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Evaluating Treatment Efficacy in Metastatic Hormone-sensitive Prostate Cancer Patients with Visceral Disease: A Systematic Review and Network Meta-analysis

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Abstract

Background and objective: Metastatic hormone-sensitive prostate cancer (mHSPC) patients with visceral disease (VD) represent a high-risk subgroup associated with poor prognosis. Despite the introduction of treatment intensification strategies, the optimal systemic therapy for these patients remains unclear. This network meta-analysis (NMA) aims to evaluate the efficacy of the current therapeutic combinations in terms of overall survival (OS) in the subgroup of patients with VD.

Methods: A systematic review and NMA was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PROSPERO: CRD42025642120). Phase 3 randomised controlled trials assessing systemic therapies for mHSPC were identified through the PubMed, Cochrane, and Embase databases. Only studies reporting OS outcomes for patients with VD were included. Hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted and analysed using a frequentist NMA framework. The risk of bias was assessed using the Confidence in Network Meta-Analysis (CINeMA) tool.

Key findings and limitations: Eight phase 3 trials (7944 patients, 1189 with VD) were included. The androgen deprivation therapy (ADT) + docetaxel + darolutamide combination was the most effective regimen (HR = 0.42, 95% CI: 0.21–0.82). Among doublets,

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Androgen receptor pathway inhibitors

ADT + docetaxel (HR = 0.53, 95% CI: 0.30–0.93) and ADT + abiraterone (HR = 0.58, 95% CI: 0.41–0.83) showed superior efficacy to other androgen receptor pathway inhibitor–based doublet regimens, including combinations with enzalutamide, apalutamide, and darolutamide. The absence of individual patient data and the lack of efficacy data stratified by metastatic site (liver or lung involvement) were the key limitations.

Conclusions and clinical implications: Treatment intensification with triplet therapy (ADT + docetaxel + darolutamide) provides the greatest OS benefit in mHSPC patients with VD. Doublet regimens incorporating chemotherapy or abiraterone remain viable alternatives. Further prospective studies are needed to refine treatment selection based on VD-specific biology and organ-specific metastatic patterns.

ADVANCING PRACTICE

What does this study add?

Previous studies have explored treatment intensification strategies in metastatic hormone-sensitive prostate cancer, but the specific efficacy in patients with visceral disease (VD) has remained unclear. This is the first network meta-analysis to comprehensively evaluate and rank all currently available systemic therapies in this high-risk subgroup. Our findings demonstrate that triplet therapy with androgen deprivation therapy + docetaxel + darolutamide offers the greatest overall survival benefit, followed by doublet regimens incorporating chemotherapy or abiraterone. Conversely, doublet therapies with second-generation androgen receptor pathway inhibitors such as enzalutamide, apalutamide, and darolutamide show limited efficacy in VD.

Clinical Relevance

Management of metastatic hormone-sensitive prostate cancer has evolved rapidly with treatment intensification strategies; yet, patients with visceral disease (VD) continue to experience poor outcomes. This study provides the first conclusive comparative analysis of all available treatment regimens, offering critical guidance for clinicians. The superiority of chemotherapy-based regimens suggests that VD represents a distinct disease phenotype, potentially less responsive to second-generation androgen receptor pathway inhibitors. This highlights the importance of personalised treatment approaches, integrating systemic intensification with future biomarker-driven strategies. These findings may influence clinical guidelines and trial design, advocating for increased representation of VD patients in future research. Associate Editor: Guillaume Ploussard.

Patient Summary

We reviewed the data from multiple clinical trials to determine the best treatment options for patients with metastatic prostate cancer that has spread to the lungs, liver, or other organs. We found that a combination of hormone therapy, chemotherapy, and an additional targeted drug offers the best survival benefits. This research helps clinicians choose the most effective treatment strategies for patients with this aggressive form of prostate cancer.

1. Introduction

Prostate cancer (PC) remains one of the leading causes of cancer-related mortality worldwide and is the most frequently diagnosed malignancy among men in Europe and the USA [1–3]. Metastatic PC at diagnosis presents a major clinical challenge, impacting prognosis and therapeutic decision-making. While bone and lymph node metastases are the most common sites of disease dissemination, visceral disease (VD) occurs in approximately 10–20% of patients with metastatic hormone-sensitive prostate cancer (mHSPC) [4,5].

Biologically, VD in metastatic PC patients represents a distinct entity, differing from bone metastases in tumour microenvironment, immune interactions, and molecular characteristics [6–8]. Clinically, VD in mHSPC patients is associated with significantly worse outcomes, including reduced overall survival (OS) [9]. A retrospective analysis of the SEER programme (2010–2013) found that patients with de novo bone disease and VD had significantly higher PC-specific mortality than those with bone-only disease, with hazard ratios (HRs) of 1.48 for bone plus brain, 2.18 for bone plus liver, and 1.33 for bone plus lung metastasis [10]. Similarly, a post hoc analysis of the ARCHES trial in patients treated with androgen deprivation therapy (ADT)

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+ enzalutamide reinforced the negative prognostic role of VD and suggested reduced efficacy of androgen receptor pathway inhibitors (ARPIs) in this setting [11].

Given the aggressive nature and poor prognosis of VD, optimisation of systemic treatment strategies remains a critical challenge. While treatment intensification has improved outcomes in mHSPC in the last decade, it is unclear whether these advances benefit patients with VD to the same extent as those with nonvisceral metastases. ADT has historically been the cornerstone of mHSPC treatment, but the past decade has seen a paradigm shift. The CHAARTED and STAMPEDE [12,13] trials demonstrated that addition of docetaxel to ADT improved OS significantly, challenging the historical reliance on ADT as the sole systemic treatment for mHSPC. The approval of abiraterone acetate (AA) for mHSPC in 2017, based on the LATITUDE trial [14] findings, expanded treatment options further, paving the way for the integration of targeted therapies in PC. More recently, the TITAN, ARCHES, and ENZAMET trials have led to the widespread adoption of ARPIs [15–17], refining the treatment landscape and establishing several effective doublet combinations.

