Contents lists available at ScienceDirect

Prostate International

Research Article

Oral chemotherapeutic agents in metastatic hormone-sensitive prostate cancer: A network meta-analysis of randomized controlled trials

Yong Seong Lee [a,†], Seong Hwan Kim [b,†], Jong Hyun Tae [c], In Ho Chang [c], Tae-Hyoung Kim [c], Soon Chul Myung [c], Myoungsuk Kim [d], Tuan Thanh Nguyen [e], Joongwon Choi [a], Jung Hoon Kim [a], Jin Wook Kim [a], Se Young Choi [c,*]

[a] Department of Urology, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gyeonggi-do, Korea
[b] Department of Orthopedic Surgery, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea
[c] Department of Urology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea
[d] Healthcare Big-Data Center, Research Institute of Clinical Medicine, Kyung Hee University Hospital at Gang Dong, Seoul, Korea
[e] Department of Urology, Cho Ray Hospital, University of Medicine and Pharmacy at Ho Chi Minh City, Viet Nam

ARTICLE INFO

ABSTRACT

Background: Multiple oral chemotherapeutic agents for metastatic hormone-sensitive prostate cancer (mHSPC) have been developed for conjugated use with conventional androgen deprivation therapy (ADT). Several randomized controlled trials (RCTs) report significant benefits in mHSPC patients. Therefore, we compared overall survival (OS) and progression-free survival (PFS) benefits among considerable mHSPC oral chemotherapeutic agents.
Materials and methods: We investigated mHSPC treatment efficacy through a systematic RCT-trial literature review (PubMed, Embase, Web of Science, the Cochrane Library, and Scopus). Two reviewers independently screened, extracted data, and assessed bias risk in duplicate.
Results: We identified 18 RCTs ($n = 13,509$). Concerning OS, ADT + abiraterone, ADT + abiraterone + docetaxel, ADT + apalutamide, ADT + bicalutamide, ADT + darolutamide + docetaxel, ADT + enzalutamide, ADT + orteronel, and ADT + rezvilutamide were more effective than the standard of care (SOC). Comparing PFS, most treatments were more effective than SOC, excluding ADT + bicalutamide, nilutamide, flutamide, ADT + bicalutamide + palbociclib, and ADT + nilutamide. ADT + docetaxel with androgen receptor targeted agent (ARTA) triplet therapy was not among the top three treatments determined through ranking analysis.
Conclusions: Novel oral chemotherapeutic agent combination therapies must replace current ADT monotherapy and ADT + docetaxel SOC. Even so, ADT + docetaxel with ARTA triplet therapy still is not the best mHSPC treatment and requires further study.
© 2023 The Asian Pacific Prostate Society. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author. Department of Urology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, 102, Heukseok-ro, Dongjak-gu, Seoul, 06973, Korea.
   E-mail addresses: yongslee@cau.ac.kr (Y.S. Lee), ksh170177@nate.com (S.H. Kim), jjongee13@gmail.com (J.H. Tae), caucih@cau.ac.kr (I.H. Chang), kthlmk@nate.com (T.-H. Kim), uromyung@cau.ac.kr (S.C. Myung), fsl10@naver.com (M. Kim), thanhtuan0131@gmail.com (T.T. Nguyen), uromedic@naver.com (J. Choi), simbauro80@hanmail.net (J.H. Kim), jinwook@cau.ac.kr (J.W. Kim), urosyc@cau.ac.kr (S.Y. Choi).
   † Both authors contributed equally to this work as the first authors.

1. Introduction

Globally, more than 1.4 million new prostate cancer cases and 375,000 related deaths were reported in 2020.[1] Approximately, 9% of all men diagnosed with prostate cancer will have metastatic disease at the time of their diagnosis (*de novo*) in the USA.[2] Furthermore, about 27% of localized prostate cancer patients will eventually develop metastatic disease depending on the

higher Gleason score or stage after radical prostatectomy.[3] Metastatic hormone-sensitive prostate cancer (mHSPC) includes synchronous (*de novo*) and metachronous disease. Eventually, mHSPC can lead to castrate-resistant prostate cancer (CRPC) and mortality.[4]

Androgen-suppressing strategies were the mHSPC standard of care (SOC) when Huggins and Hodges showcased how responsive prostate cancer is to androgen deprivation therapy (ADT) over 70 years ago.[5] However, the mHSPC treatment landscape has severely changed over the last 10 years, with novel agents expressing mCRPC survival benefits. Randomized control trials (RCTs) CHAARTED and STAMPEDE revealed a higher overall survival (OS) compared to ADT monotherapy, establishing docetaxel and ADT combinations as new mHSPC SOC.[6,7] Androgen receptor targeted agent (ARTA) is a prostate cancer treatment that targets the androgen receptor by blocking androgen activity and production. Novel ARTA medications are orally administered, making hospitalization unnecessary as patients prefer it to intravenous treatment.[8] Recent PEACE-1 and ARASENS ADT, docetaxel, and ARTA triplet therapy trials confirmed superior OS than previous SOC.[9,10] Continuously, new medicines using other pathways have been developed.[11,12]

With these dramatically changing mHSPC treatment options, clinicians are spoilt for choice. Therefore, we aimed to determine which oral chemotherapeutic agents with ADT combination therapy could most benefit mHSPC patients.

