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Review Article

Visceral Metastasis Predicts Response to New Hormonal Agents in Metastatic Castration-Sensitive Prostate Cancer

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Abstract

Visceral metastasis (VM) and a higher number of bone metastasis generally define high volume/risk in patients with metastatic castration-sensitive prostate cancer (mCSPC). Subgroup analysis of pivotal trials did not show a clear benefit of second-generation non-steroidal anti-androgens (NSAAs) in patients with VM. However, subgroup analysis of the trial assessing abiraterone acetate, a CYP 17 inhibitor, plus prednisone (AAP) showed an improved overall survival (OS) in patients with mCSPC with VM. We searched MEDLINE, Web of Science, and congress abstracts for the phase III randomized controlled trials of second-generation NSAAs and AAP in patients with mCSPC. In this pooled analysis, we included 6485 patients from the 6 phase III trials. The rate of patients with VM was 15.2%. Interestingly, in contrast to NSAAs, AAP seems to be effective in improving OS among patients with VM (hazard ratio, HR: 0.89, 95% CI, 0.72-1.11, $P = .30$ for second-generation NSAAs; HR: 0.58, 95% CI, 0.40-0.84, $P = .004$ for AAP). In contrast, both second-generation NSAAs (HR: 0.63, 95% CI, 0.57-0.70, $P < .001$) and AAP (HR: 0.68, 95% CI, 0.57-0.81, $P < .001$) improved OS in patients without VM. In this pooled analysis, we demonstrate that while AAP provided an OS improvement in patients with VM, second-generation NSAAs did not demonstrate a similar OS benefit in this population.

Key words: prostate cancer; castration-sensitive; abiraterone acetate; non-steroidal anti-androgens.

Implications for Practice

Organ metastasis may change the effectiveness of new hormonal agents in patients with metastatic hormone-sensitive prostate cancer.

Introduction

Metastatic castration-sensitive prostate cancer (mCSPC) is a heterogeneous disease. While a subset of patients present with de novo metastatic prostate cancer (PCa; approximately 4% of all patients with PCa), a population of patients presented with metachronous metastases, having prior radical local and/or systemic treatment.[1-3] Given the heterogeneity in the disease course, tumor burden categorized as low or high volume or as low high risk has helped inform prognosis and treatment options in patients with mCSPC. The presence of visceral metastasis (VM) and a higher number of bone metastasis are generally classified as high volume or high risk, respectively.[4-6] In addition to the clinical classification, genomic profiling of patients with low- and high-volume mCSPC has demonstrated that high-volume disease is enriched for mutations in driver genes, such as *TP53*, *WNT*, *PI3K/Akt/mTOR*, and the clinical course of the disease in low-volume mCSPC harboring *TP53* mutations approximated the course of those with high-volume disease.[7] Similarly, poor clinical features, such as high pretreatment PSA level and Gleason score, were prominent in patients with high-volume/risk mCSPC compared to low-volume/risk of the disease.[8]

VM is not common among patients with mCSPC and is observed in approximately 10%-20% of all patients with mCSPC.[6] The presence of VM has been associated with a worse prognosis.[9,10] Docetaxel was one of the first drugs that improved overall survival (OS) in patients with mCSPC, especially in high-volume disease.[11-13] Androgen receptor signaling inhibitors (ARSI), including second-generation non-steroidal anti-androgens (NSAAs) and abiraterone acetate (AA) plus prednisone (AAP), have improved OS for patients with mCSPC.[5,6,14-16] Recently, triplet therapies, including ARSI plus ADT with docetaxel, also improved OS, particularly in patients with high-risk disease. Data on the benefit of triple therapy in low- and high-volume disease was presented for the PEACE-1 trial of added abiraterone and seemed to show a greater benefit in those with high-volume disease without

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sufficient follow-up for the patients with low-volume disease; similarly, this subgroup analysis from the ARASENS trial of added darolutamide to ADT plus docetaxel showed that triplet therapy was more effective in patients with mCSPC with high volume than those with low volume.[17-19] In addition, subgroup analysis of pivotal trials (ie, ENZAMET, ARCHES, TITAN trials) did not show a clear benefit of second-generation NSAAs in patients with VM.[8,14,20] However, none of these trials stratified the patients according to the presence of VM. In contrast to the results of NSAAs, AAP seemed to be effective in patients with VM.[21] Similar findings were also observed in patients with metastatic castration-resistant prostate cancer (mCRPC). AAP improved OS in patients with and without VM treated after progression with docetaxel.[22] However, patients with VM treated with enzalutamide after docetaxel in the castration-resistant setting did not have better OS than the placebo.[23]

In this systematic review and meta-analysis, we aimed to evaluate the pooled data from phase III trials of ARSI in patients with mCSPC to dissect the impact of AAP versus NSAA on OS for patients with mCSPC with VM.

