Hong Kong J Radiol. 2022;25:6-15 | https://doi.org/10.12809/hkjr2217393

REVIEW ARTICLE **CME**

First-Line Therapy for Metastatic Castration-sensitive Prostate Cancer: a Network Meta-analysis

KYC Zheng[1], AKH Fong[1], SK Chan[2], TH So[2]

[1]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Clinical Oncology, The University of Hong Kong, Hong Kong

ABSTRACT

Objective: *The treatment landscape of metastatic castration-sensitive prostate cancer (mCSPC) has been transforming in the past decade. Abiraterone acetate plus prednisolone (AAP), apalutamide (APA), enzalutamide (ENZA), and docetaxel (Doce) added to androgen deprivation therapy (ADT) were shown to outperform ADT alone. However, data on direct comparison of the different regimens are sparse. We sought to review current evidence on first-line therapies in mCSPC and compare their results in terms of overall survival (OS) and progression-free survival (PFS) in a network meta-analysis.*

Methods: *We performed a systematic search of PubMed, MEDLINE, Web of Science, EMBASE, ClinicalTrials.gov, and Cochrane Library databases in September 2020. ADT was the reference category. Treatments were grouped into four categories: Doce+ADT, AAP+ADT, APA+ADT, and ENZA+ADT. The primary endpoint of our study was OS.*

Results: *We analysed eight trials with 7790 total patients, using frequentist network meta-analysis and P-score to rank the treatments. AAP+ADT showed the highest P-score of 86% with a hazard ratio (HR) of 0.63 (95% confidence interval [CI]=0.56-0.71) in OS while ENZA+ADT performed best in PFS (HR=0.40, 95% CI=0.34-0.46) with a P-score of 98%.*

Conclusion: *We found that AAP+ADT treatment was most effective in prolonging OS. ENZA+ADT might provide better PFS in mCSPC. Analysis of OS and PFS provides guidance on selecting the best choice of first-line treatments.*

Key Words: *Prostatic neoplasms; Meta-analysis; Therapeutics*

Correspondence: *Dr TH So, Department of Clinical Oncology, The University of Hong Kong, Hong Kong*
Email: sotszhim2@gmail.com

Submitted: 11 May 2021; Accepted: 5 Oct 2021

Contributors: THS designed the study. KYCZ and AKHF acquired the data. KYCZ, SKC and THS analysed the data. All authors drafted the manuscript. THS critically revised the manuscript for important intellectual content.

Conflicts of Interest: The authors have no conflicts of interest to declare.

Funding/Support: The authors received no financial support for the research or publication of this article.

Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: Approval was not required as no patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design and implementation of the study.

Declaration: The results/methods from this study were presented in part at ESMO Asia Congress 22-24 November 2019, Singapore.

中文摘要

轉移性去勢敏感性前列腺癌的一線治療：網絡薈萃分析

鄭裕誠、房嘉希、陳錫坤、蘇子謙

目的：在過去十年，轉移性去勢敏感性前列腺癌（mCSPC）的治療前景出現轉變。將阿比特龍併潑尼松龍（AAP）、阿帕魯胺（APA）、恩扎盧胺（ENZA）和多西紫杉醇（Doce）加入雄激素剝奪療法（ADT）的效果優於單純ADT。然而，有關直接比較不同方案的數據很少。本文回顧目前mCSPC一線治療的證據，並在網絡薈萃分析中比較治療方案的總生存期和疾病無進展生存期。

方法：研究於2020年9月對PubMed、MEDLINE、Web of Science、EMBASE、ClinicalTrials.gov 和 Cochrane Library 數據庫進行系統搜索。以ADT作為參考類別。治療分為四類：Doce+ADT、AAP+ADT、APA+ADT 和 ENZA+ADT。我們研究的主要終點指標是總生存期。

結果：我們分析8項試驗研究，涉及7790名患者，使用頻率學網絡薈萃分析和P評分對治療進行排名。AAP+ADT在整體存活期中的P值最高，達 86%，風險比為0.63（95%置信區間 = 0.56-0.71），而ENZA+ADT在疾病無進展生存期中表現最佳，風險比為0.40（95%置信區間 = 0.34-0.46)，P 值為98%。

結論：AAP+ADT治療對延長mCSPC總生存期最為有效，而ENZA+ADT則有助改善mCSPC疾病無進展生存期。總生存期和疾病無進展生存期的分析可為選擇最佳一線治療方案提供指引。

INTRODUCTION

Prostate cancer (PC) has the second highest incidence and is the third leading cause of cancer death among men in the world. In 2018, more than 1.2 million new cases were diagnosed and 359,000 deaths were reported worldwide.[1] Approximately 89% of newly diagnosed cases are locoregional, with a 5-year survival rate of nearly 100%; 6% are diagnosed at the metastatic stage, which has a significantly worse 5-year relative survival of 30.2%.[2]

