available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Prostate Cancer

Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis

Niranjan J. Sathianathen [a,b], *Samantha Koschel* [a], *Isaac A. Thangasamy* [a], *Jiasian Teh* [a], *Omar Alghazo* [a], *Georgiana Butcher* [a,c], *Harriet Howard* [a,c], *Jada Kapoor* [a], *Nathan Lawrentschuk* [a,b], *Shankar Siva* [d,e], *Arun Azad* [e,f], *Ben Tran* [f], *Damien Bolton* [b], *Declan G. Murphy* [a,e,*]

[a] *Division of Cancer Surgery, Peter MacCallum Cancer Centre, Parkville, Victoria, Australia;* [b] *Department of Surgery, Austin Health, The University of Melbourne, Parkville, Victoria, Australia;* [c] *University of Sheffield Medical School, Sheffield, UK;* [d] *Division of Radiation Oncology, Peter MacCallum Cancer Centre, Parkville, Victoria, Australia;* [e] *Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia;* [f] *Department of Medical Oncology, Peter MacCallum Cancer Centre, Parkville, Victoria, Australia*

Article info

Article history:
Accepted September 2, 2019

Associate Editor: Giacomo Novara

Keywords:
Androgen receptor-targeted therapies
Chemotherapy
Hormone sensitive
Meta-analysis
Metastasis
Prostate cancer

Abstract

Context: There have been substantial changes in the management of men with metastatic hormone-sensitive prostate cancer (mHSPC) over the past 5 yr, with upfront combination therapies replacing androgen-deprivation therapy (ADT) alone. A range of therapies have entered the space with no clear answer regarding their comparative efficacy.
Objective: To perform a systematic review and network meta-analysis to characterise the comparative efficacy of combination approaches in men with mHSPC.
Evidence acquisition: We searched multiple databases and abstracts of major meetings up to June 2019 for randomised trials of patients receiving first-line therapy for metastatic disease, a combination of ADT and one (or more) of taxane-based chemotherapy, and androgen receptor-targeted therapies. The primary endpoint was overall survival (OS) and we evaluated progression-free survival as a secondary outcome. We performed subgroup analysis based on the volume of disease.
Evidence synthesis: We found seven trials that met our eligibility criteria using either docetaxel, abiraterone acetate, enzalutamide, or apalutamide in combination with ADT. All agents in combination with ADT were shown to be superior to ADT alone; enzalutamide + ADT had the lowest absolute hazard ratio compared with ADT only (hazards ratio 0.53, 95% confidence interval 0.37–0.75), and an estimated 76.9% probability that it is the preferred treatment to prolong OS compared with other combination treatments, or with ADT alone. Enzalutamide appeared to have better OS compared with docetaxel in men with low-volume disease, but there was no difference in other comparisons.
Conclusions: Combination therapy with any of docetaxel, abiraterone acetate, enzalutamide, or apalutamide provides a significant OS benefit when compared with ADT alone. We did not identify significant differences in OS between different combination therapies. Subtle differences between these options provide clinicians considerable flexibility when selecting options for individual patients.
Patient summary: Many men with metastatic, hormone-sensitive prostate cancer should be managed with upfront combination therapy instead of androgen-deprivation therapy alone. Clinicians may consider many factors during the decision-making process, and thus management should be tailored for patients individually.

* Corresponding author. Division of Cancer Surgery, Peter MacCallum Cancer Centre, 305 Grattan Street, Parkville, 3000 Victoria, Australia. Tel.: +61385597424. Fax: +61385597709.
E-mail address: declan.murphy@petermac.org (D.G. Murphy).

https://doi.org/10.1016/j.eururo.2019.09.004
0302-2838/

1. Introduction

Following the recent publications of the Targeted Investigational Treatment Analysis of Novel Anti-androgen (TITAN) and Enzalutamide in First Line Androgen Deprivation Therapy (ADT) for Metastatic Prostate ancer (CENZAMET) trials, the therapeutic landscape for metastatic, hormone-sensitive prostate cancer (mHSPC) has become more crowded [1,2]. Compared with just 5 yr ago when ADT was the single systemic option available for mHSPC, clinicians now have an array of life-prolonging therapies which have been combined with ADT upfront—docetaxel, abiraterone acetate, enzalutamide, and apalutamide—all of which have been shown to have a significant survival benefit when compared with ADT alone. Although only the former two agents are recommended in current guidelines, the newer androgen receptor antagonists are also expected to soon feature [3]. The majority of the currently available evidence comes from studies in which only one of the aforementioned agents were studied, therefore limiting comparisons between therapies to determine the best choice. While we acknowledge that several factors such as toxicity profile, administration, and cost are all important in the decision-making process, we have performed a network meta-analysis (NMA) to determine the comparative efficacy of these agents in mHSPC based on currently available data.