Materials and Methods

Study Cohort

We evaluated MEDLINE, Web of Science, and congress abstracts on October 5, 2022. The following keywords and boolean operators were used: *"((enzalutamide OR darolutamide OR apalutamide OR abiraterone acetate" OR "anti-androgens" OR antiandrogens OR "hormonal therapy") AND ("castration-sensitive" OR "hormone-sensitive") AND (prostate cancer))"*

All studies complied with the following criteria: (a) patients—patients aged 18 years or above diagnosed with mCSPC, (b) Intervention—patients treated with ARSI, (c) Comparator—standard treatment (ADT ±first generation NSAA or docetaxel), (d) Outcome—OS, (e) Study design—randomized controlled phase III clinical trials. Pre-clinical studies, phases I or II clinical trials, reviews, meta-analyses, articles not in English, and articles without full text were excluded.

Data Extraction

All selected full-text articles were reviewed independently by 2 reviewers (E.Y and Y.Ü.). Data from these full-text manuscripts were extracted to a database including baseline characteristics (ie, trial names, year and first author, the median age, trial design, numbers of patients enrolled in each arm, and presence of VM). VM was defined as metastatic spread to the organs and structures, such as lung, liver, adrenal gland, brain, kidney, and pleura in all studies. Involvement of regional and non-regional lymph nodes was not considered as VM.

Risk of Bias Assessment

Two reviewers (E.Y and Y.Ü.) independently assessed the risk of bias using the RevMan 5.3 meta-analysis software (The Nordic Cochrane Centre, Copenhagen, Denmark) and following the recommendations of the "Cochrane Handbook for Systematic Reviews of Interventions." In addition, the Jadad score was computed for each study.[24] The summary of risk of bias assessment is shown in Fig. 1.