Androgen deprivation therapy (ADT) has been the standard of care for patients with metastatic PC since Huggins and Hodges discovered the hormone dependency of PC in the 1940s.[3] ADT was proven to be effective in producing improved radiological and biochemical profiles and prolonging overall survival (OS).[4] Multiple randomised controlled trials (RCTs) have been performed to evaluate the benefits of other therapies added to ADT for metastatic castration-sensitive PC (mCSPC). Following the STAMPEDE Arm C,[5,6] CHAARTED,[7,8] and GETUG-AFU 15 trials,[9,10] docetaxel (Doce) plus ADT was recommended as first-line treatment (especially for high-volume disease) for mCSPC in 2015.[11] Treatment protocols have further evolved over the past 5 years. Positive results from the LATITUDE,[12,13] STAMPEDE Arm G,[14,15] TITAN,[16] ARCHES[17] and ENZAMET[18] studies have shown that addition of abiraterone acetate plus prednisolone (AAP), apalutamide (APA), or enzalutamide (ENZA) to ADT showed superior results compared to ADT alone in mCSPC and are now considered standard treatment protocols.[19] However, no head-to-head RCT has been conducted to compare the survival benefits of these regimens. We therefore conducted a network meta-analysis to guide the selection of the best first-line combination therapy for mCSPC.

METHODS

Inclusion Criteria

This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines.[20] We included RCTs only if they included treatment of mCSPC. We specifically included trials of treatment regimens containing ADT plus AAP, APA, Doce, or ENZA to assess the efficacy in systemic treatments. Included clinical trials needed to contain a control arm with ADT alone or with placebo for carrying out indirect comparison by network meta-analysis.

Literature Search and Data Collection

We performed a comprehensive systematic literature search for full-length journal publications, which included mCSPC ADT. The PubMed/MEDLINE Ovid, Embase, Cochrane Library, CINAHL Databases, trial registries, and other sources were employed and searched from 1990 to the present day, with the most recent search carried out on 30 September 2020. Key words and medical sub-heading (MeSH) terms included: 'prostate cancer', 'metastatic', 'castration-sensitive', and 'treatment'. Key words used for searching included: "prostate" OR "prostatic"; "neoplasm" OR "cancer" OR "cancers" OR "cancerous" "tumor" OR "tumour"; "metastatic" OR "metastasis"; "treatment" OR "therapy"; and "castration-sensitive" OR "castration". We aimed at identifying any journal articles or abstract proceedings that published the efficacy of first-line therapy in mCSPC. The key words and MeSH terms within each concept were then separated by the Boolean operator 'AND'. Only articles written in English were included. The details and results of the literature search are provided in Figure 1 and Table 1.

Data Extraction

The results of the findings were first screened by title and abstract for appropriateness by two independent reviewers (KYCZ and AKHF), while the third reviewer (THS) was consulted if there were any disputes on selection of relevant literature. For relevant abstracts, the full papers would be reviewed for inclusion. More updated versions of the publications were adopted for meta-analysis when more than one version of the same studies were found. Two authors (KYCZ and AKHF) were responsible for independent data extraction based on the same criteria.