Risk stratification using the CHAARTED trial criteria, which classify patients into high- and low-volume subgroups, has become central to treatment selection, identifying patients most likely to benefit from chemotherapy-based doublet therapy. However, data from the ARASENS and PEACE-1 [18,19] trials have further reshaped the treatment paradigm, demonstrating that triplet therapy, adding darolutamide or AA to ADT and docetaxel, provides an additional OS benefit when compared with ADT plus docetaxel. Nonetheless, these triplet combinations have not been compared directly with doublet therapies combining ADT and ARPIs.

Despite these advancements, the optimal treatment strategy for treating VD in mHSPC patients remains uncertain. Although novel therapeutic combinations have improved OS significantly in the overall mHSPC population, their benefit in VD is less clear. The growing number of treatment options has introduced complexity in clinical decision-making, particularly in the absence of head-to-head comparisons between doublet and triplet combinations. Furthermore, patients with VD have been underrepresented in major clinical trials, comprising only about 10% of the enrolled participants [12–19].

Given the significant prognostic implications of VD in mHSPC, a comprehensive evaluation of systemic therapies in this population is needed urgently. This study addresses this gap through a systematic literature review and network meta-analysis (NMA), assessing the impact of currently approved systemic therapies on OS in patients with mHSPC and VD.

2. Methods

2.1. Registration and search strategy

This systematic review and NMA was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for NMA guidelines, the checklist of which is provided in Supplementary Table 1 [20]. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the following registration number: CRD42025642120. PubMed, Cochrane Central Register of Controlled Trials, and Embase were screened systematically for phase 3 randomised controlled trials (RCTs) evaluating systemic therapies in mHSPC.

The population, intervention, comparator, outcomes, study design (PICOS) framework used to define eligibility criteria is described in Supplementary Table 2). The following keywords were used to select papers for inclusion in the NMA: "Metastatic" AND "Prostate Cancer" AND "Phase III clinical trial." The complete search strategy is reported in Supplementary Table 3.

Updates of the included studies were searched manually up to February 24, 2025, and included in the analysis. Websites of relevant oncology conferences were screened, including the American Society of Clinical Oncology (ASCO), the ASCO Genitourinary Cancers Symposium, the European Society for Medical Oncology, and ClinicalTrials.gov. Selected studies and other meta-analyses or reviews were also searched through the reference sections.

2.2. Inclusion and exclusion criteria

Phase 3 RCTs evaluating the efficacy of systemic treatments in patients with mHSPC were eligible. Trials investigating the addition of locoregional treatments to systemic regimens were excluded. Eligible studies were required to report an efficacy analysis for patients with VD, though site-specific stratification was not mandatory. For studies with data published in multiple reports, the most recent update, as of the data cut-off on February 24, 2025, was selected. Trials focusing on metastatic castration-resistant prostate cancer (mCRPC) or lacking VD-specific efficacy were excluded. For trials without preplanned VD stratification, data were extracted from subgroup analyses presented in forest plots.

ADT was required as the comparator backbone, given its role as the historical standard of care in mHSPC and its consistent inclusion in all approved treatment regimens. Accordingly, studies were eligible if the control arm included ADT, either as monotherapy, with placebo, or in combination with docetaxel, AA, or ARPIs. The presence of ADT treatment across comparator arms allowed for consistent linkage of treatment nodes within the network structure. Conversely, trials assessing the efficacy of targeted therapies in patients with actionable genetic alterations were not considered, as these fell outside the scope of this research.

OS was selected as the primary outcome due to its consistent definition and availability across all included trials, as well as its relevance in a population with a high disease burden and poor prognosis. Progression-free survival was not considered, given the heterogeneity in assessment methods across included trials—radiographic, biochemical, or clinical—which limited comparability. Accordingly, additional outcome measures such as prostate-specific antigen response and time to castration-resistant PC were also

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excluded, as these were not reported consistently across all included trials.

2.3. Data extraction

Two independent reviewers (F.F. and G.N.) screened titles and abstracts for relevance. The software "Rayyan" [21] was used to assess the suitability of the screened papers for inclusion. Full-text articles of potentially eligible studies were retrieved and assessed based on previously defined criteria, with disagreements resolved through discussion or consultation with a third reviewer (L.F.). The final selection of studies was documented following the PRISMA guideline flow diagram methodology.

The following data were extracted from the selected studies: trial title and name, first author, publication year, journal, study design, therapeutic regimens, total number of patients in the experimental and control arms, VD subgroup size, number of events in VD subgroups, trial primary endpoints, HRs with corresponding 95% confidence intervals (CIs), and safety data as reported by the authors.

2.4. Risk of bias and statistical analysis

Two reviewers (F.F. and G.N.) independently assessed the risk of bias (RoB) for each study and the overall network using the Cochrane Risk of Bias 2 Tool (RoB2) and the Confidence in Network Meta-Analysis (CINeMA) framework, respectively [22,23]. Disagreements were resolved through consensus or consultation with a third author (L.F.).

Trials were evaluated independently based on six key methodological aspects: randomisation, allocation concealment, blinding of participants/personnel and outcome assessment, incomplete outcome data, and selective reporting bias. RoB for each domain was graded using the Grading of Recommendations Assessment, Development, and Evaluation system [24] and categorised as "very low", "low", "moderate", or "high". Accordingly, the network-wide RoB was evaluated based on each CINeMA domain: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence [23].

The potential bias related to small sample sizes was evaluated, given the limited number of patients with VD in the included RCTs. To assess the small-study effects and publication bias, Begg's and Egger's tests were conducted. Begg's test evaluated the publication bias using rank correlation, while Egger's test assessed asymmetry in a combined-adjusted funnel plot through a regression analysis. HRs and their corresponding standard errors (SEs) were calculated for each study. A p value of <0.05 in Egger's test was considered indicative of a potential small-study bias. Heterogeneity was assessed using the I2 statistic, and both fixed- and random-effect meta-analyses were conducted.

The z statistic was calculated to assess the significance of the treatment effects in the network. Derived from the estimated effect sizes of HRs and their corresponding SEs, the z statistic evaluated whether the observed treatment effects were significantly different from zero.

Global and local inconsistency tests were performed to assess the consistency of treatment effect estimates across the network. The global inconsistency test evaluated whether direct and indirect evidence in the network was consistent, using a χ^2 test. A p value of <0.05 could suggest significant inconsistency. Local inconsistency tests were conducted on individual loops to check for inconsistencies between the direct and indirect treatment comparisons for specific treatment pairs.