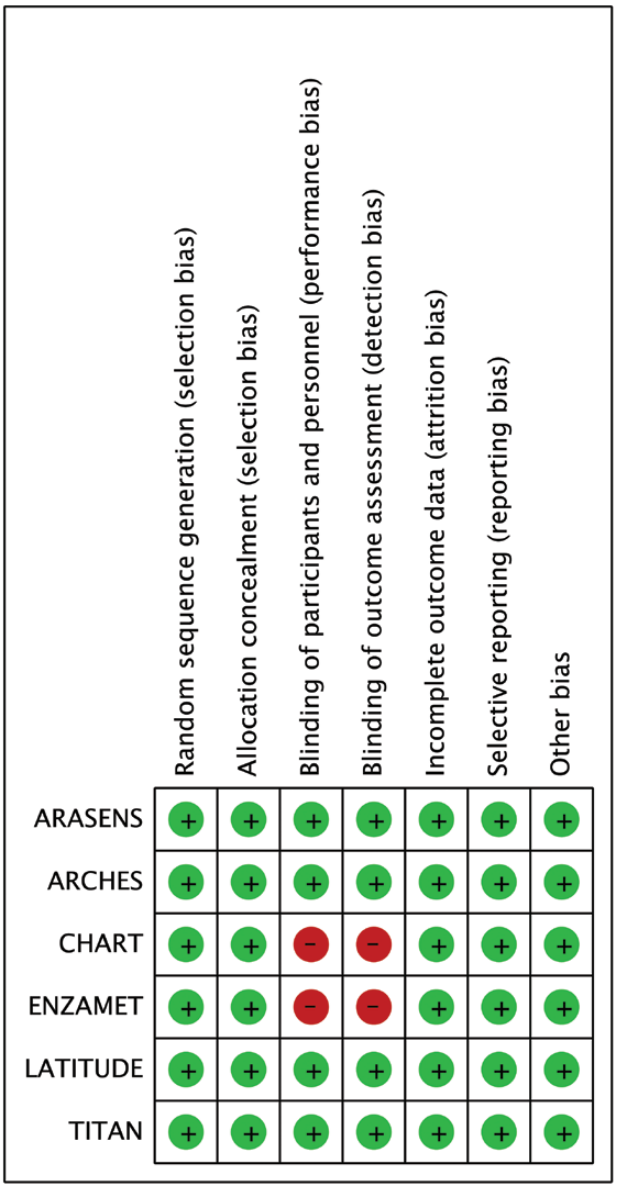

Figure 1. Risk of bias assessment.

Statistical Analysis

The meta-analysis was performed using a random-effects model and the Mantel-Haenszel method to account for heterogeneity in OS between the studies. Subgroup analysis for second-generation NSAAs and AAP was performed to account for the expected source of heterogeneity and indirectly compare OS between subgroups. The calculated effect size was the Hazard Ratio (HR) and its 95% confidence interval (95% CI). The primary comparison was the OS between ARSI and standard treatment. All analyses were done using the Review Manager software, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The threshold for statistical significance for the tests of overall effect and subgroup comparison was 0.05 and for the tests of heterogeneity, within each subgroup and overall, was 0.10. The I^2 coefficient was additionally used to quantify the degree of heterogeneity within and between subgroups.

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Results

After searching the criteria described earlier, we identified 1502 articles. We removed duplicated results and assessed 950 articles. After excluding reviews, pre-clinical studies, articles not in English, and phase I or II trials, we assessed 9 full-text articles. Finally, we included 6 pivotal trials (ENZAMET,[25] ARCHES,[20] TITAN,[8] ARASENS,[19] LATITUDE,[21] CHART[26]) with the latest and updated reports of these studies. We excluded PEACE-1, STAMPEDE, and SWOG-1216 trials due to a lack of data regarding patients with VM. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram of search results is shown in Supplementary Fig. S1.

A total of 6485 patients from the 6 phase III trials were included in this pooled analysis. The rate of patients with VM was 15.2% (n = 986). A higher rate of patients with VM was observed in the second-generation NSAAs group than in the AAP group (19.1% vs. 13.7%, P < .001). A total of 4 trials presented data regarding the number of patients with liver or lung metastases.[8,20,21,25] The most common metastatic site was the lung followed by the liver and other sites, such as the adrenal, kidney, brain, and pleura. The baseline characteristics of the included trials are shown in Table 1.

Pooled data showed that ARSI improved OS both in patients with VM (HR: 0.80, 95% CI, 0.67-0.97, P = .02) and those without VM (HR: 0.64, 95% CI, 0.59-0.70, P < .001). However, when dissecting the effect of AAP and second-generation NSAAs, in contrast to NSAAs, AAP seems to be effective in improving OS among patients with VM (HR: 0.89, 95% CI, 0.72-1.11, P = .30 for second-generation NSAAs; HR: 0.58, 95% CI, 0.40-0.84, P = .004 for AAP). In contrast, both second-generation NSAAs (HR: 0.63, 95% CI, 0.57-0.70, P < .001) and AAP (HR: 0.68, 95% CI, 0.57-0.81, P < .001) improved OS in patients without VM (Figs. 2 and 3).

Discussion

This pooled analysis showed that ARSI improve OS in patients with and without VM. However, second-generation NSAAs did not improve OS in patients with VM compared to the control arm. To the best of our knowledge, this is the first analysis to assess the survival outcomes in patients with mCSPC with VM treated with second-generation NSAAs and AAP.

To date, 2 meta-analyses evaluated the effect of ARSI and chemotherapy on patients with VM.[27,28] A study by Roviello et al, including ENZAMET, TITAN, LATITUDE, and CHAARTED trials, showed that ARSI or docetaxel was associated with improved OS in both patients with and without VM. However, this analysis included the CHAARTED trial, which was primarily assessed the effect of docetaxel, and it might cause heterogeneity in findings.[28] Conversely, another study by Buonerba et al, including ENZAMET, TITAN, and LATITUDE trials, showed that ARSI did not improve OS in patients with VM. The immature data for OS in the included trials might explain the negative result in the study of Buonerba et al.[27] In contrast, our meta-analysis included the updated OS data from all the trials included.