Endpoint Definitions

The primary endpoint of our study was OS, defined as

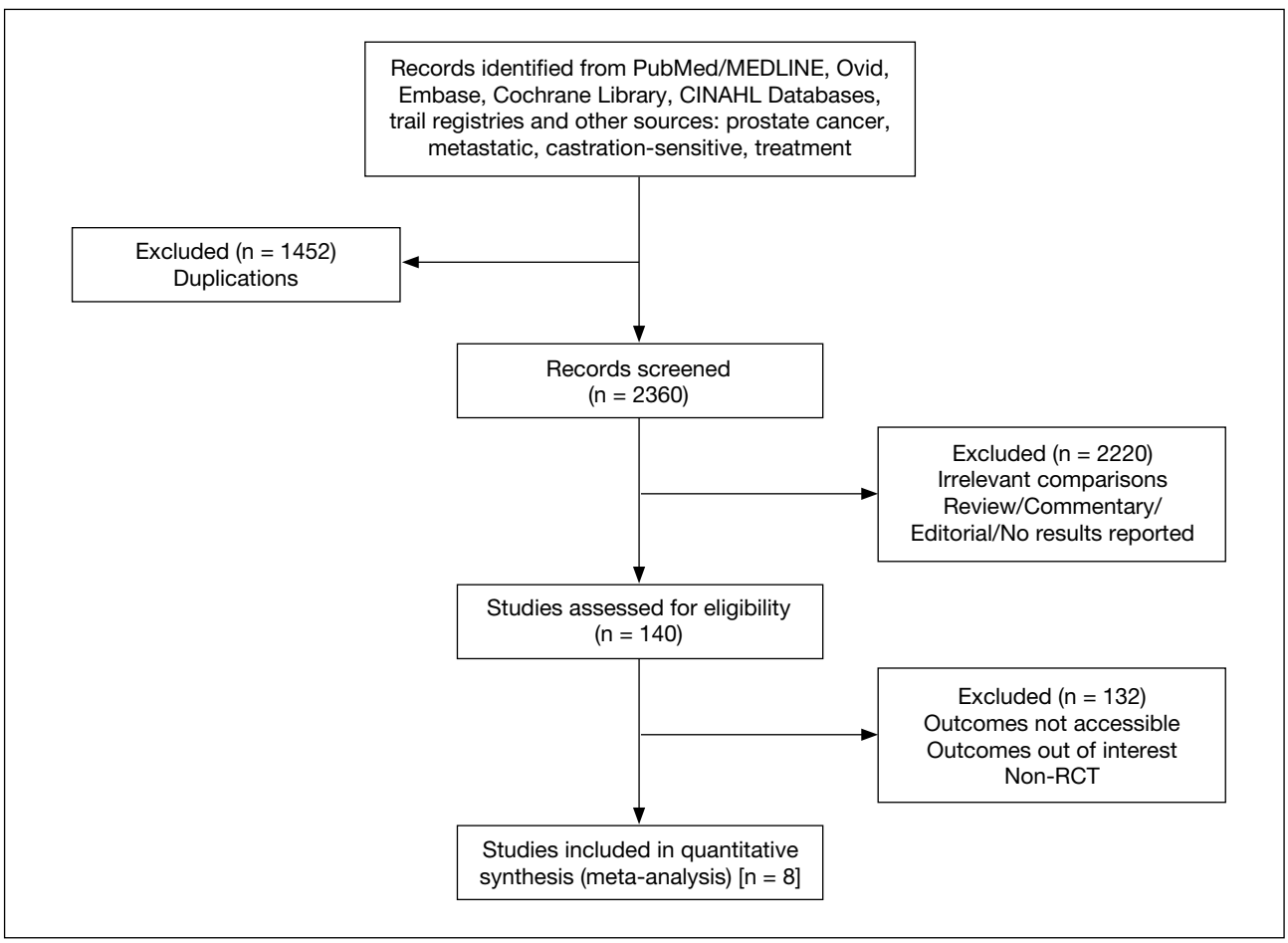

Figure 1. PRISMA flowchart showing the results of systematic review identified from PubMed/MEDLINE, Ovid, Embase, Cochrane Library, CINAHL Databases, trial registries and other sources.
Abbreviation: RCT = randomised controlled trial.

Table 1. Characteristics of included trials.

	ARCHES[17] *	TITAN[16] *	CHAARTED (2015)[7]	CHAARTED (2018)[8] *	GETUG-AFU 15 (2013)[9]	GETUG-AFU 15 (2016)[10]*
Patient inclusion period	Mar 2016 to Jan 2018	Dec 2015 to Jul 2017	Jul 2006 to Dec 2012		Oct 2004 to Dec 2008	
Treatment	Enzalutamide and ADT	ADT and APA	Docetaxel and ADT		Docetaxel and ADT	
Control	ADT and placebo	ADT	ADT alone		ADT alone	
Type of study	Double-blind	Double-blind	Open-label		Open-label	
Staging of the diseases	- Prostate adenoCA - Metastasis proven by bone scans, CT or MRI scan	- Prostate adenoCA - Metastasis proven by least one lesion on bone scanning - With/without visceral or lymph node involvement	- Metastatic CA prostate - Confirmed by pathology or clinical observations proven by elevated PSA - Radiologically proven metastasis		- Metastatic CA prostate	
Performance status	ECOG 0-1	ECOG 0-1	ECOG 0-2		Karnofsky score ≥70%	
Median follow-up, mo	14.4	22.7	28.9	53.7	50	83.9
Study population	North and Latin American	23 countries worldwide	United States		France and Belgium	
Primary endpoints	rPFS	rPFS and OS	OS		OS	
Secondary endpoints	- OS - Time to PSA progression - Time to initiation of new antineoplastic therapy - PSA undetectable rate - Objective response rate - Time to deterioration in urinary symptoms - Time to first symptomatic skeletal event - Time to castration resistance - PROs - Time to deterioration of QOL - Time to pain progression	- Time to cytotoxic chemotherapy - Time to pain progression - Time to chronic opioid use - Time to skeletal-related event	- PSA level <0.2 ng/mL - Time to castration-resistant prostate cancer - Time to clinical progression - Adverse events		- Early PSA progression - bPFS - cPFS - Toxic effects	- bPFS - PFS
No. of treatments vs. control	574 vs. 576	525 vs. 527	397 vs. 393		192 vs. 193	

Abbreviations: adenoCA = adenocarcinoma; ADT = androgen deprivation therapy; APA = apalutamide; bPFS = biochemical progression-free survival; cPFS = conditional progression-free survival; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FFS = failure-free survival; MRI = magnetic resonance imaging; OS = overall survival; PFS = progression-free survival; PROs = patient-related outcomes; PSA = prostate-specific antigen; QOL = quality of life; rPFS = radiographic progression-free survival; WHO = World Health Organization.

