173) versus ARTA (AA or ENZ)→ARTA (n = 102) versus ARTA→Taxane→ARTA (n = 27) **PSA response (%) to both lines of treatment; a decline of ≥ 50% from baseline** – 63.6 versus 20.6 versus 29.6 – ARTA versus ARTA→ARTA; *P* < 0.001 – ARTA versus ARTA→Taxane→ARTA; *P* = 0.0018 – ARTA→ARTA versus ARTA→Taxane→ARTA; *P* = 0.46 **Time to PSA progression or PSA-PFS (median, months)** – 10.8 versus 4.7 versus 4.1 – ARTA versus ARTA→ARTA; *P* < 0.001 – ARTA versus ARTA→Taxane→ARTA; *P* < 0.001 – ARTA→ARTA versus ARTA→Taxane→ARTA; *P* = 0.80	*"In conclusion, cross-resistance between the ARTA may be commonly observed in patients with mCRPC, irrespective of the use of taxanes between the ARTA therapies; accordingly, following the failure of either ARTA, the sequential administration of another ARTA should be avoided."*[28] p.e221
Miyake et al., 2017[29]	
AA→ENZ (n = 49) versus ENZ→AA (n = 59) **PSA response (%) to both lines of treatment; a decline of ≥ 50% from baseline** – 18.4 versus 5.1; *P* = 0.029 **Combined PFS (median, months)** – 18.4 versus 12.8 – HR (95% CI) = 0.44 (0.37 to 0.81); *P* = 0.0091	*"Although cross-resistance between ARTA is a common phenomenon in docetaxel-naïve patients with mCRPC, different efficacies were observed favoring the AA-to-Enz rather than ENZ-to-AA sequence in this series with respect to*

Main Study Findings	Author's Conclusions
OS (median; months) – Not reached versus 22.1 – HR (95% CI) = 0.80 (0.27 to 1.31); *P* = 0.21	*combined PSA PFS but not OS."*[29] p.e591
Mori et al., 2017[30]	
AA→ENZ (n = 46) versus ENZ→AA (n = 23) **Combined PFS (median, months)** – Not reached versus 11; *P* = 0.043 – Univariate analysis: HR (95% CI) = 0.44 (0.19 to 1.01); *P* = 0.054 – Multivariate analysis: HR (95% CI) = 0.39 (0.15 to 1.03); *P* = 0.056 – Combined PFS was significantly longer (17 months versus 8 months; *P* = 0.015) among patients with low LDH (< 210 IU/L) compared to those with high LDH (≥210 IU/L) **Time to PSA progression or PSA-PFS (median, months)** – Longer in AA→ENZ group; *P* = 0.049 **OS (median; months)** – No significant difference between groups; *P* = 0.62 – Univariate analysis: HR (95% CI) = 0.79 (0.31 to 2.02); P = 0.63 **Adverse events** – No significant difference between groups	*"The results of this study suggested the AA-ENZ sequence had longer combined PFS and total PSA-PSF compared to ENZ-AA sequence in patients with CRPC. LDH values in sequential therapy may serve as a predictor of longer combined PFS."*[30] p.1144
Oh et al., 2017[31]	
ARTA (AA or ENZ)→ARTA (n = 340) versus ARTA→ DTX or CTX (n = 206) **OS (median; months)** – 12.2 versus 13.3 – Adjusted HR (95% CI) = 0.90 (0.65 to 1.24); *P* = 0.511 **OS (median; months) among poor prognosis patients** – low hemoglobin (< 11 g/dL): Adjusted HR (95% CI) = 0.52 (0.34 to 0.82); *P* = 0.004 – low albumin (< 1 x lower limit of normal): Adjusted HR (95% CI) = 0.36 (0.19 to 0.70); *P* = 0.003 – intermediate-to-high Halabi risk scores: Adjusted HR (95% CI) = 0.71 (0.48 to 1.06); *P* = 0.094 **Clinical response (%) to second-line therapy** – 34.0% versus 50.5% – Adjusted OR (95% CI) = 1.54 (0.99 to 2.32); *P* = 0.054 **PSA response (%) to second-line therapy; a decline of ≥ 50% from baseline** – 29.9 versus 45.3 – Adjusted OR (95% CI) = 2.08 (1.20 to 3.62); *P* = 0.009	*"Taken together, these findings suggest that after first-line AR-targeted therapy second-line chemotherapy, versus alternative AR-targeted therapy, may be associated with improved treatment outcomes, particularly among patients with worse disease prognosis."*[31] p.56
Terada et al., 2017[32]	
AA→ENZ (n = 113) versus ENZ→AA (n = 85) **PSA response (%); a decline of ≥ 50% from baseline**	*"The abiraterone-to-enzalutamide sequence might have more favorable efficacy in*