The ARASENS and PEACE-1 trials recently showed improved OS using ARSI plus ADT with docetaxel in patients with mCSPC.[17-19] According to the data from these 2 trials, treatment intensification may be considered, especially in patients with a high tumor burden and VM. Of note, other pivotal trials of second-generation NSAAs conducted among patients with mCSPC permitted the inclusion of patients treated with previous or concurrent docetaxel. Unfortunately, we did not include the PEACE-1 trial because of the lack of available data about the survival outcomes of VM. In light of this, it is difficult to interpret the effect of docetaxel added to ARSI on OS in our pooled analysis. An individual patient data (IPD) meta-analysis of these trials may enable investigation of the effect of docetaxel in those patients.

It should be noted that when we separate the trials of second-generation NSAAs and AAP, second-generation NSAAs did not improve OS in patients with VM. However, AAP was effective in those patients. It is hard to further comment on the difference between second-generation NSAAs and AAP with the results of our analysis; however, we can hypothesis about the underlying reason for our study results. While AAP and second-generation NSAAs both aim to decrease the effect of androgens in tumor tissue, their mechanisms of action are different. AA is a CYP-17 inhibitor, which decreases testosterone production in the adrenal glands, testicles, and tumor itself, while second-generation NSAAs potently inhibit the androgen receptor and without concurrent ADT would result in elevated testosterone levels. In addition to the blockade of AR, second-generation NSAAs also inhibit the translocation of the androgen-AR complex to the nucleus and the activation of transcription factors.[29,30] CYP-17 inhibition decreases glucocorticoid levels, and AA is combined with prednisone. Including prednisone in AAP may be one of the possible mechanisms of action on tumor microenvironment, thus, the response to ARSI in patients with VM. Both AR and glucocorticoid receptor (GR) are members of the nuclear receptor superfamily, and they are classified in the subgroup-3 subfamily. They usually bind similar DNA regions and activate common response elements.[31,32] The diverse physiologic effects of these receptors are mainly caused by their different expression rates in the tissues.[31] It is hypothesized that they may compensate for each other's activities. Arora et al and Isikbay et al elucidated how GR causes NSAA resistance.[33,34] Arora et al showed that GR binds similar target genes to bypass AR blockade. According to this study, in the CRPC cells treated with NSAA, *serum and glucocorticoid-regulated kinase-1* (*SGK-1*) expression—a common target of AR and GR—increased. In contrast, other AR-induced genes expression (eg, *PMEPA1, SNAI2*, *KCNN2*, *LONRF1*, and *SPOCK1*) decreased.[34] Similarly, Isikbay et al showed that AR and GR share common anti-apoptotic gene targets, including *SGK-1* and *Map kinase phosphatase-1* (*MKP-1*)*/dual specificity phosphatase 1* (*DUSP1*). Thus, anti-apoptotic proteins synthesized from these anti-apoptotic genes lead to tumor growth.[33] However, the relationship between the GR expression level and the response to steroids is unclear.[35] However, prednisone induces glucocorticoid-mediated apoptosis of tumor cells via increasing transforming growth factor-beta (TGF-β) and decreasing interleukin-6, and it may cause tumor shrinkage.[35]

The difference between the AAP and second-generation NSAAs in improving survival among mCSPC patients with VM might be explained by the effect of second-generation NSAAs on AR. Tumor biology likely is different by the site of metastasis.[36] As in CSPC, sites of metastasis are prognostic in patients with mCRPC; liver metastasis has a poorer prognosis than lung metastasis.[37] Post hoc analysis of the latitude trial

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Table 1. Characteristics of the included phase III randomized controlled trials of androgen receptor signal inhibitors.