The impact of collateral variables on the analysis outcomes was assessed using the R^2 test.

All the statistical analyses were performed using the "R" Software, version 4.4.2, with the "netmeta" and "ggplot 2" libraries [25].

3. Results

3.1. Study selection and network structure

A total of 4344 eligible articles were identified through literature screening. After removing 1146 duplicates, 3198 records remained for evaluation. Exclusions were made for reviews, editorials, meta-analyses, preclinical studies, phase 1/2 trials, non-English articles, and studies focusing on mCRPC, leaving 18 full-text articles for assessment. Trials in the mHSPC setting lacking VD-specific efficacy data, including the PEACE-1 and STAMPEDE trials, were excluded further. This resulted in the inclusion of eight RCTs published between 2015 and 2024: CHAARTED, ARCHES, ENZAMET, TITAN, ARANOTE, CHART, LATITUDE, and ARASENS. The study selection process is outlined in the PRISMA flowchart (Fig. 1).

A total of 7944 patients were included in the analysis, with 1189 (15%) having VD at baseline. VD was defined across the included trials as the presence of at least one metastasis in at least one solid organ, such as the liver, lung, or brain. VD status was found to be a predefined stratification factor in four trials (LATITUDE, ARANOTE, ARASENS, and CHART). The number of VD patients varied across trials, ranging from 80 (ARANOTE) to 229 (ARASENS). The median follow-up duration across the included trials was 45.1 mo, with ENZAMET reporting the longest (68 mo) and ARANOTE the shortest (25.3 mo) follow-up durations.

Treatment regimens included ADT combined with ARPIs, AA, or docetaxel. Triplet therapy (ADT + ARPI/AA + docetaxel) was evaluated only in the ARASENS trial, while the remaining trials investigated ADT-based doublets as experimental arms. Four trials incorporated a placebo in the control arm. Baseline characteristics of the selected trials are summarised in Supplementary Table 4).

The treatment network included nine unique interventions, forming eight direct comparisons. A network plot diagram was generated to illustrate the relationships between various treatments (Supplementary Fig. 1). While some comparisons were based on direct connections, others relied on indirect evidence through shared comparators. Notably, no disconnected nodes were present, ensuring a coherent and well-connected network (Fig. 2).

3.2. RoB assessment

The RoB assessment was conducted at both the study and the network level. Six of the eight included trials were judged to have an overall low risk, with minimal concerns

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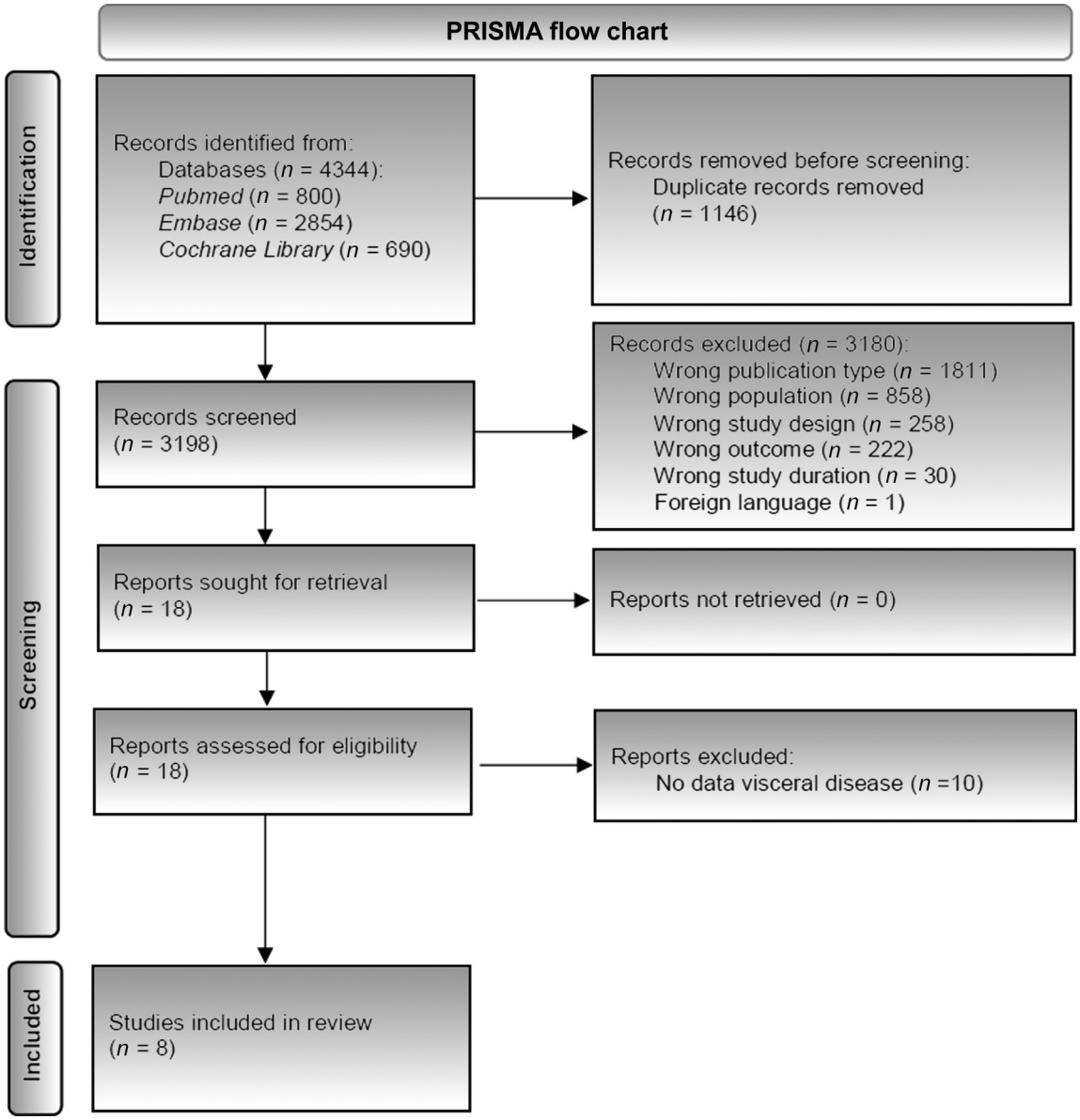