2. Methods

The protocol for this systematic review and NMA was registered a priori in PROSPERO. We performed an extensive search of multiple databases (MEDLINE, Embase, ScienceDirect, Cochrane Libraries, HTA database, and Web of Science) using a range of keywords related to randomised controlled trials and mHSPC (Supplementary Table 1), focusing on papers published from January 2014 up to June 2019. We also searched the grey literature and the abstracts of the leading oncology and urology meetings published in the past 5 yr. We only included randomised and quasi-randomised controlled trials. Interventions of interest included taxane-based chemotherapy (eg, docetaxel), and androgen-axis-targeted therapies such as abiraterone acetate, apalutamide, and enzalutamide.

We included randomised trials of patients with mHSPC who were receiving first-line therapy for metastatic disease, combining ADT with one (or more) of the additional agents aforementioned listed earlier. Both patients who had previously undergone local treatment of their prostate cancer and those who have been diagnosed with de novo metastatic disease were eligible. The diagnosis of metastatic prostate cancer was based on conventional imaging.

The results of the search were screened initially by title and abstract for relevance by two independent authors with a third author consulted to resolve any disagreements. Articles that were determined to be of interest then proceeded to full-text review to determine whether they satisfied the inclusion/exclusion criteria outlined previously. If more than one report of the same trial was found, only the most up-to-date publication was included in the analysis. Data extraction was performed by two independent authors using a form developed a priori.

Our primary outcome was overall survival (OS) measured as time from randomisation to death from any cause. We also evaluated progression-free survival defined as the time from randomisation to prostate-specific antigen (PSA) progression, and radiographic and/or clinical progression as a secondary endpoint. We performed subgroup analysis based on the volume of disease (high vs low, according to the Chemo-Hormonal Therapy versus Androgen Ablation Randomised Trial for Extensive Disease in Prostate Cancer (CHAARTED) criteria [4]) as we hypothesised that there may be differences in treatment effect based on this characteristic. Subgroup analysis was only performed for the primary outcome.

2.1. Statistical analysis

We initially performed traditional pairwise meta-analysis of the included studies (data not shown). We applied the model proposed by Woods et al [5] to conduct these analyses by extracting available hazard rates and/or events of interest from each of the included studies. Unlike traditional meta-analyses, an NMA permits indirect comparisons of treatments based on common comparison arms, for example, ADT.

For this we adopted a Bayesian approach [6], according to the National Institute for Health and Care Excellence (NICE) framework [7,8], using Markov chain Monte Carlo methods with a 50 000 run-in iteration phase and a 50 000 iteration phase for parameter estimation. Convergence of iterations was assessed with trace plots and the Gelman–Rubin–Brooks statistic [9]. We used non-informative prior distributions to prevent previous assumptions from impacting the results [10]. We fitted a consistency model and assessed heterogeneity using a common variance [8]. Treatment effects were estimated using posterior means with corresponding 95% credible intervals which can be interpreted in the same manner as 95% confidence intervals (95% CI). The estimated treatment effects incorporate both available direct and indirect evidence. Heterogeneity was assessed visually using forest plots and the I^2 statistic. An $I^2 > 50\%$ was considered to present statistically significant heterogeneity. We calculated a surface under the cumulative ranking (SUCRA) to rank the preference of each treatment. This probability is determined by calculating the proportion of iterations in the Markov chain for the ranking of each treatment's hazard ratio (HR). Sensitivity analysis was performed using a random-effects model. The Bayesian deviance information criterion (DIC) was used to assess model fit. This statistic penalises complex models and a difference of two to five between models is considered significant [11]. These methods have been utilised in similar NMAs on this subject [12].

All analyses were performed using RJAGS and R (R Foundation for Statistical Computing, Vienna, Austria) version 3.4. Risk of bias was performed according to the Cochrane framework [13].

Table 1 – Details and baseline of included studies.