Trial name	Author, year	Design	Patient population	Primary endpoint	Median age (years)	Intervention/ control arms	Patients (all)(*n*)	Patients with VM (*n*)	Patients with liver metastasis (*n*)	Patients with lung metastasis (*n*)	Patients with other* visceral metastasis (*n*)	Patients treated with docetaxel(*n*)	Jadad score
ARAS-ENS[1]	Smith et al (2022)	Phase III	mCSPC	OS	67	Darolutamide + ADT+ Docetaxel	651	111	N/A	N/A	N/A	651	5
					67	Placebo + ADT + Docetaxel	654	118	N/A	N/A	N/A	654	
ARCHES[2]	Armstrong et al, 2022	Phase III	mCSPC	rPFS	70	Enzalutamide + ADT	574	64	8	55	5	103	5
					70	Placebo + ADT	576	64	16	47	4	102	
CHART[3]	Gu et al, 2022	Phase III	mCSPC	rPFS/OS	69	Rezvilutamide + ADT	326	64	N/A	N/A	N/A	0	3
					69	Bicalutamide+ ADT	328	70	N/A	N/A	N/A	0	
EN-ZAMET[4]	Davis et al, 2022	Phase III	mCSPC	OS	69	Enzalutamide + ADT	563	69	13	55	4	254	3
					69	Standard NSAA + ADT	562	70	11	48	15	249	
TITAN[5]	Chi et al, 2021	Phase III	mCSPC	rPFS/OS	69	Apalutamide + ADT	525	56	12	47	N/A	58	5
					68	Placebo + ADT	527	72	13	64	N/A	55	
LATI-TUDE[6]	Baciarello et al, 2021	Phase III	mCSPC	rPFS/OS	68	Abiraterone + ADT	597	114	32	73	20	0	3
					67	Placebo + ADT	602	114	30	72	13	0	

ADT: androgen deprivation therapy; mCSPC: metastatic castration-sensitive prostate cancer; NSAA: non-steroidal anti-androgen; Standard NSAA: bicalutamide, nilutamide, or flutamide; OS: overall survival; rPFS: radiographic progression-free survival; VM: visceral metastasis
*Other visceral metastasis: Adrenal, kidney, brain, and pleura.

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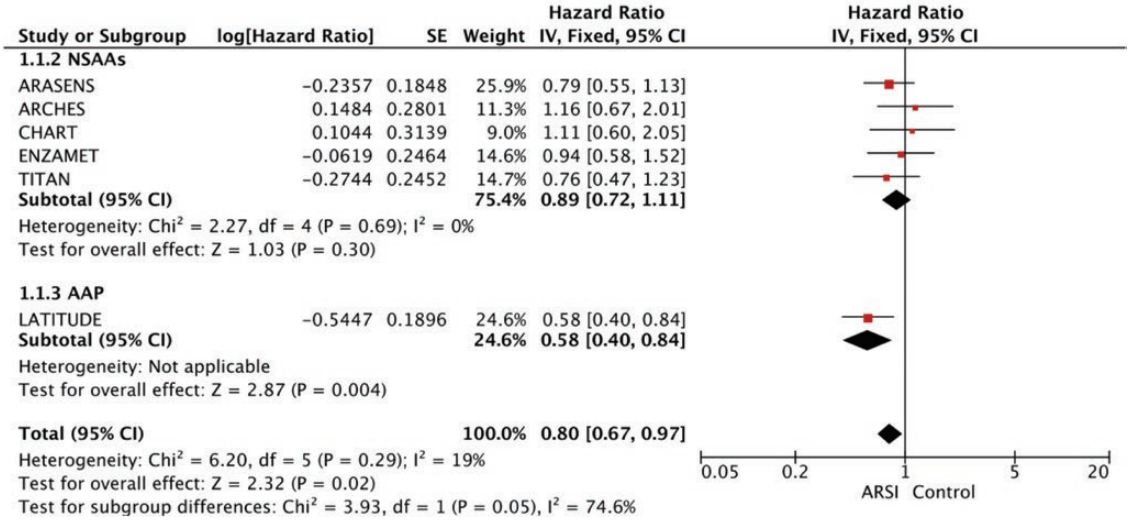

Figure 2. Forest plot of overall survival in patients with visceral metastasis.AAP: abiraterone acetate plus prednisone; CI: confidence interval; IV: inverse variance; NSAAs: non-steroidal anti-androgens; SE: standard error.