Fig. 1 – PRISMA flow chart diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

across domains such as randomisation, allocation concealment, outcome assessment, and selective reporting. Conversely, the CHART and ENZAMET trials were rated as having a moderate RoB due to their open-label design, while ARANOTE raised concerns regarding the population selection bias due to the inclusion of patients with a prior favourable ADT response (Supplementary Fig. 1). At the network level, CINeMA assessment revealed moderate concerns in comparisons involving CHART, ENZAMET, and ARANOTE, primarily due to indirectness and imprecision, as illustrated in the corresponding heatmap (Supplementary Fig. 2). A funnel plot analysis showed no strong indication of any publication bias (Egger's p = 0.3119; Begg's p = 0.4579), though some dispersion among smaller studies suggested mild small-study effects. Adjustments via the trim-and-fill method, taking into account potential missing studies, confirmed the overall robustness of the pooled results (Supplementary Fig. 3).

The funnel plot in Supplementary Fig. 3 provided the visual assessment of the potential publication bias and small-study effects. The relatively symmetrical distribution of studies suggested no strong evidence of bias, supporting the results of Egger's (p = 0.3119) and Begg's (p = 0.4579) tests. However, some dispersion among smaller studies was noticeable, indicating mild small-study effects or heterogeneity. The trim-and-fill method was performed in order to adjust the distribution taking into account potential missing studies (Supplementary Fig. 3). Accordingly, the overall distribution remained relatively balanced, reinforcing the robustness of the results.

3.3. *Efficacy analysis and forest plot*

The initial evaluation focused on the HRs derived from each individual trial, limited to the subgroup of patients with VD, and based exclusively on direct, within-trial comparisons

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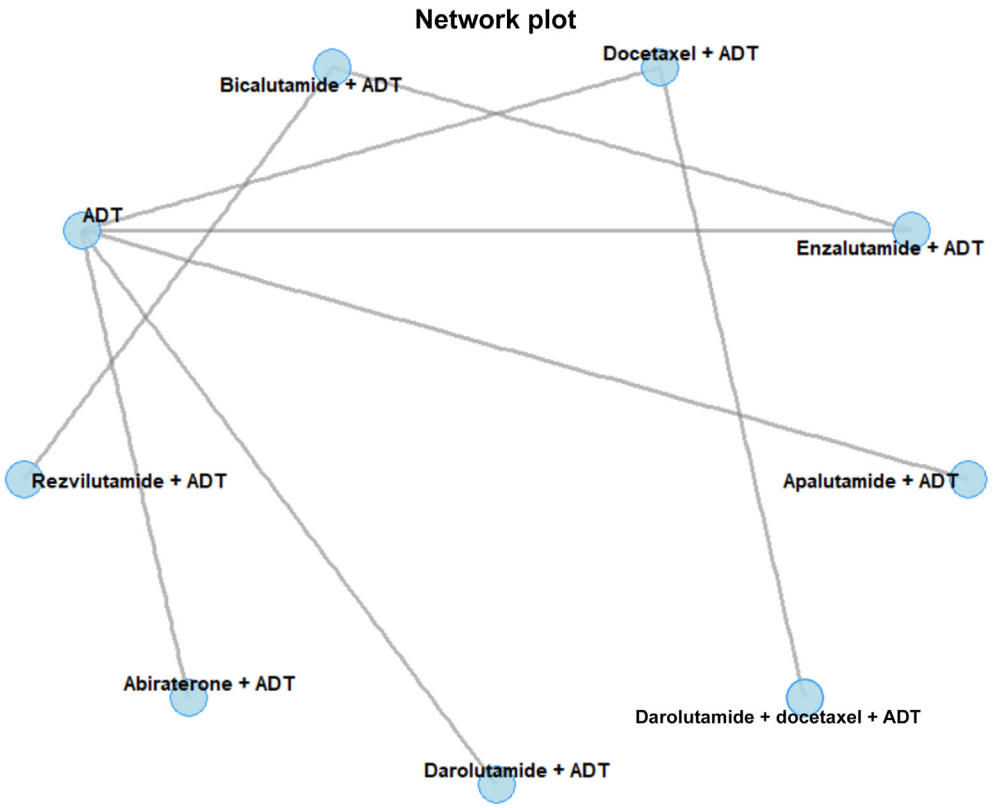

Fig. 2 – Network plot diagram. The network plot illustrates the structure of the comparisons among different systemic therapies. Each node represents a treatment, and the size of the node is proportional to the number of patients receiving that specific therapy. The lines connecting the nodes indicate direct comparisons between treatments in randomised controlled trials, with the thickness of the edges corresponding to the number of studies available for each comparison. ADT serves as the common comparator in multiple trials, linking various treatment regimens, including next-generation ARPIs, chemotherapy, and triplet therapy combinations. The presence of indirect comparisons allows for the estimation of treatment effects beyond direct evidence. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor.

between randomised treatment arms (Supplementary Table 2).

The LATITUDE trial, evaluating the combination of ADT + AA, demonstrated a statistically significant survival benefit (HR = 0.58, 95% CI: 0.41–0.83). Similarly, the CHAARTED trial, assessing the efficacy of the combination ADT + docetaxel, showed a marked reduction in the risk of death (HR = 0.53, 95% CI: 0.30–0.93), highlighting the benefit of chemotherapy intensification. The TITAN trial, which evaluated ADT + apalutamide, reported moderate efficacy (HR = 0.76, 95% CI: 0.47–1.23), while the ARANOTE study on ADT + darolutamide (HR = 0.82, 95% CI: 0.36–1.87) yielded less conclusive results, mainly due to a small sample size and short follow-up. The CHART trial, examining ADT + rezvilutamide, showed the least favourable outcome (HR = 1.11, 95% CI: 0.60–2.05), confirming the limited efficacy of this regimen in mHSPC patients with VD. Finally, the ARASENS trial, assessing the efficacy of triplet therapy with ADT + docetaxel + darolutamide, reported a nonsignificant result (HR = 0.79, 95% CI: 0.55–1.14) when compared directly with ADT + docetaxel.