* The results in these most updated studies were included in our final analysis.

† STAMPEDE 2017 and 2020 compared abiraterone, prednisolone and ADT vs. ADT.

‡ STAMPEDE 2016 and 2019 compared docetaxel and ADT vs. ADT and placebo.

the time from the date of randomisation until the date of death from any cause. The secondary endpoint was progression-free survival (PFS), the time from the date of randomisation to the date of first disease progression (locoregional or distant) or death from any cause, whichever occurred earlier.

Risk of Bias Assessment

The assessment of study quality for all RCTs was carried out independently by two authors (KYCZ and AKHF) using the Cochrane Collaboration tool.[21] Domains for the risk of bias assessment included: (1) the randomisation process; (2) deviations from

Table 1. Characteristics of included trials (cont'd.)

	ENZAMET[18] *	STAMPEDE 2020[15] *	STAMPEDE 2017[14]	STAMPEDE 2016[5]	STAMPEDE 2019[6] *	LATITUDE 2017[12]	LATITUDE 2019[13] *
		(Arm G vs. Arm A)†		(Arm C vs. Arm A)‡			
Patient inclusion period	Mar 2014 to Mar 2017	Nov 2011 to Jan 2014		Oct 2005 to Mar 2013		Feb 2013 to Dec 2014	
Treatment	Enzalutamide and ADT	Abiraterone, prednisolone and ADT		Docetaxel and ADT		Abiraterone and ADT	
Control	ADT	ADT		ADT and placebo		ADT and placebo	
Type of study	Open-label	Open-label				Double-blind	
Staging of the diseases	- Prostate adenoCA - With metastases on CT, or bone scan	- M1 patients	- Newly diagnosed CA prostate, either: - metastatic; - node-positive; or - OR ≥2 of T3/4, Gleason score of 8-10, and PSA ≥40 ng/mL) - Previously treated with radical surgery, radiotherapy, or both and relapsing with high-risk features, either: - in those no longer receiving therapy; - PSA >4 ng/mL with a doubling time of <6 mo; - PSA level >20 ng/mL; - nodal or metastatic relapse; or - <12 mo of total ADT with an interval of >12 mo without treatment	- Newly diagnosed CA prostate, either: - metastatic; - node-positive; or - ≥2 of T3/4, Gleason score of 8-10, and PSA ≥40 ng/mL) - Previously treated with radical surgery, radiotherapy, or both and relapsing with high-risk features		- Newly diagnosed metastatic CA prostate - Pathologically confirmed prostate adenoCA - With distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI - With 2/3 of the following: - Gleason score of ≥8; - presence of ≥3 on bone scan; or - visceral metastasis except nodal metastasis	
Performance status	ECOG 0-2		WHO 0-2			ECOG 0-2	
Median follow-up, mo	34	~73.2 (6.1 y)	40	43	78.2	30.4	51.8
Study population	Australia, Canada, United Kingdom, Ireland, New Zealand, and United States		United Kingdom and Switzerland			France and Belgium	
Primary endpoints	OS		OS			OS, rPFS	
Secondary endpoints	- PFS - Adverse events	- FFS - PFS - Metastasis-free survival - Skeletal-related events - Toxicity	- Adverse events - Symptomatic skeletal events - PFS - Prostate CA–specific survival - QOL			- Time to PSA progression - Time to next symptomatic skeletal event - Time to new treatment (including) chemotherapy - Time to next prostate CA therapy	
No. of treatments vs. control	563 vs. 562	501 vs. 502	960 vs. 957	362 vs. 724		597 vs. 602	

the intended interventions; (3) missing data; (4) measurements of the outcomes (OS, PFS); and (5) selection of reported results. Risk of bias was judged as 'low risk', 'some concerns', or 'high risk' for individual domains based on the information provided by the authors of the included trials (Table 2).

Statistical Analysis

Our primary analysis in comparing the efficacy of different therapies on mCSPC was performed with both random- and fixed-effects models under a frequentist framework. Reported hazard ratios (HRs) for OS and PFS in eight included trials were incorporated into the mathematical model. Since PFS was displayed in various forms among different studies, we adopted radiological PFS as our primary interest. For the studies with no radiological PFS provided, clinical or biochemical PFS was adopted as a surrogate in our analysis.