Combination agent	Trial name	Performance status	Disease stage	Definition of high volume disease	Previous treatment	Pre-treatment with docetaxel	Control arm treatment	Patients in control arm (*n*)	Age (yr)	PSA (ng/mL)	Gleason grade group 4 and 5, *n* (%)	Experimental arm treatment (added to the control arm treatment)	Patients in the experimental arm (*n*)	Age (yr)	PSA (ng/mL)	Gleason grade groups 4 and 5	Primary endpoint	Secondary endpoint	Median follow-up
Docetaxel	GETUG-AFU15	Karnofsky ≥70	Metastatic	NR CHAARTED definition used retrospectively	Chemotherapy or ADT only if discontinued >12 mo prior	Nil	Medical or surgical castration ± nonsteroidal antiandrogen	193	Median 64 (IQR 58–70)	Median 25.8 (IQR 5.0–126.9)	113 (59)	Docetaxel up to nine cycles without prednisone	192	Median 63 (IQR 57–68)	Median 26.7 (IQR 5.0–106.2)	103 (55)	OS	rPFS and bPFS	82.9 mo
	CHAARTED	ECOG ≤2	Metastatic	Visceral metastases or ≥4 bone lesions with ≥1 beyond spine/pelvis	ADT only if duration <24 mo and discontinued >12 mo prior	Nil	Medical or surgical castration ± nonsteroidal antiandrogen	393	Median 63 (range 39–91)	Median 50.9 (range 0.2–8450.1)	243 (62)	Docetaxel up to six cycles without prednisone	397	Median 64 (range 36–88)	Median 52.1 (range 0.1–8056.0)	241 (61)	OS	PSA < 0.2 ng/ml at 6 mo; PSA < 0.2 ng/ml at 12 mo; time to CRPC; time to clinical progression	28.9 mo
	STAMPEDE	WHO ≤2	Metastatic or node-positive or ≥2 of T3/4, Gleason 8–10, PSA ≥ 40 ng/ml	NR Multiple definitions used retrospectively	ADT only if duration <12 mo and discontinued >12 mo prior	Nil	Medical or surgical castration	1184	NR separately for the metastatic subgroup	NR separately for the metastatic subgroup	NR separately for the metastatic subgroup	Docetaxel up to 6 cycles with daily prednisone 10 mg ± zoledronic acid	1185	NR separately for the metastatic subgroup	NR separately for the metastatic subgroup	NR separately for the metastatic subgroup	OS	Failure-free survival; time to any treatment after progression including docetaxel or abiraterone	43 mo
Abiraterone	LATITUDE	ECOG ≤2	Metastatic with ≥2 of Gleason ≥8, ≥3 bone lesions, visceral metastasis	NR (see inclusion criteria)	ADT only if duration ≤3 mo; or orchidectomy ± first-generation AR antagonist; or one course palliative radiation/surgery for metastatic symptoms	Nil	Medical or surgical castration	602	Median 67 (range 33–92)	NR	586 (97)	Abiraterone acetate plus prednisone 5 mg daily	597	Median 68 (range 38–89)	NR	584 (98)	OS and rPFS	Time to PSA progression; time to symptomatic SRE; time to any new treatment including chemotherapy	30.4 mo
	STAMPEDE	WHO ≤2	Metastatic or node positive or ≥2 of T3/4, Gleason 8–10, PSA ≥ 40 ng/ml or previous surgery/ radiotherapy now relapsing with of PSA > 4 ng/ml, doubling time <6 mo, PSA > 20 ng/ml, nodal or metastatic recurrence	NR	ADT only if short term	Nil	Medical or surgical castration	957	Median 67 (62–72)	Median 56 (19–165)	721 (75)	Abiraterone acetate plus prednisone 5 mg daily	960	Median 67 (63–72)	Median 51 (19–158)	715 (74)	OS	PFS; DSS; symptomatic SRE; adverse events; QOL	40 mo
Enzalutamide	ENZAMET	ECOG ≤2	Metastatic	Visceral metastases or ≥4 bone lesions with ≥1 beyond spine/pelvis	ADT only if duration <24 mo and discontinued >12 mo prior	15% in the control arm 17% in the experimental arm (within 3 mo prior to randomisation)	ADT + nonsteroidal antiandrogen + early docetaxel up to six cycles ± prednisone in 76%	562	Median 69.0 (range 63.2–74.5)	NR	321 (57)	Enzalutamide daily + early docetaxel up to six cycles ± prednisone in 65%	563	Median 69.2 (range 63.2–74.5)	NR	335 (60)	OS	PFS; adverse events	34 mo
Apalutamide	TITAN	ECOG ≤1	Metastatic	Visceral metastases with at least one bone lesion or ≥4 bone lesions with ≥1 beyond spine/pelvis	Docetaxel up to six cycles prior to randomisation; or ADT only if duration <6 mo for mHSPC; or ADT only if duration <36 mo for localised prostate cancer; or one course palliative radiation/surgery for metastatic symptoms; or local surgery/ radiation at least 12 mo prior	10% in the control arm 11% in the experimental arm	ADT + placebo	527	Median 68 (range 43–90)	NR	358 (68)	Apalutamide daily	525	Median 68 (range 43–90)	NR	351 (67)	OS and rPFS	Time to chemotherapy; time to pain progression; time to chronic opioid use; time to SRE	22.7 mo

ADT = androgen-deprivation therapy; AR = androgen receptor; bPFS = biochemical progression-free survival; CRPC = castration-resistant prostate cancer; DSS = disease-specific survival; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; mHSPC = metastatic hormone-sensitive prostate cancer; NR = not reported; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; QOL = quality of life; rPFS = radiographic progression-free survival; SRE = skeletal related event; WHO = World Health Organisation.