2. Materials and methods

2.1. Ethics statement

This meta-analysis did not require ethical approval because the data were synthesized from previously published studies.

2.2. Protocol and registration

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. In addition, this review was registered in the PROSPERO International Prospective Registry of Systematic Reviews.

2.3. Search strategy

A comprehensive literature search was conducted using several databases: PubMed, Embase, Web of Science, the Cochrane Library, and Scopus. The date was restricted to articles published on or before November 12, 2022, as the search transpired on November 13, 2022. The search specifics were as follows: (Prostate cancer OR prostate carcinoma OR prostatic cancer OR prostatic cancer disease) AND (metastatic OR M1 OR high volume disease OR low volume disease OR advanced) AND (hormone-sensitive OR hormone naïve OR castration sensitive) AND (randomized). The search criteria were used to identify all potentially relevant articles. After combining the results, two authors (S.Y.C. and M.S.H.) independently selected the relevant studies. The Kappa value (κ) was assessed for interrater validity. Any conflicts between the two reviewers were resolved through discussion.

2.4. Eligibility criteria

The inclusion criteria were as follows: (1) mHSPC patients; (2) oral chemotherapeutic agent use; (3) control group comparisons; (4) OS or progression-free survival (PFS) outcomes; and (5) only RCTs. The exclusion criteria were review articles, basic studies, non-English articles, and duplicated studies.
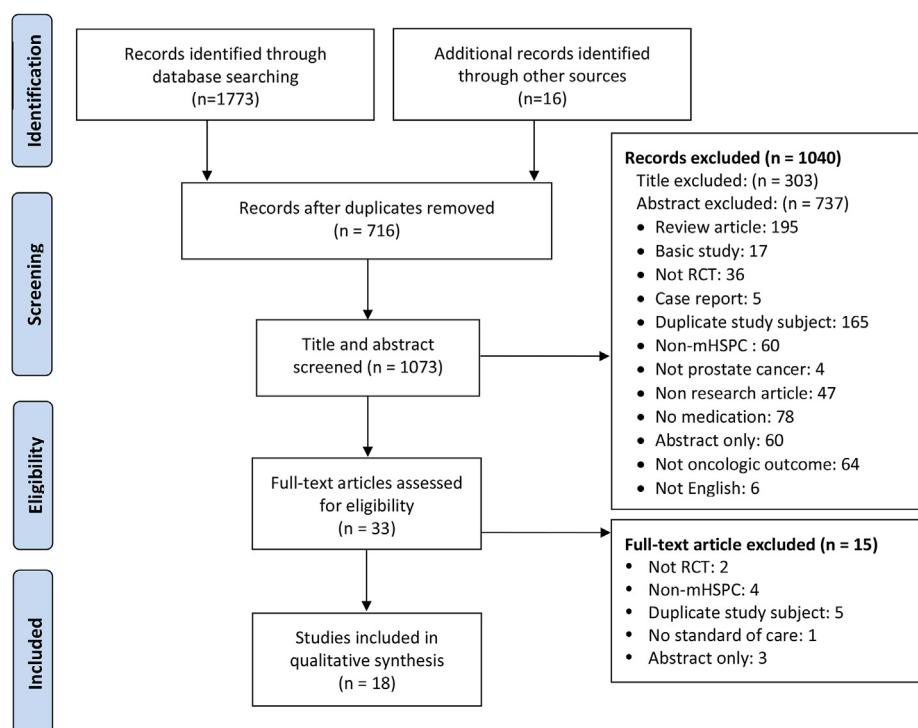

Fig. 1. Study design flow chart. RCT, randomized control trial; mHSPC, metastatic hormone-sensitive prostate cancer.

2.5. Data extraction and collection

Two authors (S.Y.C. and M.S.H.) independently reviewed each eligible article and extracted: (1) publication (first author name and publication year); (2) population (each group's sample size); (3) tumor (high and low volumes); (4) treatment (oral chemotherapeutic agents); and (5) outcome (OS, and PFS) data.

2.6. Risk of bias assessment

Randomization process, intended intervention deviation, missing outcome data, outcome measurement, reported result selection, and overall biases were assessed. Any disagreements were resolved through discussion.