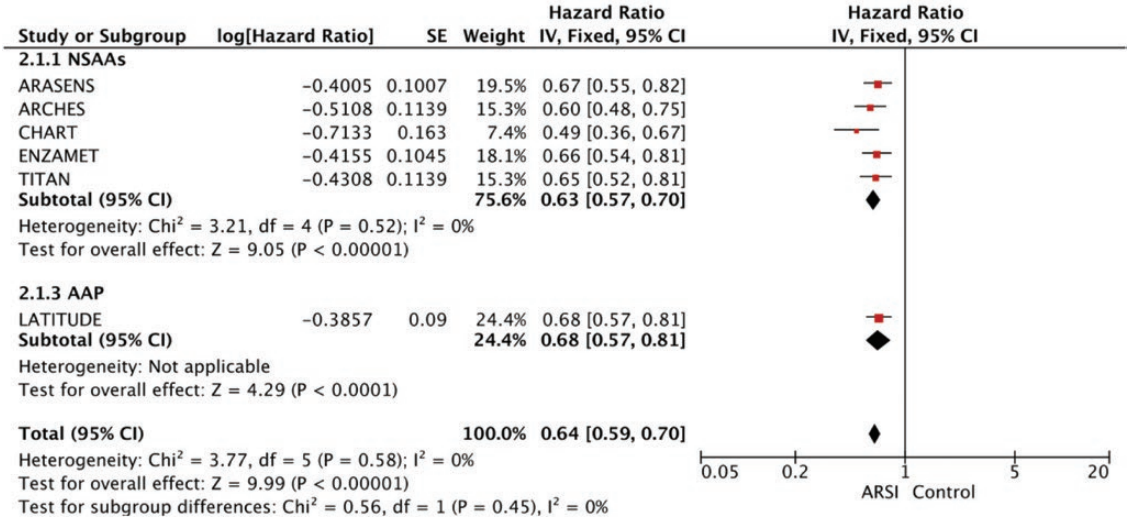

Figure 3. Forest plot of overall survival in patients without visceral metastasis. AAP: abiraterone acetate plus prednisone; CI: confidence interval; IV: inverse variance; NSAAs: non-steroidal anti-androgens; SE: standard error.

concluded that liver metastasis led to a worse response to AAP than lung metastasis. In light of this data, it should also be considered that the location of the VM might affect the response to ARSI. The rate of patients was higher in the LATITUDE trial than in the ENZAMET, TITAN, and ARCHES trials.[8,14,20,21] Despite this difference between the trials, OS was longer in the AAP subgroup than in the NSAAs group. In a study of Kase et al evaluating the survival outcomes of mCSPC with lung-only metastasis concluded an indolent clinical course of disease in those patients. They also highlighted that resection of the lung metastases might improve OS.[38] One of the possible mechanisms of better prognosis in lung-only metastatic disease may be considered as the higher prevalence of mutations in actionable DNA-repair genes in those patients.[39] In a study of Shenderov et al, ADT was associated with better survival outcomes in patients harboring mutations in DNA-repair genes compared to historical data.[39] Taken together, the different possible rates of patients with lung and liver metastases in the AAP and second-generation NSAAs groups might have affected the results in our analysis.

Unfortunately, we did not have any data about patients receiving triplet therapies in the trials of second-generation NSAAs. As mentioned earlier, triplet therapy might have influenced the results.

One of the main differences between AAP and NSAAs was the inhibition of intratumoral androgen synthesis by AAP.[40] Interestingly, this difference may explain our findings about the effect of AAP and NSAAs in mCSPC patients with VM. A study of Montgomery et al showed an increased intratumoral androgen synthesis in metastatic tissues of patients with mCRPC.[41] This could be a reason for the resistance to NSAAs.