The efficacy data from each trial, obtained from VD-specific subgroup analyses of direct comparisons, were subsequently incorporated into the NMA framework, allowing for the integration of both direct and indirect comparisons, with ADT serving as a common comparator (Fig. 3).

Therefore, the indirect HRs were estimated within the network for treatment regimens that were not directly compared in the original trials. Hence, when indirectly compared within the network, ADT + docetaxel + darolutamide emerged as the most effective regimen, exhibiting the lowest HR (0.42, 95% CI: 0.21–0.82). The pooled HR across the entire network was 0.72 (95% CI: 0.59–0.88) under the fixed-effect model and 0.75 (95% CI: 0.57–0.99) under the random-effect model, confirming the overall superiority of combination regimens over ADT alone. Notably, doublet therapies incorporating ADT + docetaxel (HR = 0.53, 95% CI: 0.30–0.93) and ADT + AA (HR = 0.58, 95% CI: 0.41–0.83) remained among the most effective options. Conversely, other next-generation ARPI doublets, including enzalutamide, apalutamide, and darolutamide, demonstrated only moderate efficacy, with ADT + apalutamide showing the best performance among these regimens (HR = 0.76, 95% CI: 0.47–1.23).

To further validate the robustness of these findings, the z-statistic value was calculated, yielding an absolute z score of 3.04 ($p = 0.0024$) meeting the prespecified thresholds for statistical significance ($|Z| \geq 2.58$; $p < 0.05$), reinforcing the reliability of the observed network-based treatment rankings.

The rankogram analysis provided additional insight into treatment ranking, based on P scores and surface under the

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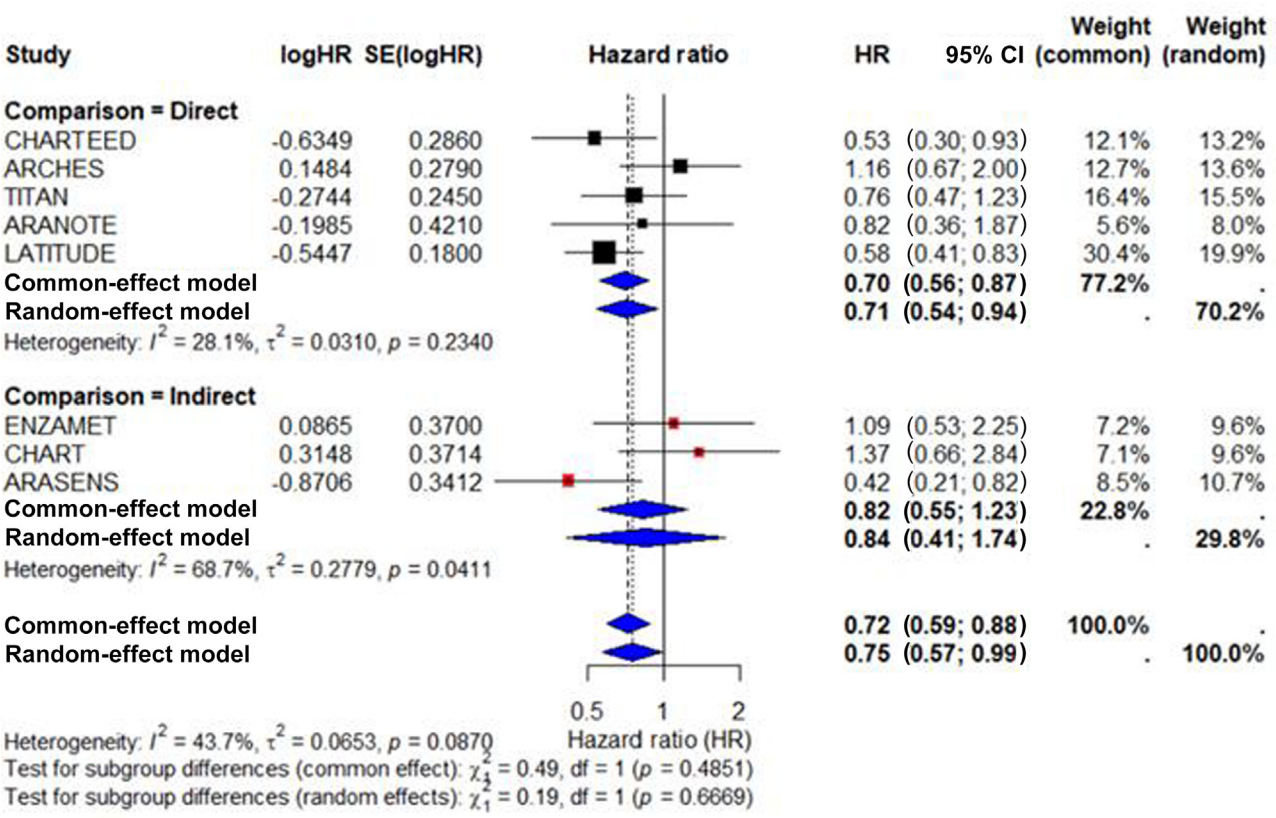

Fig. 3 – Network meta-analysis forest plot for direct and indirect comparisons. CI = confidence interval; HR = hazard ratio; SE = standard error.

cumulative ranking curve (SUCRA) values. Both ranking approaches consistently identified ADT + docetaxel + darolutamide as the most effective regimen, achieving the highest P score (0.91) and SUCRA score (0.899), confirming its status as the most effective regimen in the network. Among doublets, ADT + docetaxel (P score: 0.809; SUCRA score: 0.784) and ADT + AA (P score: 0.768; SUCRA score: 0.736) emerged as the most effective treatment combinations. Conversely, ADT + enzalutamide (P score: 0.244; SUCRA score: 0.193), ADT + bicalutamide (P score: 0.194; SUCRA score: 0.165), and ADT + rezvilutamide (P score: 0.159; SUCRA score: 0.122) ranked among the least effective treatments, consistent with their higher HR values (Fig. 4).