2.7. Statistical analysis

Network meta-analysis (NMA) determined the relative treatment effect correlations.[13] Hazard ratio (HR) and confidence intervals (CIs) estimated OS and PFS differences.[13] Relative rankings were assessed through surface under the cumulative ranking curve (SUCRA) probabilities. NMAs were applied by high- and low-mHSPC volumes.[6] All statistical analyses were performed with R software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Study selection

We identified 1,773 articles through the initial database search and 16 from other sources; thus, 716 were duplicate publications. Among these, title and abstract reviews eliminated 1,040 articles; full-text reviews excluded another 33. Finally, 18 articles were selected for the meta-analysis ($\kappa = 0.84$, almost perfect agreement). The flow diagram in Fig. 1 illustrates this selection process.

3.2. Study characteristics

The 18 eligible studies, published between 1997 and 2022, involved 13,509 patients (treatment group: 6,753 and control group: 6,756; Table 1). Ten studies focused on high-volume disease patients, and 14 treatment types were used, including SOC. The SOC included PEACE-1 and ARASENS ADT monotherapy and ADT + docetaxel. Supplementary Table 1 summarizes the assessment results for bias risk in the included studies.

3.3. Network meta-analysis

Fig. 2 displays the network plot. The mHSPC OS analysis evaluated and ranked 12 treatments: SOC had the highest patient number ($n = 4,623$; related studies = 10), ADT + bicalutamide the second ($n = 1,510$; related studies = 5), and ADT + flutamide the third ($n = 1,259$; related studies = 3). Similarly, mHSPC PFS analysis evaluated and ranked 14 treatments: SOC the highest ($n = 3,783$; related studies = 8), ADT + bicalutamide the second ($n = 1,569$; related studies = 7), and ADT + enzalutamide the third ($n = 1,173$; related studies = 3). Finally, high- and low-volume mHSPC OS analysis assessed six treatments.

3.4. Network comparison

Fig. 3 denotes the forest plots. In the total mHPSC OS comparison, ADT + abiraterone, ADT + abiraterone + docetaxel, ADT + apalutamide, ADT + bicalutamide, ADT + darolutamide

Table 1
Randomized controlled trials included in network meta-analysis

Study	Year	Name	Medicine		No. of patients		Age		High volume (%)		Outcomes
			Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	
Smith[10]	2022	ARASENS	ADT + Darolutamide + Docetaxel	ADT + Docetaxel	651	654	67 (41–89)	67 (42–86)	61.7	64.8	OS, PFS
Armstrong[22]	2022	ARCHES	ADT + Enzalutamide	ADT	574	576	70 (46–92)	70 (42–92)			OS, PFS
Akaza[14]	2009		ADT + Bicalutamide	ADT	102	101	≥75: 48%	≥75: 50.5%			OS
Usami[15]	2007		ADT + Bicalutamide	ADT	102	101	≥75: 48%	≥75: 50.5%			PFS
Vaishampayan[23]	2021		ADT + Enzalutamide	ADT + Bicalutamide	36	35	66 (54–86)	63 (51–84)	56	49	OS, PFS
Davis[24]	2019	ENZAMET	ADT + Enzalutamide	ADT + Bicalutamide, Nilutamide, Flutamide	563	562	69 (64–73)	69 (63–75)	51.7	52.8	OS, PFS
Tyrrell[16]	2000		ADT + Flutamide	ADT	152	151	73 (47–91)	73 (50–90)			OS
Fizazi[25]	2019	LATITUDE	ADT + Abiraterone	ADT	597	602	67.3	66.8	81.6	77.7	OS
Fizazi[9]	2022	PEACE-1	ADT + Abiraterone + Docetaxel	ADT + Docetaxel	583	589	67 (61–72)	66 (59–72)	57	57	OS, PFS
Gu[26]	2022	CHART	ADT + Rezvilutamide	ADT + Bicalutamide	326	328	69 (64–74)	69 (64–75)	100	100	OS, PFS
Chi[27]	2021	TITAN	ADT + Apalutamide	ADT	525	527	69 (45–94)	68 (43–90)	61.9	63.6	OS, PFS
Schellhammer[17]	1997		ADT + Bicalutamide	ADT + Flutamide	404	409	70 (43–91)	70 (42–93)			OS, PFS
Eisenberger[18]	1998		ADT + Flutamide	ADT	698	687	71 (65–76)	71 (65–76)			OS
Alghandour[21]	2021	MANSMED	ADT + Metformin + Bicalutamide	ADT + Bicalutamide	36	39	67 (46–81)	69 (46–87)	50	59	PFS
Reijke[19]	2002		ADT + Nilutamide	ADT	225	232	71 (50–85)	72 (46–86)			OS, PFS
Agarwal[28]	2022		ADT + Orteronel	ADT + Bicalutamide	638	641	68 (46–90)	68 (19–92)	49	49	OS, PFS
Palmbos[20]	2021		ADT + Bicalutamide + Palbociclib	ADT + Bicalutamide	40	20	68	66			PFS
James[29]	2022	STAMPEDE	ADT + Abiraterone	ADT	501	502	67 (62–71)	67 (62–72)	48.7	51.3	OS, PFS