3. Results

Following abstract screening and full-text review, seven trials met our inclusion criteria (Supplementary Fig.). Three trials used docetaxel + ADT [4,14–16] as the intervention, two each used abiraterone + prednisone + ADT [17–19] and enzalutamide + ADT [2,20], and one used apalutamide + ADT [1] (Table 1). The risk of bias for each of the trials is reported in Supplementary Table 2. The network was created using the ADT arm of each trial as the comparator (Supplementary Fig. 2).

3.1. Overall survival

The survival data from the randomised phase 3 study of enzalutamide plus androgen deprivation therapy versus placebo plus ADT in men with mHSPC (ARCHES trial), are currently immature and have not been reported, and therefore these were excluded. The remaining studies reported on OS and were included in the primary analysis. It should be noted that the TITAN study also included patients that were planned to receive early docetaxel, and although the data on this subgroup were not reported separately, we still included this study in the analysis because only approximately 10% of participants were planned to receive early docetaxel, and we did not believe that this would influence the results significantly. The ENZAMET study also included both patients who had received upfront docetaxel treatment and those who did not and because these groups were reported separately, we only included the latter subpopulation.

The results of the NMA with ADT alone and enzalutamide + ADT are depicted in Fig. 1A and 1B, respectively. All four interventions demonstrated significantly improved OS compared with ADT alone. These four interventions were statistically comparable to each other with none being clearly superior. However, enzalutamide + ADT had the absolute lowest HR compared with ADT alone (HR 0.53, 95% CI 0.37–0.75). Estimated HRs for all comparisons of treatments are reported in Supplementary Table 3 (see data for "Overall survival"). There was no significant heterogeneity (I^2 = 0%). There was no difference between the fixed and random effects models with the former demonstrating a better fit (DIC 23.7 vs 25.3). The result of the random effects model is reported in Supplementary Table 4 (see data for "Overall survival"). The SUCRA estimated that there is a 76.9% probability that enzalutamide is the preferred treatment to prolong OS (Fig. 2). Apalutamide had a 19.8% probability of being the best treatment from an OS perspective. Each of the treatments was relatively well tolerated.

3.2. Subgroup analysis: volume of disease

The GETUG-AFU15, CHAARTED, LATITUDE, ENZAMET, and TITAN trials reported data based on volume of disease which was included in the subgroup analysis.

For low-volume disease, only enzalutamide demonstrated improved survival compared with ADT (Fig. 3A). Enzalutamide had the lowest absolute HR compared with ADT (HR 0.38, 95% CI 0.20–0.68). The other treatments were all statistically similar to each other except that enzalutamide appeared to be superior to docetaxel in men with low-volume disease (HR 0.38, 95% CI 0.19–0.72; Fig. 3B). All treatment comparisons are reported in Supplementary Table 3 (see data for "Low-volume disease"). There was no significant heterogeneity (I^2 = 8%). There was no difference between the fixed and random effects models with the former demonstrating a better fit (DIC 18.7 vs 19.0). The result of the random effects model is reported in Supplementary Table 4 (see data for "Low-volume disease"). The calculated SUCRA suggests that there is an 84.2% probability that enzalutamide in addition to ADT is the preferred treatment option in this subgroup (Fig. 3C).