Relative effects of each treatment were evaluated in indirect comparison by network meta-analysis. The I^2 and Q statistics were used to quantify the heterogeneity among different trials; an I^2 value of >50% and/or significant Q statistic at $p < 0.1$ was regarded as significant heterogeneity. P-scores were further employed to evaluate the mean extent of probability that one treatment outperforms the others.[22] In other words, the higher the P-score, the higher the certainty that a treatment is better than the others. Efficacy of treatments on OS and PFS was ranked by the relative P-score in our analysis.

Publication bias could not be formally assessed in this network meta-analysis because of the small number of trials included. Despite the real potential for this bias, given the relatively small number of trials, we judged the certainty in the evidence was unlikely to be decreased by this concern.

All statistical analyses were performed using open-source software, (R version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria, 2018). A p value of <0.05 was considered statistically significant.

RESULTS

The network meta-analysis consisted of eight trials and 7790 patients, including CHAARTED, GETUG, LATITUDE, TITAN, ARCHES, and ENZAMET. Two studies from STAMPEDE (with Doce+ADT and AAP+ADT as their experimental regimens, respectively).[5-10,12-18] We also included the most updated results of STAMPEDE, from the 2020 European Society for Medical Oncology Congress.[15]

ADT was the reference category. Treatments were grouped into four categories: Doce+ADT, AAP+ADT, APA+ADT and ENZA+ADT. The network is displayed in Figure 2.

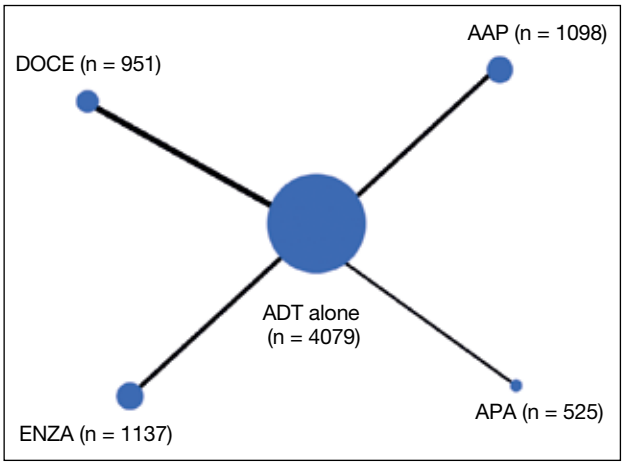

Figure 2. Schematic of the Network of Evidence Used in Network Meta-analysis for metastatic castration-sensitive prostate cancer treatments. The size of nodes of the diagram represents the total study population adopting the treatment and the thickness of the line is proportional to the number of comparisons among the studies.
Abbreviations: AAP = abiraterone acetate plus prednisolone; ADT = androgen deprivation therapy; APA = apalutamide; ENZA = enzalutamide; DOCE = docetaxel.

Overall Survival

AAP+ADT had the longest OS, followed by APA+ADT, ENZA+ADT and Doce+ADT with respective P-scores of 86%, 70%, 61% and 33% where a higher score means a higher probability of being the best treatment (Figure 3). Their corresponding HRs (95% confidence interval; 95% CI) compared to ADT alone were 0.63 (0.56-0.71), 0.67 (0.51-0.89), 0.70 (0.57-0.87), and 0.79 (0.71-0.89). There was no significant heterogeneity observed ($I^2 = 0\%$; $p = 0.610$ for the Q statistic).

Progression-Free Survival

Results of our study in PFS did not match with our analysis in OS. Figure 4 shows that ENZA+ADT had the highest P-score of 98%, implying a high certainty that ENZA+ADT was the best treatment in terms of PFS (HR=0.40, 95% CI=0.34-0.46). APA+ADT, AAP+ADT and Doce+ADT had P-scores of 75%, 51% and 26%, respectively. Their corresponding HRs (95% CI) were 0.48 (0.39-0.60), 0.58 (0.52-0.65) and 0.67 (0.60-0.74).

The same results were obtained in fixed- and random-effects models in both OS and PFS analyses.

Exploratory Analysis

Figure 3 shows our explorative analysis in OS comparing

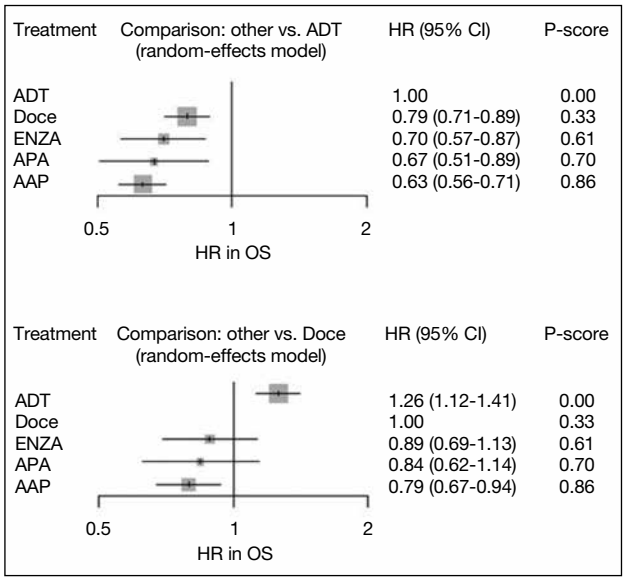

Figure 3. Forest plot for OS showing results comparing mCSPC treatments against ADT alone (upper) and Doce+ADT (lower) from network meta-analysis. HR<1 is in favour of ADT alone (upper) / docetaxel (lower).