ADT, Androgen deprivation therapy; OS, overall survival; PFS, progression-free survival.
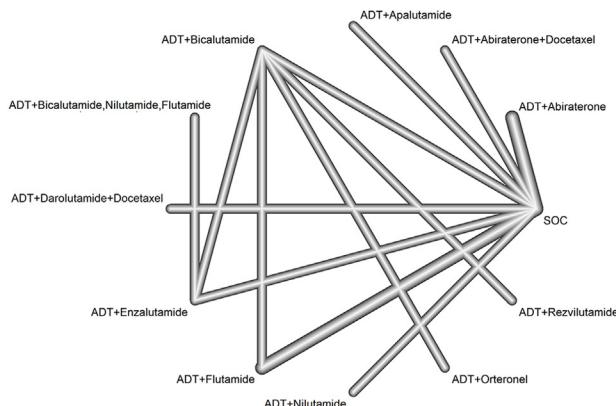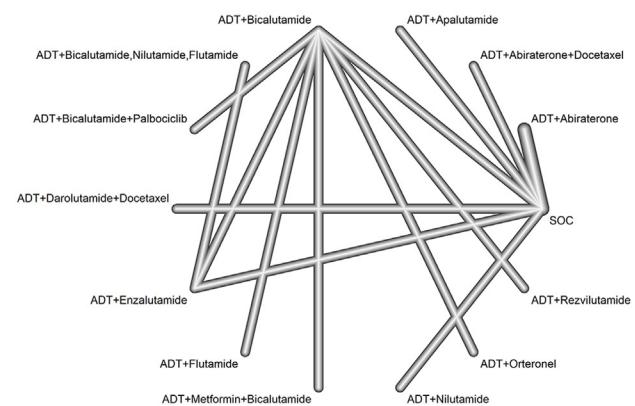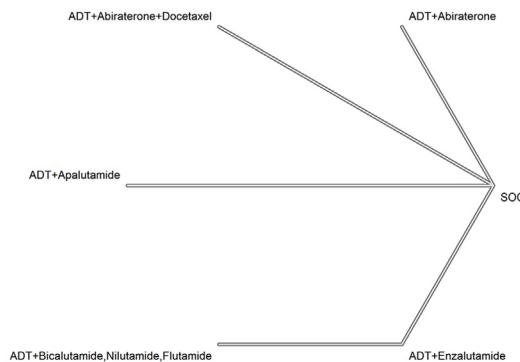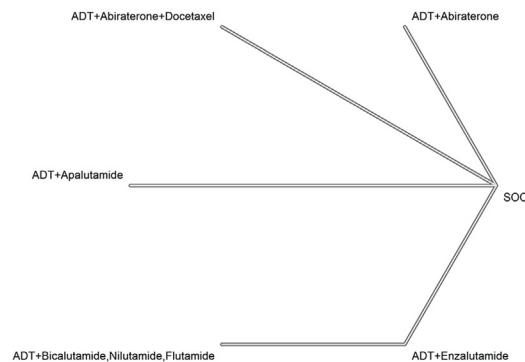
Fig. 2. Network plot **(A)** Overall and **(B)** progression-free survival in total metastatic hormone-sensitive prostate cancer. Overall survival in **(C)** high- and **(D)** low-volume metastatic hormone-sensitive prostate cancer.

+ docetaxel, ADT + enzalutamide, ADT + orteronel, and ADT + rezvilutamide were more effective than SOC. In the total mHPSC OS comparison, ADT + abiraterone was more effective than ADT + abiraterone + docetaxel, ADT + bicalutamide, ADT + bicalutamide, nilutamide, flutamide, ADT + flutamide, and SOC. In the total mHPSC PFS comparison, most treatments were more effective than SOC, except ADT + bicalutamide, nilutamide, flutamide, ADT + bicalutamide + palbociclib and ADT + nilutamide. In the total mHPSC PFS comparison, ADT + apalutamide, ADT + darolutamide + docetaxel, ADT + orteronel, and ADT + rezvilutamide were more effective than ADT + abiraterone. In the high-volume mHSPC OS comparison, ADT + abiraterone, ADT + abiraterone + docetaxel, ADT + apalutamide, and ADT + enzalutamide were more effective than SOC. In the low-volume mHSPC OS comparison, ADT + apalutamide was more effective than SOC.

3.5. Treatment ranking

Total mHSPC OS SUCRA value rankings were ADT + rezvilutamide (98%), ADT + enzalutamide (77%), and ADT + abiraterone (76%). Total mHPSC PFS SUCRA value rankings were ADT + rezvilutamide (95%), ADT + metformin + bicalutamide (88%), and ADT + orteronel (81%). High-volume mHSPC OS SUCRA value rankings were ADT + abiraterone (84%), ADT + enzalutamide

(70%), and ADT + apalutamide (58%). Low-volume mHSPC OS SUCRA value rankings were ADT + apalutamide (91%), ADT + enzalutamide (70%), and ADT + abiraterone (62%) (Fig. 4).