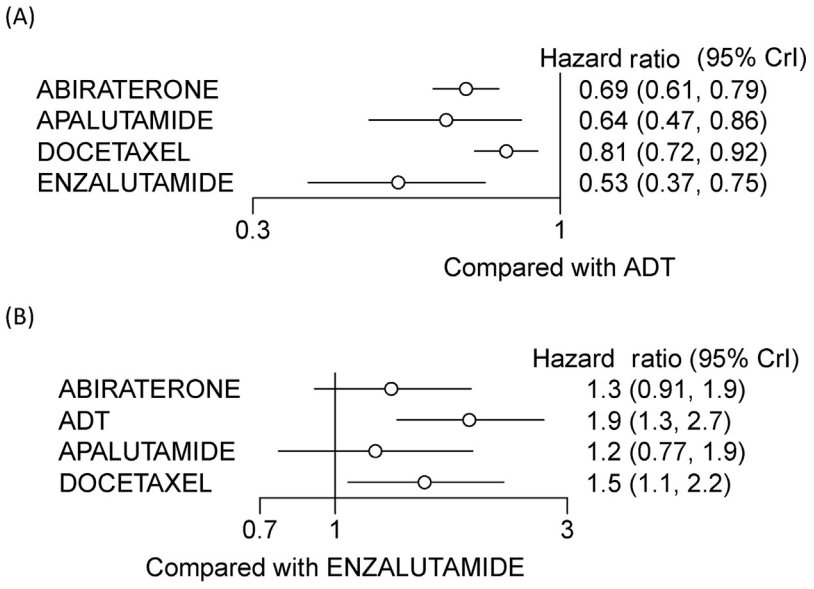


Fig. 1 – Overall survival for each intervention compared with (A) ADT and (B) enzalutamide.
ADT = androgen-deprivation therapy; CrI = credible interval.

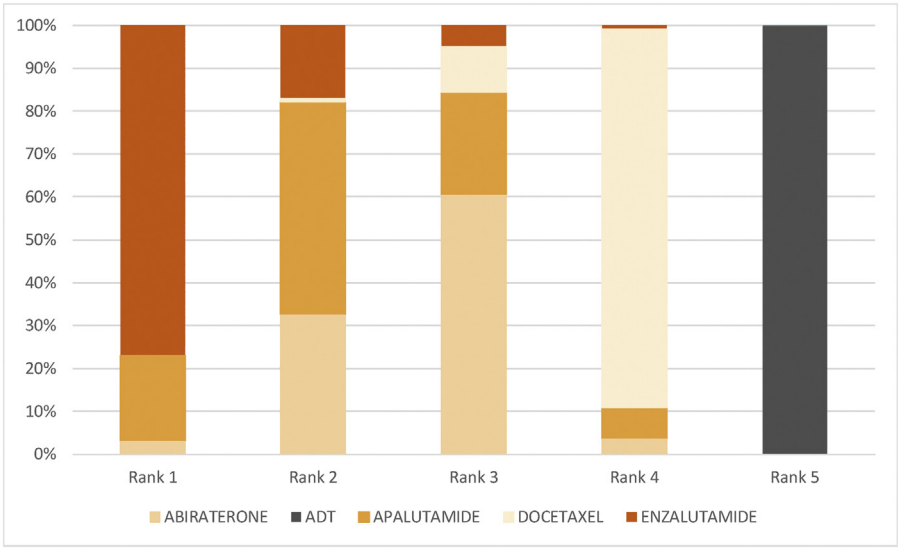


Fig. 2 – Rank probabilities graph for overall survival: primary analysis.
ADT = androgen-deprivation therapy.