To complement these findings, the pairwise comparison heatmap (Fig. 5) provided a comprehensive overview of the relative efficacy of each treatment within the network, based on the integrated estimates derived from both direct and indirect comparisons across trials. Consistent with the primary NMA results, ADT + docetaxel + darolutamide consistently outperformed all the regimens in direct and indirect comparisons. Similarly, ADT + AA and ADT + docetaxel maintained a favourable position among doublet regimens. Conversely, ADT + rezvilutamide and ADT + bicalutamide ranked among the least effective regimens, demonstrating inferior outcomes to both chemotherapy- and ARPI-based combinations. Full pairwise comparison details, including HR estimates and the relative 95% CIs, are provided in Supplementary Table 5.

To explore the potential impact of follow-up duration on treatment outcomes, a metaregression analysis was performed using median follow-up time as a covariate (Fig. 6). The regression plot demonstrated an R^2 value of 0% (p = 0.463), indicating no significant influence of the follow-up time on HR estimates across the included trials. This finding suggests that variations in studies' follow-up periods did not introduce a bias into the analysis, reinforcing the robustness of the observed findings.

4. Discussion

To our knowledge, this NMA represents the most comprehensive and up-to-date evaluation of systemic therapies for mHSPC patients with VD, incorporating the latest updates from all therapeutic combinations currently available. The treatment landscape of mHSPC has undergone a paradigm shift over the past decade, with combination therapies improving patient outcomes significantly. However, the optimal management of VD remained uncertain. VD represents a distinct clinical and biological entity, associated with more aggressive behaviour, resistance to ARPIs, and significantly worse prognosis compared with nonvisceral metastases [26].

Our findings confirm that treatment intensification provides a survival advantage in patients with mHSPC and VD, although the magnitude of benefit varies across different therapeutic strategies. The triplet combination of ADT

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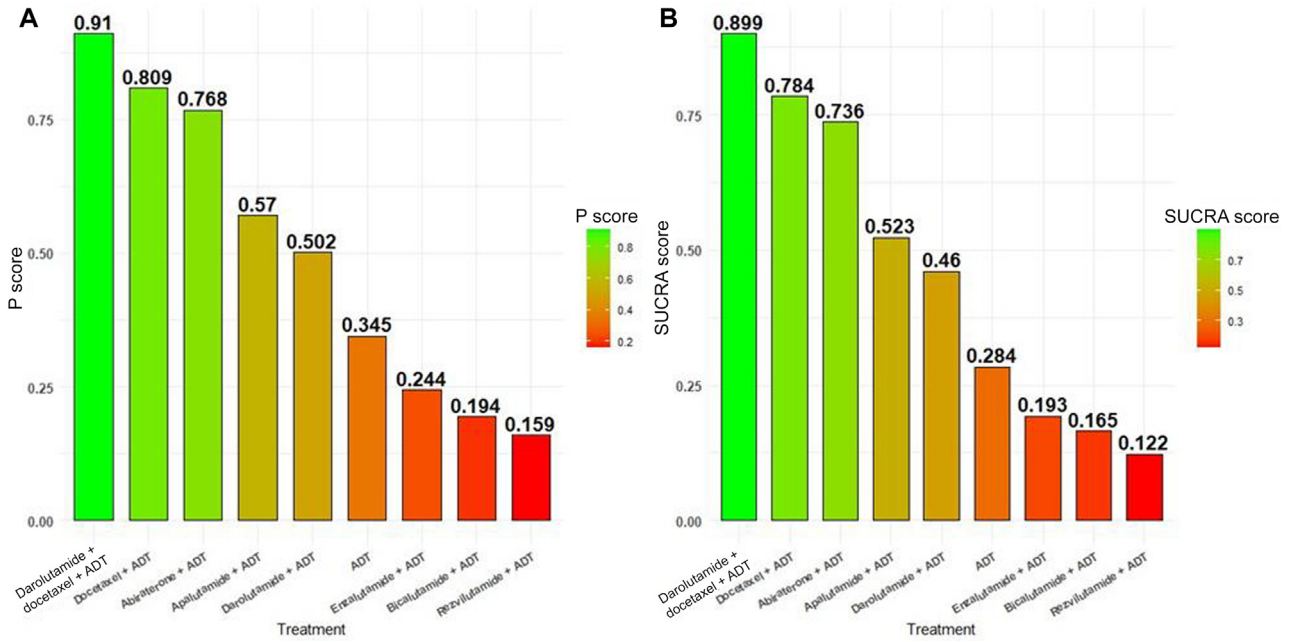

Fig. 4 – Rankograms for OS benefit among treatments. The figure presents the comparative ranking of systemic treatments, using (A) P score and (B) SUCRA score. Both metrics assess the probability of each treatment being the most effective option, with higher scores indicating superior treatment efficacy. ADT = androgen deprivation therapy; SUCRA = surface under the cumulative ranking curve.