3.6. Publication bias

The funnel plot does not suggest a publication bias in eligible studies (Supplementary Fig. 1). In addition, the funnel plot shape does not convey any evidence of pronounced asymmetry.

4. Discussion

Effective mHSPC treatment is imperative for managing advanced prostate cancer, improving survival, delaying disease progression, and improving patient quality of life. Traditionally, maximum androgen blockade involves medical or surgical castration and anti-androgen medications to reduce androgen levels.[14—19] However, some maximum androgen blockade trials with additional medicine utilized alternative pathways to inhibit prostate cancer growth.[20,21] Additionally, several clinical trials have signified that earlier ARTA uses with conventional ADT considerably improve oncologic outcomes.[22—29] For instance, two recent RCTs garnered increased interest in ARTA and ADT + docetaxel triplet therapy.[9,10] Although these trials could represent a patient survival
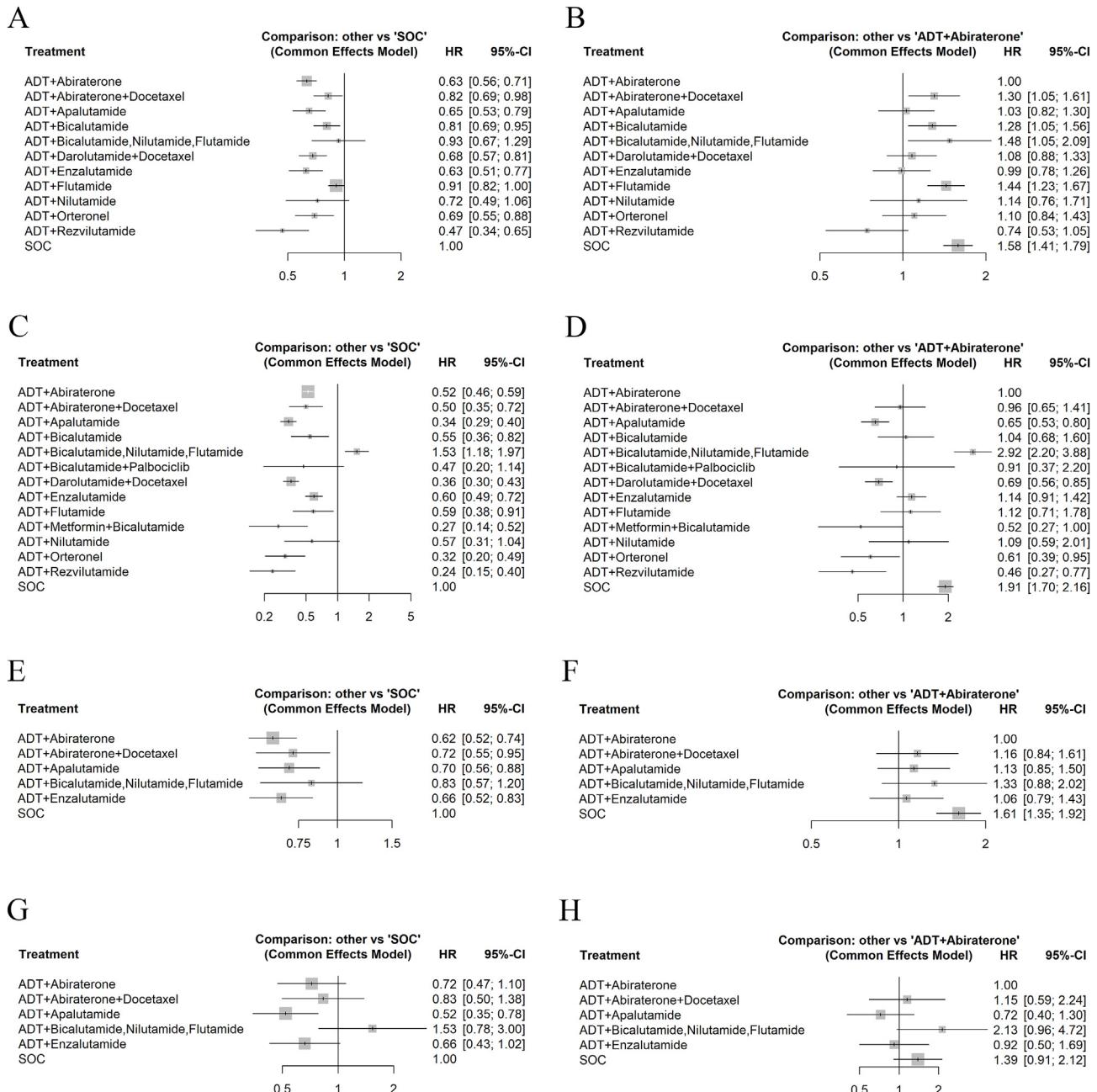
Fig. 3. Forest plot Overall survival compared to **(A)** standard of care (SOC) and **(B)** ADT + abiraterone in total metastatic hormone-sensitive prostate cancer. Progression-free survival compared to **(C)** SOC and **(D)** ADT + abiraterone in total metastatic hormone-sensitive prostate cancer. Overall survival compared to **(E)** SOC and **(F)** ADT + abiraterone in high-volume metastatic hormone-sensitive prostate cancer. Overall survival compared to **(G)** SOC and **(H)** ADT + abiraterone in low-volume metastatic hormone-sensitive prostate cancer.

breakthrough, dramatic mHSPC treatment changes challenge physicians' decision-making.