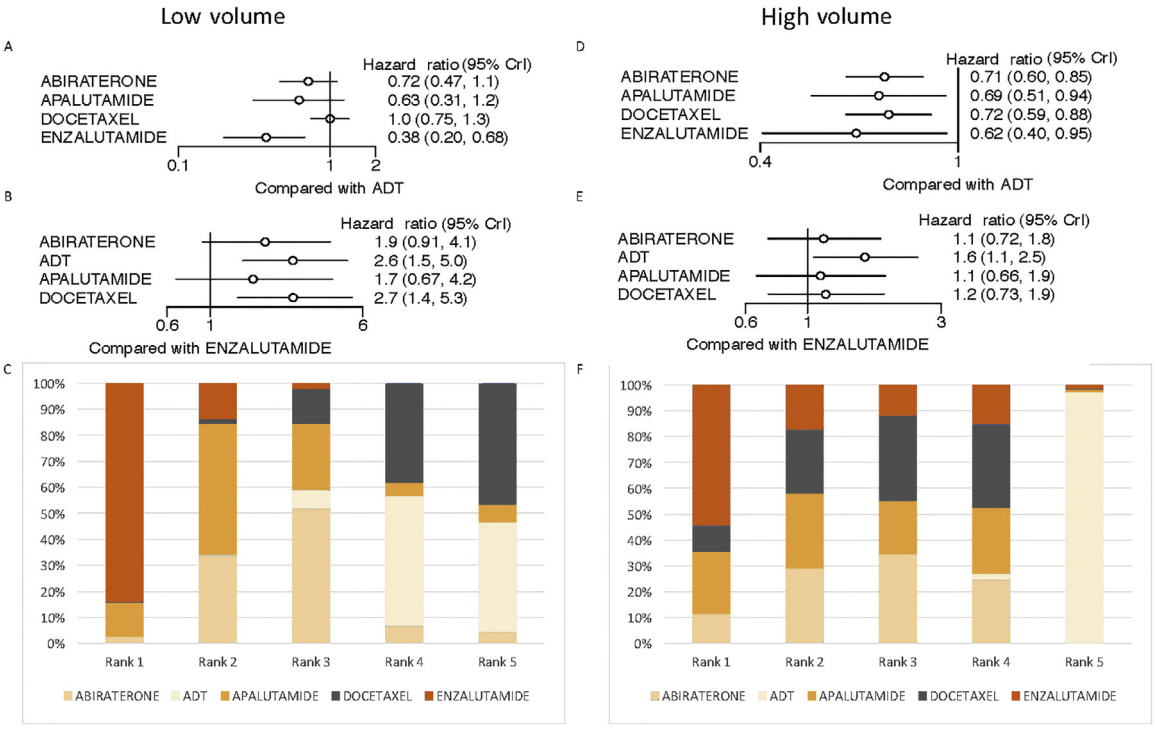


Fig. 3 – Subgroup analysis for volume of disease: low-volume disease forest plot with (A) ADT as reference, (B) enzalutamide as reference, and (C) SUCRA; high-volume disease forest plot with (D) ADT as reference, (E) enzalutamide as reference, and (F) SUCRA.
ADT = androgen-deprivation therapy; CrI = credible interval; SUCRA = surface under the cumulative ranking.

For high-volume disease, all four interventions had superior OS compared with ADT (Fig. 3D). Similar to the primary OS analysis, none of abiraterone, apalutamide, enzalutamide, or docetaxel was better than another (Fig. 3E). Estimated HRs for all comparisons of treatments are reported in Supplementary Table 3 (see data for "High-volume disease"). There was no significant heterogeneity (I^2 = 1%). There was no difference between the fixed and random effects models with the former demonstrating a better fit (DIC 18.1 vs 19.4). The result of the random effects model is reported in Supplementary Table 4 (see data for "High-volume disease"). The SUCRA estimated that there is a 54.4%, 2413%, and 11.5% probability that enzalutamide, apalutamide, and abiraterone are the preferred agents in men with high-volume disease (Fig. 3F).

3.3. Progression-free survival

The GETUG-AFU15, CHAARTED, STAMPEDE, ENZAMET, and TITAN trials were included in this secondary endpoint. All four interventions delayed progression compared with ADT only (Supplementary Fig. 3). Abiraterone and enzalutamide were comparable to each other and preferred over both docetaxel and apalutamide. All treatment comparisons are outlined in Supplementary Table 3 (see data for "Progression-free survival"). There was no significant heterogeneity (I^2 = 4%). There was no difference between the fixed and random effects models with the former demonstrating a better fit (DIC 21.4 vs 22.8). The result of the random effects model is reported in Supplementary Table 4 (see data for "Progression-free survival"). The former two had a 42.7% and 57.3% probability of being the preferred agent, respectively.

3.4. Risk of bias

The risk of bias for the included trials are outlined in Supplementary Table 2. Overall, the trials were of moderate quality with downgrading primarily occurring for a lack of blinding.

4. Discussion

The primary endpoint of each of these randomized controlled trials was reached, thereby demonstrating that each of abiraterone acetate, apalutamide, enzalutamide, and docetaxel, when combined with ADT, prolongs OS compared with ADT alone in men with mHSPC. The current available evidence does not provide a clear answer regarding which agent might be preferred, although our findings suggest that enzalutamide in combination with ADT may be the most effective in terms of delaying death from any cause. This is an important development from previous NMAs that did not include studies on apalutamide and enzalutamide, and concluded that abiraterone acetate was likely the preferred treatment option [21,22]. Moreover, enzalutamide appears to be more effective than docetaxel which was the first agent to be used as a combination therapy in mHSPC, although in the subgroup analyses within ENZAMET, there was no significant survival advantage when adding enzalutamide to ADT + docetaxel, versus ADT + docetaxel alone.