Abbreviations: 95% CI = 95% confidence interval; AAP = abiraterone acetate plus prednisolone; ADT = androgen deprivation therapy; APA = apalutamide; Doce = docetaxel; ENZA = enzalutamide; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; OS = overall survival.

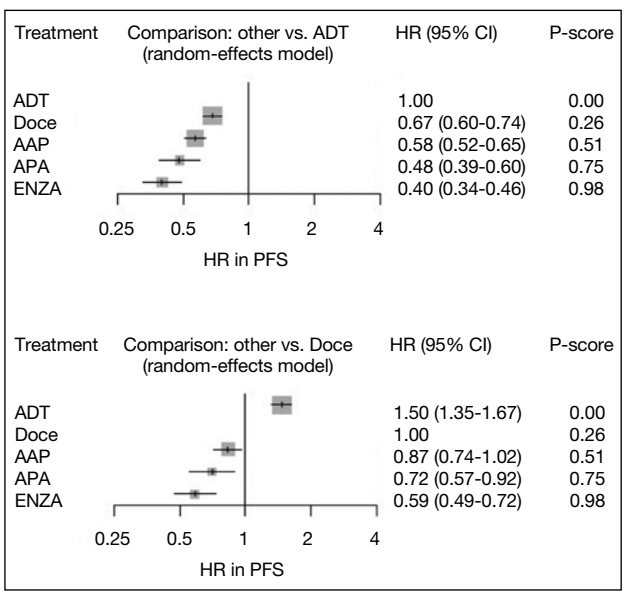

Figure 4. Forest plot for PFS showing results comparing mCSPC treatments against ADT alone (upper) and Doce+ADT (lower) from network meta-analysis. HR<1 is in favour of ADT alone (upper) / docetaxel (lower).

Abbreviations: 95% CI = 95% confidence interval; AAP = abiraterone acetate plus prednisolone; ADT = androgen deprivation therapy; APA = apalutamide; Doce = docetaxel; ENZA = enzalutamide; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; PFS = progression-free survival.

different treatment combinations against Doce+ADT. Our study revealed that only AAP+ADT showed a significant benefit when compared with Doce+ADT (HR=0.79, 95% CI=0.67-0.94). A P-score of 86% was recorded when compared with Doce+ADT. Other modalities, including APA+ADT and ENZA+ADT, had no significant OS benefit compared to Doce+ADT.

In the explorative analysis against Doce+ADT, ENZA+ADT (HR=0.59, 95% CI=0.49-0.72) and APA+ADT (HR=0.72, 95% CI=0.57-0.92) had significant benefit in PFS. Although all four treatment options showed superiority over ADT alone (HR=1.50, 95% CI=1.35-1.67), AAP+ADT did not show a significant difference in improving the PFS of mCSPC patients, as compared to Doce+ADT (HR=0.87, 95% CI=0.74-1.02).

Similarly, the results of exploratory analysis were consistent in fixed- and random-effects models.

DISCUSSION

With updated evidence in 2020, the primary and secondary endpoints were reached and revealed that the addition of AAP, ENZA, APA, or Doce to ADT prolonged the OS and PFS of mCSPC patients. Among the four treatment modalities, AAP+ADT provided the best effect in prolonging OS. This result differs from that of another network meta-analysis published in early 2020, which suggested that ENZA+ADT is the most effective in prolonging OS.[22] This discrepancy may be because the ARCHES trial, which compared ENZA+ADT versus ADT alone in mCSPC (median OS HR = 0.81, 95% CI = 0.53-1.25, p = 0.3361) was not included in their analysis. Furthermore, the most updated OS data in 2020 from the STAMPEDE trial for AAP+ADT versus ADT alone is included in our analysis.[15] One must also notice that some RCTs had a rather short median follow-up and the OS can be considered premature; for instance, the median follow-ups for ARCHES and TITAN were 14.4 months and 22.7 months, respectively.[16,17]

In contrast to the OS results, our network meta-analysis showed that ENZA+ADT is the most favourable in terms of prolonging PFS. Despite the differences in PFS definition in each trial — be it radiographic, biochemical, or clinical—the PFS HRs were rather consistent across the trials concerning the same drug. We therefore postulate that the prevention of all forms of progression may be best achieved by ENZA+ADT as compared to other treatment modalities.