Our NMAs confirmed that even though some portion of SOC included ADT + docetaxel, SOC was still inferior to most new ARTA. Similar NMA studies comparing ARTA and docetaxel in mHSPC reported that enzalutamide, apalutamide, and abiraterone expressed more efficacy in PFS,[30] possibly from each medicine's duration. ARTA was continuously used until CRPC progression, but docetaxel was only used for six cycles. Considering adverse effects, docetaxel exhibited the highest risk among new drugs,[31] provoking fatigue, neuropathy, neutropenia, anemia, and thrombocytopenia.[30] In addition, efficacy, safety, and administration method

influence treatment preference.[8] Docetaxel administration is age-limited, so only highly selected patients with favorable health status are considered intravenous chemotherapy candidates.[32] Therefore, we focused on oral chemotherapeutic agents in mHSPC.

In our ranking analysis, triplet therapy did not offer more pronounced OS or PFS benefits than current doublet therapy, such as rezvilutamide, orteronel, enzalutamide, or abiraterone. Rezvilutamide is a novel androgen-receptor inhibitor with a low blood-brain barrier penetration rate, reducing seizure risk.[26] Although all CHART trial patients with high-volume mHSPC and previous docetaxel were excluded, the rezvilutamide treatment group demonstrated improved OS and PFS compared to
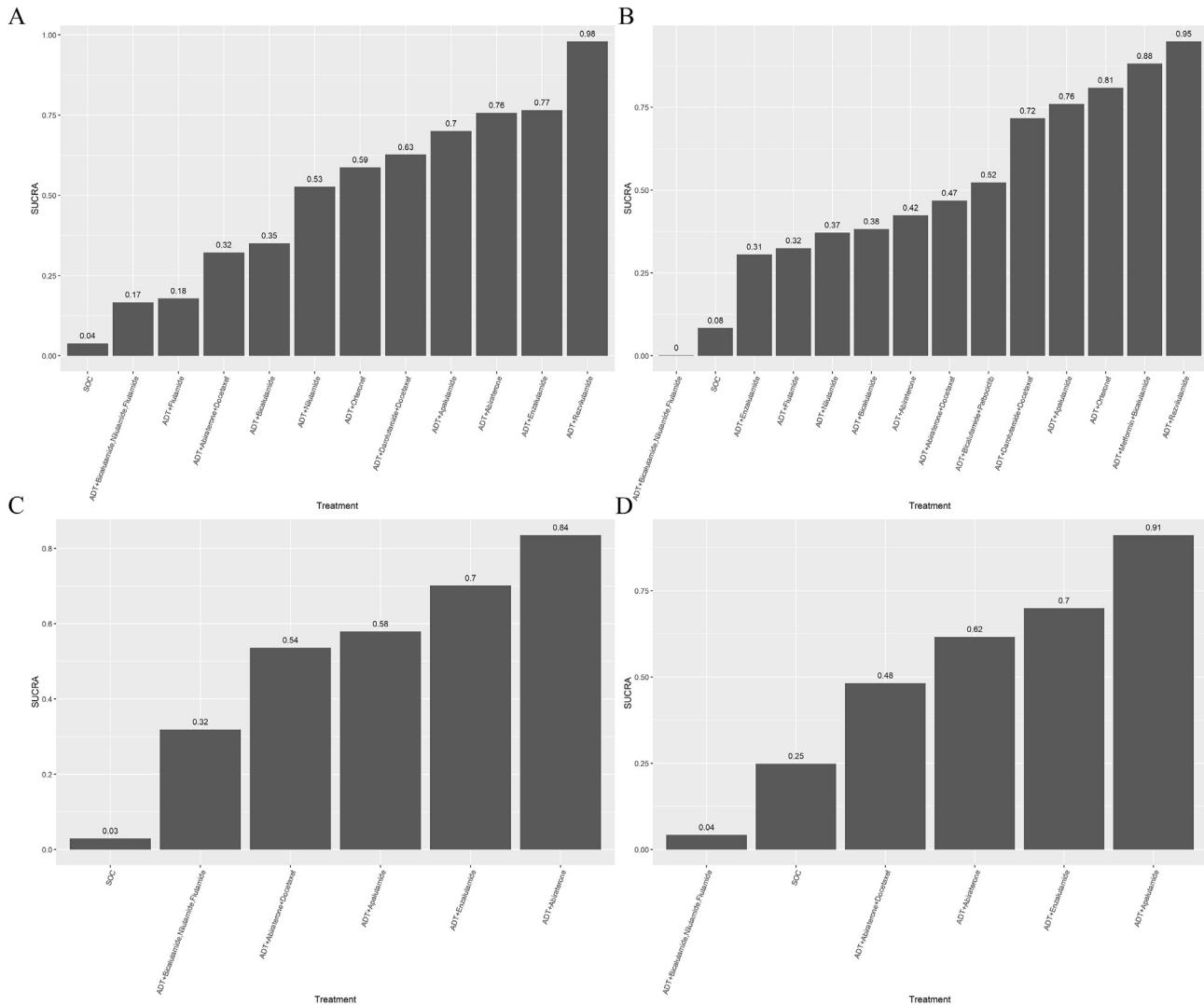
Fig. 4. Ranking analysis (A) Overall and **(B)** progression-free survival in total metastatic hormone-sensitive prostate cancer. Overall survival in **(C)** high- and **(D)** low-volume metastatic hormone-sensitive prostate cancer.