As mentioned previously, there are several factors that influence the choice of agent in mHSPC and therefore the decision should still be individually tailored to the patient. First, this analysis does not include any information on quality of life and this should be an important consideration from a patient viewpoint. The literature reports that patients on ADT + docetaxel initially have inferior quality of life while on treatment compared with ADT alone, but this improves over time and surpasses treatment with ADT only [23]. By contrast, the LATITUDE trial reported that patients on abiraterone acetate had a consistently better quality of life compared with those receiving ADT only at most time points measured [24]. Meanwhile, apalutamide was shown to be comparable to ADT only from a quality of life perspective [1]. Second, there are also substantial differences in the toxicity profile of each medication and nuances regarding monitoring. Although the adverse effects of docetaxel are well understood, it is interesting to note that 25% of patients receiving enzalutamide in ENZAMET reported grade 2 fatigue, compared with 14% in the standard of care arm. Furthermore, in those patients who received both docetaxel and enzalutamide in addition to ADT, grade 2 peripheral neuropathy was reported in 9% of patients, compared with 3% in those who received enzalutamide + ADT. Seizures were also reported in 1% of patients receiving enzalutamide. Regarding abiraterone acetate, prednisolone must be prescribed concomitantly which is an additional consideration. There are further distinctions regarding the mode of administration (intravenous or oral) and the duration of treatment. The cost of each agent is variable and therefore needs to be a factor in the decision-making process. A recent comparative analysis of ADT alone, ADT + docetaxel, and ADT + abiraterone acetate demonstrated that although the latter may provide the best quality-adjusted survival, it was not a cost-effective option in the US health setting [25]. It is evident from these array of factors, which need to be considered, that this is a complex decision and that each agent is optimal for certain clinical scenarios or characteristics. Further research is required to define these and guide clinicians to make the best choice of agent. Androgen-axis-targeted therapies are likely to be attractive to clinicians (urologists) and patients who may wish to avoid chemotherapy, and enzalutamide and apalutamide have the additional attraction of avoiding steroids.

The findings of this review should be interpreted within the context of its limitations. First and foremost, many conclusions are reliant on indirect comparisons which is not an adequate replacement for direct comparisons from randomised data and thus the results need to be interpreted with caution. Although these head-to-head trials are ongoing (PEACE-1, NCT01957436), they are not expected to complete and report for many years and therefore we need to rely on the best available data from indirect comparisons in the interim. Furthermore, the results of the ARASENS (NCT02799602: darolutamide + ADT vs ADT only) and ARCHES (NCT02677896) trials may also impact these findings. Moreover, there are differences in each of the populations of the included trials that may contribute to the differences in treatment effect rather than being due to the treatment alone. Along these lines, the ENZAMET trial administered nonsteroidal anti-androgen therapy with ADT in the control arm, and this was allowed at investigator discretion in CHAARTED. Complete androgen blockade may have a small survival benefit and would therefore bias the results against enzalutamide [26]. Furthermore, this review also only considered systemic treatment for mHSPC and therefore did not include radiotherapy which may be beneficial, especially in low-volume disease [27]. There are also differences in definitions of volume of disease that limit our confidence in the findings of the subgroup analysis. These concerns are also amplified by the emergence of newer imaging modalities into the prostate

cancer landscape which are superior to conventional computed tomography and bone scintigraphy and likely shift the classification of disease burden [28].

5. Conclusion

Our findings demonstrate that combination therapy with any of docetaxel, abiraterone acetate, enzalutamide, or apalutamide provides a significant OS benefit when compared with ADT alone. Subtle differences between these options allow clinicians considerable flexibility when selecting options for individual patients. We await the results of ongoing randomised studies directly comparing upfront combination interventions to provide further guidance for clinicians. In the meantime, it is reasonable to conclude that upfront combination approaches are the new standard of care for men with mHSPC, and ADT alone will likely only be used in limited circumstances or when economic factors constrain options.

Author contributions: Declan G. Murphy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sathianathen, Murphy, Lawrentschuk.
Acquisition of data: Sathianathen, Thangasamy.
Analysis and interpretation of data: Sathianathen, Thangasamy, Teh, Alghazo.
Drafting of the manuscript: Sathianathen, Murphy, Lawrentschuk, Howard, Butcher, Koschel.
Critical revision of the manuscript for important intellectual content: Sathianathen, Murphy, Lawrentschuk, Tran, Azad, Bolton, Siva.
Statistical analysis: Sathianathen.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Murphy, Bolton.
Other: None.

Financial disclosures: Declan G. Murphy certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Declan G. Murphy has served as an advisor and/or paid speaker for Astellas, Janssen, Bayer, Ferring, Ipsen and Astra Zeneca.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.09.004.