Table 2. Risk of bias summary.

	Randomisation process	Deviations from the intended interventions (effect of assignment to intervention)	Missing outcome data	Measurement of the outcome (overall survival)	Measurement of the outcome (progression-free survival)	Selection of the reported result
LATITUDE 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
STAMPEDE 2020	Low risk	Some concerns	Low risk	Low risk	Some concerns	Low risk
ARCHES 2019	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
ENZAMET 2019	Low risk	Some concerns	Low risk	Low risk	Some concerns	Low risk
TITAN 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
STAMPEDE 2019	Low risk	High risk	Low risk	Low risk	High risk	Low risk
CHAARTED 2018	Low risk	Some concerns	Low risk	Low risk	Some concerns	Low risk
GETUG 2016	Low risk	High risk	Low risk	Low risk	Some concerns	Low risk

With the difference in OS and PFS results in mind, it is however important to note that there is no established evidence towards PFS being a surrogate for OS, while the latter is considered a golden endpoint. Moreover, OS is also affected by subsequent salvage treatment beyond progression and therefore the sequence of drugs may contribute to the difference in PFS and OS results. Cross-resistance exists between androgen receptor-targeted therapies, for instance, AAP+ADT and ENZA+ADT.[23] The sequence of agent initiation may affect the OS. There is some evidence suggesting that the use of AAP+ADT before ENZA+ADT gives rise to better outcomes. A phase 2 randomised crossover trial conducted by Khalaf et al[24] has compared the prostate-specific antigen (PSA) decline >50% (PSA50) on second-line therapy and the median time to second PSA progression for AAP+ADT followed by ENZA+ADT (arm A) versus ENZA+ADT followed by AAP+ADT (arm B). It was shown that the sequence of AAP+ADT followed by ENZA+ADT (arm A) achieved superior PSA50 and time to second PSA progression (HR=0.75, 95% CI=0.53-1.06). Although this trial was designed for metastatic castration-resistant PC, it is still a direct comparison of the biochemical effectiveness between the two sequences on PC. We believe this might explain the different results in PFS and OS.

In addition, the follow-up period of ARCHES (14.4 mo) and ENZAMET (34 mo) for ENZA+ADT were relatively short compared with that of LATITUDE (51.8 mo) and STAMPEDE (73.2 mo) for AAP+ADT. It remains unclear whether extended follow-up of studies of ENZA+ADT would lead to a better OS outcome. Thus, further analysis may be required in the future.

The above results on OS, PFS and time to PSA progression do not provide a clear answer to which agent is more preferable. Several other factors including the potential toxicity profile and quality of life (QOL) should be taken into account. Apart from the general adverse effects shared among androgen receptor targeting agents, there are some adverse events unique to each specific agent that may influence the treatment choice. For example, ENZA is commonly associated with fatigue (24.1%) and musculoskeletal events (26.4%) including falls and fractures[17]; abiraterone acetate exerts excessive mineralocorticoid activity; thus, it must be given together with prednisolone, leading to some steroid-specific adverse events which are not common in other agents[13]; APA causes particularly high incidence of rash (27.1%) as compared to ADT alone (8.5%).[16] Patients' QOL with different agents is a considerable factor. A QOL sub-study extended from the STAMPEDE trial suggested a significantly higher global QOL score in the first 2 years of treatment with AAP+ADT as compared with Doce+ADT.[25] The health-related QOL, Patient Health Questionnaire-9 depression score, and Montreal Cognitive Assessment score of AAP+ADT and ENZA+ADT were assessed in another trial.[26] Minimal difference was seen in terms of Montreal Cognitive Assessment score; while AAP+ADT was shown to be associated with better health-related QOL and Patient Health Questionnaire-9 scores over time, with greater significance in the elderly group.[26]

The choice of treatment should always include careful discussion and shared decision making among physicians, the patient, and caregivers. It is observed that AAP+ADT is superior to Doce+ADT, ENZA+ADT, and APA+ADT in terms of OS, QOL, and being the first agent initiated in mCSPC patients. However, the abovementioned evidence on OS, PFS, sequence of treatments, adverse events, and QOL may only serve as a guide; no single factor should be used to pursue one treatment over another.