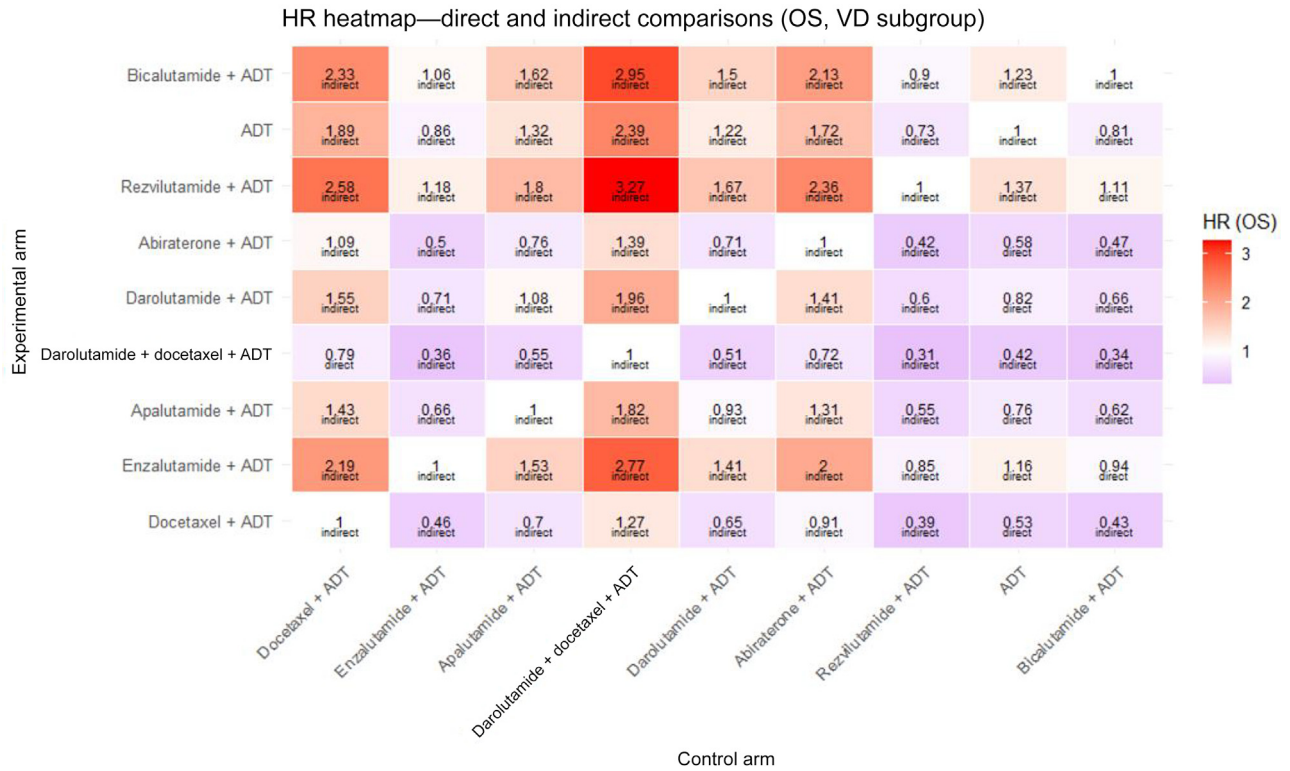

Fig. 5 – Heatmap for efficacy of each pairwise comparison. Rows represent the reference treatment, while columns represent the comparator. Each cell contains the HR for OS for the reference treatment relative to the comparator treatment. The colour gradient represents HR values, with lower HRs (purple) indicating a survival benefit for the reference treatment over the comparator and higher HRs (red) indicating inferior efficacy. The nature of the HR value for each pairwise comparison—whether derived from direct or indirect evidence—is indicated below the numerical value in each cell. HR <1 indicates that the comparator treatment is associated with a lower risk of death than the reference, HR >1 (red shades) indicates that the comparator treatment is associated with a higher risk of death compared with the reference, and HR = 1 (white) indicates no difference in survival benefit between the two treatments. ADT = androgen deprivation therapy; HR = hazard ratio; OS = overall survival; VD = visceral disease.

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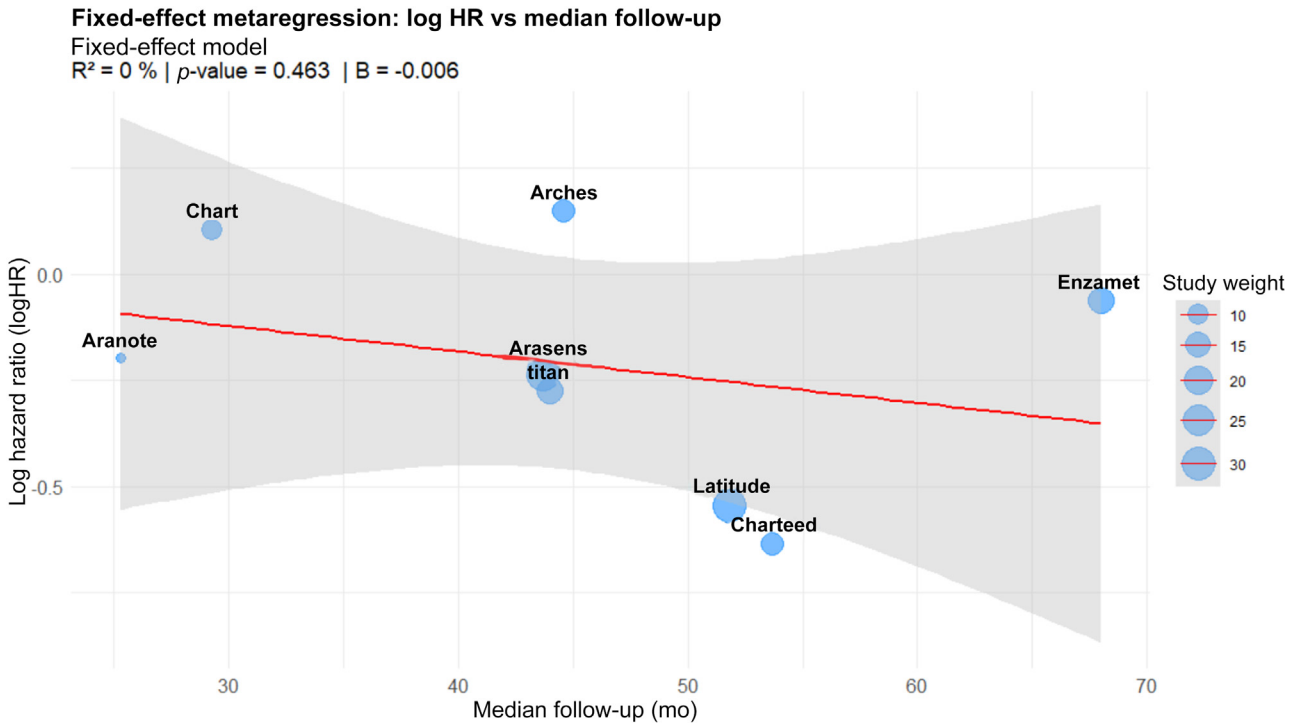

Fig. 6 – Metaregression plot evaluating the influence of follow-up time on trial results. The R^2 value of 0% indicates that follow-up duration does not explain any variability in log HR across trials. The *p* value (0.463) is nonsignificant, meaning that there is no statistically significant association between follow-up duration and treatment effect. The regression line (red) is almost flat, indicating a very weak, nonsignificant negative trend. The confidence interval (shaded area) is wide, further suggesting a lack of a strong relationship. HR = hazard ratio.