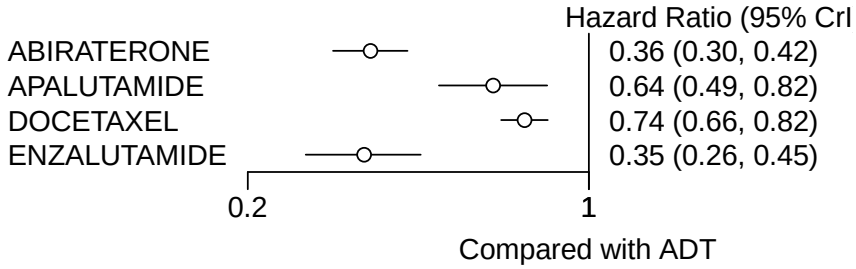
References

[1] Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13–24.
[2] Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019;381:121–31.
[3] Mottet N, van den Bergh R, Briers E, et al. EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–29.
[4] Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
[5] Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Med Res Methodol 2010;10:54.
[6] van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades A, Welton NJ. Automating network meta-analysis. Res Synth Methods 2012;3:285–99.
[7] Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. Med Decis Making 2013;33:597–606.
[8] Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2:a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;33:607–17.
[9] Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. J Comput Graph Stat 1998;7:434–55.
[10] Ades AE, Sculpher M, Sutton A, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. Pharmacoeconomics 2006;24:1–19.
[11] Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian data analysis. Boca Raton, FL: Chapman and Hall/CRC; 2013.
[12] Feyerabend S, Saad F, Li T, et al. Survival benefit, disease progression and quality-of-life outcomes of abiraterone acetate plus prednisone versus docetaxel in metastatic hormone-sensitive prostate cancer: a network meta-analysis. Eur J Cancer 2018;103:78–87.
[13] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[14] James ND, Sydes MR, Clarke NW, 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.
[15] Gravis G, Fizazi K, Joly F, 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.
[16] Gravis G, Boher J-M, Joly 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.
[17] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60.
[18] Fizazi K, Tran N, Fein L, 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.
[19] James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–51.

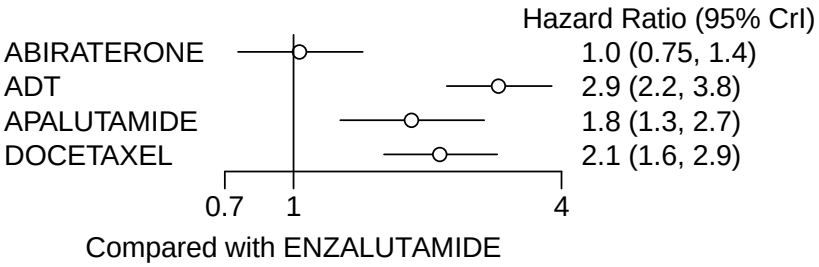
[20] Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. Phase III study of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): The ARCHES trial. J Clin Oncol 2019;37:687.
[21] Wallis CJD, Klaassen Z, Bhindi B, et al. Comparison of abiraterone acetate and docetaxel with androgen deprivation therapy in high-risk and metastatic hormone-naive prostate cancer: a systematic review and network meta-analysis. Eur Urol 2018;73:834–44.
[22] Vale CL, Fisher DJ, White IR, et al. What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis. Ann Oncol 2018;29:1249–57.
[23] Morgans AK, Chen YH, Sweeney CJ, et al. Quality of life during treatment with chemohormonal therapy: analysis of E3805 chemohormonal androgen ablation randomized trial in prostate cancer. J Clin Oncol 2018;36:1088–95.
[24] Chi KN, Protheroe A, Rodriguez-Antolin A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol 2018;19:194–206.
[25] Sathianathen NJ, Alarid-Escudero F, Kuntz KM , et al. A cost-effectiveness analysis of systemic therapy for metastatic hormone-sensitive prostate cancer. Eur Urol Oncol 2019;2:649–55.
[26] Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T. Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev 2000Cd001526.
[27] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353–66.
[28] Perera M, Papa N, Roberts M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2019.01.049.

Supplementary Figure 3. Progression-free survival: forest plot compared to (A) ADT only, (B) enzalutamide, (C) abiraterone and (D) SUCRA rank probabilities graph

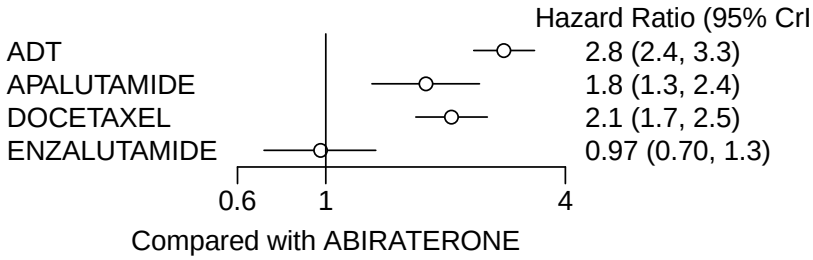
A



B



C



D