ADT + bicalutamide. Orteronel is a novel CYP17 inhibitor with a higher CYP17,20-lyase specificity and reduces secondary mineralocorticoid excess syndrome risks.[28] In other NMA triplet therapy studies, ADT + darolutamide + docetaxel ranked first, and ADT + abiraterone + docetaxel second compared to ARTA doublet therapy[33]; however, the triplet therapies failed to demonstrate more significant OS benefits.[33] In addition, we used more RCTs, including maximum androgen blockade and novel oral chemotherapeutic agents. In the PEACE-1 trial, triplet therapy showed an 11% higher rate of grade 3 or more adverse effects than doublet therapy.[9] In the ENZAMET trial, planned early docetaxel use (almost triplet therapy) increased adverse effects during the first six months, possibly related to a drug–drug interaction between enzalutamide and docetaxel.[24] Therefore, mHSPC triplet therapies need further grounding to be considered SOC.

In high-volume mHSPC subgroup analysis, ARTA doublet or triplet therapies were superior to SOC, but maximum androgen blockade was not. In low-volume mHSPC, only apalutamide revealed significantly better OS than SOC. Apalutamide's maximal efficacy at lower steady-state plasma may have a higher therapeutic effect than enzalutamide.[34] However, the low-volume subgroup might be underpowered to confirm differences between

experimental and SOC groups. In addition, favorable low-volume OS between groups might mature results during follow-up periods.

This study has some limitations. First, indirect comparison cannot replace direct, well-designed RCT. However, NMA was used for our indirect comparison because no direct data existed. Second, heterogeneous patient characteristics and study designs were included. Surgical orchiectomy was regarded as SOC ADT.[18] Previous or early docetaxel was allowed in some studies.[22,24,27] Third, ADT + docetaxel was used as SOC. ADT + docetaxel offered better OS than ADT monotherapy and became the new SOC. During the PEACE-1 trial, a new docetaxel trend had a heterogenous SOC composition.[9] Lastly, the ARASENS trial recently reported their subgroup analysis by disease volume[35] but was excluded because of search date restrictions.

5. Conclusions

In this mHSPC patient study, we indirectly compared OS and PFS data from RCTs employing oral chemotherapeutic agents. We determined that new oral chemotherapeutic agents with ADT are effective treatment options. Combination therapies with new oral chemotherapeutic agents must replace previous mHSPC SOC,

including ADT monotherapy and ADT + docetaxel. However, ADT + docetaxel with ARTA triplet therapy is still not the best mHSPC treatment option, and further triplet therapy studies are essential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2023.06.003.