Main Study Findings	Author's Conclusions
– First-line: AA (48%); ENZ (55%); P = 0.353 – Second-line: ENZ (29%); AA (13%); P = 0.011 – AA→ENZ was more effective than ENZ→AA **Time to PSA progression or PSA-PFS (median, days)** – 455 versus 296 – HR (95% CI) = 0.67 (0.41 to 0.76); *P* < 0.001 – Multivariate analysis: HR (95% CI) = 0.65 (0.42 to 0.99); *P* = 0.044 **OS (median; days)** – 919 versus 899 – HR (95% CI) = 0.88 (0.53 to 1.43); *P* = 0.599 – Multivariate analysis: HR (95% CI) = 0.81 (0.49 to 1.35); *P* = 0.427	*terms of combined prostate-specific antigen progression-free survival than the enzalutamide-to abiraterone sequence, although no differences in overall survival were observed. This could possibly be attributable to longer prostate-specific antigen progression-free survival with second line enzalutamide compared with abiraterone."*[32] p.441
Zhang et al., 2015[33]	
AA→ENZ (n = 9) versus AA→DTX (n = 13) versus AA→DTX→ENZ (n = 19) **PSA response (%) to second-line therapy; a decline of ≥ 50% from baseline** – 11% versus 55% versus 5% **Time to PSA progression or PSA-PFS (median, months)** – 4.0 versus 5.6 versus 3.0 **Combined PFS (median, months)** – 3.7 versus 5.1 versus 2.8 **OS (median; months)** – 8.5 versus "not estimable" versus 9.6	*"In this chart review of consecutive men with progressive mCRPC after AA, we found modest activity for enzalutamide and docetaxel, with clear cross-resistance for AA and enzalutamide."*[33] p.392
Suzman et al., 2014[34]	
AA→ENZ (n = 30) versus AA→DTX (n = 31) **PSA response to second-line therapy; a decline of ≥ 50% from baseline** – OR (95% CI) = 1.68 (0.51 to 5.66); *P* = 0.40 **Time to PSA progression or PSA-PFS (median, months)** – 4.1 versus 4.1; *P* = 0.327 – HR (95% CI) = 1.35 (0.53 to 3.66); *P* =0.502 **Combined PFS (median, months)** – 4.7 versus 4.4 – HR (95% CI) = 1.44 (0.77 to 2.71); *P* = 0.257	*"Treatment with either enzalutamide or docetaxel produces modest PSA responses and PFS intervals in this abiraterone-pretreated mCRPC population. In this retrospective study with small sample size, no significant differences in outcomes were observed between groups. Therefore, either enzalutamide or docetaxel may be a reasonable option in men who have progressed on abiraterone."*[34] p.1278

AA = abiraterone acetate; ALT = alanine amino transferase; ARTA = androgen receptor-targeted agent; AST = Aspartate amino transferase; CTX = cabazitaxel; DTX = docetaxel; ENZ = enzalutamide; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR = hazard ratio; LDH = lactate dehydrogenase; OR = odds ratio; OS = overall survival; P = prednisone; PFS = progression free survival