We have several limitations in our analysis. First, we did not assess the progression-free survival (PFS) because of the

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distinct endpoints for PFS, such as radiological, biochemical, or clinical PFS, in the included trials. Second, we pooled the tabulated data, and our study was not an IPD meta-analysis. Indeed, this was the main limitation of our analysis. Because of this reason, it is hard to draw an exact conclusion about the selection of ARSI in patients with mCSPC and VM. Third, control arms were not homogenous in the included trials. Patients received ADT + first-generation NSAAs (eg, bicalutamide) in the control arms of ENZAMET and CHART trials, while patients received only ADT in the LATITUDE, TITAN, and ARCHES trials.[8,20,21,25,26] Fourth, while only one trial was in the AAP group, we included 5 in the NSAAs group. Because of this reason, it is difficult to compare the groups exactly. One of the main purposes of this study is to compare NSAAs and AAP in terms of their activity on VM in the castration-sensitive setting. Because the efficacy of docetaxel is well-known, especially in patients with mCSPC with high-volume/high-risk disease, we did not include the trials of docetaxel. However, new ARSI were effective irrespective of disease volume and limited data about the difference in their activity on VM is available. Therefore, as the fifth limitation, we only assessed trials of ARSI.

Conclusion

Our pooled analysis including data from the phase III trials demonstrated that AAP and second-generation NSAAs might not have the same effect in mCSPC patients with VM. A clinical decision by using the results of our study is difficult. However, these results warrant further studies on a molecular basis, with an IPD-level meta-analysis and clinical trial, to evaluate the mechanisms of action of AAP and second-generation NSAAs in mCSPC patients with VM.

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Conflict of Interest

Rana R. McKay reported consulting or advisory role for AstraZeneca, Aveo, Bayer, BMS, Calithera, Caris, Dendreon, Exelixis, Janssen, Merck, Myovant, Novartis, Pfizer, Sanofi, Sorrento Therapeutics, Seagen, Tempus, and Telix and research funding from Bayer, AstraZeneca, Oncternal, Tempus. Silke Gillessen reported consulting or advisory role for Sanofi, Orion, Roche, Amgen, AstraZeneca, Novartis, Myriad Genetics, and MSD; honoraria from Televisione Svizzera Italiana; invited speaker for ESMO, SAKK, SAMO, Orikata Academy Research Group, China Anti-Cancer Association Genitourinary Oncology Committee, S. Grasso Consulting, and Deso; speaker's bureau for Janssen Cilag; travel grant from ProteoMEdiX and AstraZeneca; institutional honoraria for advisory boards and Independent Data Monitoring or Steering Committees for Bayer, Janssen Cilag, Roche, AAA International, Amgen, Menarini Silicon Biosystems, Astellas Pharma, Tolero Pharmaceuticals, MSD, Pfizer, Telixpharma, BMS, and Orion; honoraria for the institution from WedMedMedscape; patent royalties and other intellectual property for a research method for biomarker WO2009138392. Toni K. Choueiri reported institutional and personal support, paid and unpaid support for research, participating in advisory boards, consultancy, and honoraria from AstraZeneca, Aravive, Aveo, Bayer, Bristol Myers Squibb, Calithera, Circle Pharma, Eisai, EMD Serono, Exelixis, GlaxoSmithKline, IQVA, Infinity, Ipsen, Jansen, Kanaph, Lilly, Merck, Nikang, Nuscan, Novartis, Pfizer, Roche, Sanofi/Aventis, Surface Oncology, Takeda, Tempest, UpToDate, and CME events (Peerview, OncLive, and MJH), outside the submitted work; institutional patents filed on molecular mutations, immunotherapy response and toxicity, and ctDNA; equity in Tempest, Pionyr, Osel, Precede Bio; being part of committees in the National Comprehensive Cancer Network, GU Steering Committee, American Society of Clinical Oncology, European Society for Medical Oncology, Academic and Community Cancer Research United, and KidneyCAN; having mentored several non-US citizens on research projects partly funded by non-US sources; and additional independent funding from drug companies or royalties for research around the subject matter paid to institution. Yüksel Ürün reported receipt of honoraria or consultation fees from Astellas, AstraZeneca, Bristol-Myers Squibb, Janssen Oncology, MSD, Pfizer, and Roche; participation in a company-sponsored speaker's bureau for Astellas, Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen Oncology, Pfizer, and Roche. Emre Yekedüz indicated no financial relationships.

Author Contributions

Conception/design: all authors. Provision of study material or patients: Collection and/or assembly of data: all authors. Data analysis and interpretation: E.Y., Supervision: T.K.C., Y.U. Manuscript writing: E.Y., R.R.M., S.G. Final approval of manuscript: all authors.

Data Availability

The datasets generated during and analyzed during the current study are available from the corresponding author upon reasonable request.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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