References

1. Wang L, Lu B, He M, Wang Y, Wang Z, Du L. Prostate cancer incidence and mortality: global status and temporal trends in 89 countries from 2000 to 2019. Front Public Health 2022;10811044.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17–48.
3. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al. Radical prostatectomy or watchful waiting in prostate cancer - 29-year follow-up. N Engl J Med 2018;379:2319–29.
4. Choi SY, Ryu J, You D, Hong JH, Ahn H, Kim CS. Simple risk assessment in prostate cancer patients treated with primary androgen deprivation therapy: the Korean Cancer Study of the Prostate risk classification. Int J Urol 2019;26: 62–8.
5. Schroder F, Crawford ED, Axcrona K, Payne H, Keane TE. Androgen deprivation therapy: past, present and future. BJU Int 2012;109(Suppl 6):1–12.
6. 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.
7. 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.
8. de Freitas HM, Ito T, Hadi M, Al-Jassar G, Henry-Szatkowski M, Nafees B, et al. Patient preferences for metastatic hormone-sensitive prostate cancer treatments: a discrete choice experiment among men in three European countries. Adv Ther 2019;36:318–32.
9. Fizazi K, Foulon S, Carles J, Roubaud G, McDermott R, Flechon A, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet 2022;399:1695–707.
10. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med 2022;386:1132–42.
11. Pan J, Ye D, Zhu Y. Olaparib outcomes in metastatic castration-resistant prostate cancer: first real-world experience in safety and efficacy from the Chinese mainland. Prostate Int 2022;10:142–7.
12. Kim Y, Yoo S, Lim B, Hong JH, Kwak C, You D, et al. A novel biguanide derivative, IM176, induces prostate cancer cell death by modulating the AMPK-mTOR and androgen receptor signaling pathways. Prostate Int 2022;11:83–90.
13. 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.
14. Akaza H, Hinotsu S, Usami M, Arai Y, Kanetake H, Naito S, et al. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. Cancer 2009;115:3437–45.
15. Usami M, Akaza H, Arai Y, Hirano Y, Kagawa S, Kanetake H, et al. Bicalutamide 80 mg combined with a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A monotherapy in advanced prostate cancer: findings from a phase III randomized, double-blind, multicenter trial in Japanese patients. Prostate Cancer Prostatic Dis 2007;10:194–201.
16. Tyrrell CJ, Altwein JE, Klippel F, Jurincic-Winkler C, Varenhorst E, Lunglmayr G, et al. Comparison of an LH-RH analogue (Goeserelin acetate, 'Zoladex') with combined androgen blockade in advanced prostate cancer: final survival results of an international multicentre randomized-trial. International Prostate Cancer Study Group. Eur Urol 2000;37:205–11.
17. Schellhammer PF, Sharifi R, Block NL, Soloway MS, Venner PM, Patterson AL, et al. Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized, multicenter trial. Casodex Combination Study Group. Urology 1997;50:330–6.
18. Eisenberger MA, Blumenstein BA, Crawford ED, Miller G, McLeod DG, Loehrer PJ, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998;339:1036–42.
19. de Reijke T, Derobert E, Anandron/Nilutamide Study G. Prognostic factor analysis in patients with advanced prostate cancer treated by castration plus anandron or placebo: a final update. Eur Urol 2002;42:139–46.
20. Palmbos PL, Daignault-Newton S, Tomlins SA, Agarwal N, Twardowski P, Morgans AK, et al. A randomized phase II study of androgen deprivation therapy with or without palbociclib in RB-positive metastatic hormone-sensitive prostate cancer. Clin Cancer Res 2021;27:3017–27.
21. Alghandour R, Ebrahim MA, Elshal AM, Ghobrial F, Elzaafarany M, ELbaiomy MA. Repurposing metformin as anticancer drug: randomized controlled trial in advanced prostate cancer (MANSMED). Urol Oncol 2021;39: 831 e1–e10.
22. Armstrong AJ, Azad AA, Iguchi T, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2022;40:1616–22.
23. Vaishampayan UN, Heilbrun LK, Monk 3rd P, Tejwani S, Sonpavde G, Hwang C, et al. Clinical efficacy of enzalutamide vs bicalutamide combined with androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a randomized clinical trial. JAMA Netw Open 2021;4:e2034633.
24. 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.
25. Fizazi K, Tran L, 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.
26. Gu W, Han W, Luo H, Zhou F, He D, Ma L, et al. Rezvilutamide versus bicalutamide in combination with androgen-deprivation therapy in patients with high-volume, metastatic, hormone-sensitive prostate cancer (CHART): a randomised, open-label, phase 3 trial. Lancet Oncol 2022;23:1249–60.
27. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. J Clin Oncol 2021;39:2294–303.
28. Agarwal N, Tangen CM, Hussain MHA, Gupta S, Plets M, Lara PN, et al. Orteronel for metastatic hormone-sensitive prostate cancer: a multicenter, randomized, open-label phase III trial (SWOG-1216). J Clin Oncol 2022;40:3301–9.
29. James ND, Clarke NW, Cook A, Ali A, Hoyle AP, Attard G, et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476). Int J Cancer 2022;151:422–34.
30. Mori K, Mostafaei H, Sari Motlagh R, Pradere B, Quhal F, Laukhtina E, et al. Systemic therapies for metastatic hormone-sensitive prostate cancer: network meta-analysis. BJU Int 2022;129:423–33.
31. 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.
32. Boyle HJ, Alibhai S, Decoster L, Efstathiou E, Fizazi K, Mottet N, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. Eur J Cancer 2019;116: 116–36.

33. Mandel P, Hoeh B, Wenzel M, Preisser F, Tian Z, Tilki D, et al. Triplet or doublet therapy in metastatic hormone-sensitive prostate cancer patients: a systematic review and network meta-analysis. Eur Urol Focus 2023;9:96–105.
34. Clegg NJ, Wongvipat J, Joseph JD, Tran C, Ouk S, Dilhas A, et al. ARN-509: a novel antiandrogen for prostate cancer treatment. Cancer Res 2012;72:1494–503.
35. Hussain M, Tombal B, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide plus androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III ARASENS trial. J Clin Oncol 2023. https://doi.org/10.1200/JCO.23.00041:JCO2300041.