Our results are in line with a recently published study by Wang et al[27] suggesting that AAP+ADT treatment were more effective in prolonging OS, while ENZA+ADT might provide better PFS in mCSPC patients. The strength of our study is that we have included the most up-to-date data from all these major trials, including the STAMPEDE with AAP+ADT as the experimental regimen.[15] Also, the comprehensive inclusion of all the most updated studies in this network meta-analysis covering more than 7500 patients provides a clearer comparison of survival data among different treatment modalities, in addition to our previously published preliminary results.[28]

However, several limitations exist in our comparison and the findings should be interpreted within this context. Similar to the other network meta-analyses in the field, this analysis only provided indirect comparisons and rankings among the named systematic treatments by comparing the efficacy in the RCTs, which cannot replace head-to-head clinical trials for comparison. As shown in Table 1, the study population and inclusion criteria varied among the different RCTs. The variations among different studies may contribute to heterogeneity in treatment effect, which limits our power in comparing the efficacy among the systematic treatments. Furthermore, our study did not account for other outcomes, such as QOL and cost-effectiveness. Given that the relevant data in either prospective or retrospective clinical trials are not adequate among our study populations, current clinical trials provide limited insights on the effects on QOL and cost-effectiveness among different patients.

Another possible weakness of our study is that we have not performed subgroup analysis according to low/high risk (according to LATITUDE study) and low/high volume (according to CHAARTED study). However, recent studies have disproven the importance of risk and volume classification in selecting treatment regimens.[29] Also, our analysis only included drug regimens and did not include radiotherapy to the primary site as a comparison arm.

CONCLUSION

We found that AAP+ADT is the most effective first-line treatment for mCSPC in terms of OS, while ENZA+AA may provide better PFS. Clinicians should take these findings into consideration when planning treatment of mCSPC.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144:1941-53.
2. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. SEER, Surveillance, Epidemiology, and End Results Program [electronic resource]. Bethesda, MD. 2005. Available from: https://seer.cancer.gov/. Accessed 22 Oct 2021.
3. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol. 2002;168:9-12.
4. 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;6:76-85.
5. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387:1163-77.
6. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol. 2019;30:1992-2003.
7. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373:737-46.
8. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol. 2018;36:1080-7.
9. Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14:149-58.
10. Gravis G, Boher JM, Joly F, Soulié M, Albiges L, Priou F, et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol. 2016;70:256-62.
11. Parker C, Gillessen S, Heidenreich A, Horwich A, ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v69-77.
12. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017;377:352-60.
13. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2019;20:686-700.
14. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD,

Dearnaley DP, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med. 2017;377:338-51.
15. James N, Rush H, Clarke N, Attard G, Cook A, Dearnaley D, et al. 611O abiraterone acetate plus prednisolone for hormone-naïve prostate cancer (PCa): long-term results from metastatic (M1) patients in the STAMPEDE randomised trial (NCT00268476). Ann Oncology. 2020;31 Suppl 4:S509.
16. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med. 2019;381:13-24.
17. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol. 2019;37:2974-86.
18. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med. 2019;381:121-31.
19. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:1119-34.
20. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162:777-84.
21. Cochrane Training. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane. 2020. Available from: http://www.training.cochrane.org/handbook. Accessed 22 Oct 2021.
22. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15:58.
23. Lombard AP, Liu L, Cucchiara V, Liu C, Armstrong CM, Zhao R, et al. Intra versus inter cross-resistance determines treatment sequence between taxane and AR-targeting therapies in advanced prostate cancer. Mol Cancer Ther. 2018;17:2197-205.
24. Khalaf D, Annala M, Finch DL, Oja CD, Vergidis J, Zulfiqar M, et al. Phase 2 randomized cross-over trial of abiraterone + prednisone (ABI+P) vs enzalutamide (ENZ) for patients (pts) with metastatic castration resistant prostate cancer (mCPRC): Results for 2nd-line therapy. J Clin Oncol. 2018;36(15 Suppl):5015.
25. Rush HL, Cook AD, Brawley CD, Murphy L, Macnair A, Millman R, et al. Comparative quality of life in patients randomized contemporaneously to docetaxel or abiraterone in the STAMPEDE trial. J Clin Oncol. 2020;38(6 Suppl):14.
26. Khalaf DJ, Sunderland K, Eigl BJ, Kollmannsberger CK, Ivanov N, Finch DL, et al. Health-related quality of life for abiraterone plus prednisone versus enzalutamide in patients with metastatic castration-resistant prostate cancer: results from a phase ii randomized trial. Eur Urol. 2019;75:940-7.
27. Wang L, Paller CJ, Hong H, De Felice A, Alexander GC, Brawley O. Comparison of systemic treatments for metastatic castration-sensitive prostate cancer: a systematic review and network meta-analysis. JAMA Oncol. 2021;7:412-20.
28. So TH, Chiang CL, Lam TC, Chan FT, Choi HH. What is the best first-line therapy for metastatic castration-sensitive prostate cancer in 2019? A network meta-analysis. Ann Oncol. 2019;30 (Suppl 9):ix69.
29. Sathianathen NJ, Koschel S, Thangasamy IA, Teh J, Alghazo O, Butcher G, et al. Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis. Eur Urol. 2020;77:365-72.