+ docetaxel + darolutamide emerged as the most effective regimen, demonstrating the highest OS benefit, followed by ADT + docetaxel and ADT + AA. Conversely, doublet therapies with apalutamide, enzalutamide, and darolutamide demonstrated limited efficacy in this population.

The biological rationale for these differences warrants further exploration. Unlike bone metastases, which remain highly androgen receptor (AR) dependent even in the mCRPC setting, VD frequently exhibits molecular alterations that drive AR-independent progression, including TP53 and PTEN loss, RB1 deletions, MYC amplifications, and neuroendocrine differentiation [27–30]. Particularly, liver metastases are associated with increased genomic instability and resistance to AR-targeted agents [31]. These findings could provide a plausible biological rationale for the inferior efficacy of ARPI-based doublet for VD, as observed in both our NMA and previous RCTs. In contrast, cytotoxic chemotherapy with docetaxel, which induces apoptosis through microtubule stabilisation independently of AR-mediated signalling, may provide superior therapeutic efficacy in this patient population, potentially explaining the improved outcomes observed with triplet therapy.

Moreover, a noteworthy finding of our analysis is the superior efficacy of AA to that of other ARPIs, positioning it as the most effective chemotherapy-free option. However, the underlying mechanisms driving this difference remain uncertain. One potential explanation may be related to pharmacodynamic differences between these agents: unlike direct AR antagonists such as enzalutamide, apalutamide, and darolutamide, which inhibit AR signalling downstream, AA acts upstream by suppressing androgen biosynthesis at the CYP17A1 level [32]. This mechanism results in a deeper systemic castration by reducing testosterone production at adrenal, testicular, and intratumoral sites. Nevertheless, while biologically plausible, this hypothesis remains speculative and requires further validation through dedicated translational research. Importantly, no evident clinical or patient selection bias emerges as a determinant of this observed difference in efficacy. Particularly, the inclusion criteria of the LATITUDE trial [14] specifically excluded patients with prior chemotherapy exposure, thereby reducing the potential confounding effect of previous systemic treatments on the observed OS benefit. Conversely, trials evaluating ARPIs included a higher proportion of patients treated previously with docetaxel, raising concerns about residual confounding. However, a cross-trial comparison does not support this explanation. The TITAN trial, which evaluated ADT + apalutamide, included only ~10% of patients with prior docetaxel exposure, yet reported more favourable results than ARCHES and ENZAMET, in which prior chemotherapy exposure was higher (18% and 45% of patients, respectively) and VD-specific efficacy outcomes were less favourable [15–17]. This suggests that prior exposure to docetaxel alone is unlikely to account for the differences in OS observed between AA and ARPIs. Therefore, while the possibility that pharmacodynamic differences contribute to the observed results remains an intriguing hypothesis, the available evidence does not allow definitive

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conclusions regarding the superiority of one treatment over another. Further studies, particularly individual patient data (IPD) meta-analyses, could help elucidate the mechanisms underlying this difference in efficacy between AA and the other ARPIs.

From a clinical perspective, our findings highlight the necessity of risk-adapted treatment strategies based on metastatic burden and disease biology. While ARPI-based doublet regimens remain an option for patients with non-visceral or low-volume mHSPC, our analysis suggests that the presence of VD warrants a more intensive treatment approach incorporating chemotherapy in triplet combinations. This aligns with evidence from the ARASENS and PEACE-1 [18,19] trials, which demonstrated that addition of an ARPI to ADT and docetaxel improves OS significantly in high-volume mHSPC patients, a subgroup in which VD is largely represented. Although the PEACE-1 trial could not be included in this NMA due to the absence of VD-specific efficacy data, its regimen—ADT + docetaxel + AA—would likely have yielded favourable results. Indeed, docetaxel and AA emerged as the most effective agents, suggesting that the PEACE-1 triplet may further reinforce the benefits of treatment intensification in VD. Therefore, the exclusion of PEACE-1 remains a notable limitation, as its inclusion could have strengthened the reliability of our findings.

Despite these compelling results, critical gaps remain, and this analysis has limitations that should be considered when interpreting its findings. Firstly, none of the included RCTs performed a site-specific differential analysis of VD, despite well-documented heterogeneity in prognosis among different visceral metastatic sites. A retrospective analysis from the TAX327 trial [33] demonstrated that liver metastases were associated with the worst prognosis, whereas lung metastases exhibited a more indolent course. Accordingly, brain metastases, though rare, were linked to particularly aggressive disease [34]. Similarly, a post hoc analysis from the LATITUDE trial [35] demonstrated that in patients with lung metastases, the combination of ADT + AA improved clinical outcomes in both OS and radiographic progression-free survival, with benefits comparable with those observed in patients without VD. Conversely, men with liver metastases benefited less from ADT + AA than all other subgroups. These findings align with prior mHSPC and mCRPC studies [36,37], which showed that men with lung-only metastases had survival outcomes similar to those with bone-only disease. Thus, the absence of this site-specific stratification remains a critical knowledge gap, limiting a more nuanced understanding of how treatment efficacy may differ across visceral subtypes.

Finally, this analysis used OS as the primary outcome measure, which is highly influenced by subsequent treatments and overall treatment sequencing. This limitation may become even more critical in the coming years, as several highly effective treatments continue to emerge in the mCRPC setting, most notably radioligand therapy with Lu-PSMA [38,39]. Moreover, heterogeneity in trial inclusion criteria may limit the generalisability of our findings. Notable differences included the definition of metastatic disease, which was based on high-risk features in the LATITUDE trial and on disease volume in the CHAARTED trial, varying thresholds for Eastern Cooperative Oncology Group performance status, and allowance for prior docetaxel treatment in trials such as ARCHES and ENZAMET. Baseline demographic and clinical characteristics also varied across studies, further complicating direct comparisons and pooled efficacy estimates. Therefore, a more direct approach, such as an IPD meta-analysis, would allow for patient-level adjustments and stratified analyses, mitigating residual confounding and enhancing the precision of survival estimates.

5. Conclusions

This NMA represents the most comprehensive and updated synthesis of available evidence regarding systemic treatment strategies in mHSPC patients with VD. The findings reinforce the importance of treatment intensification, as triplet therapy with ADT + docetaxel + darolutamide emerged as the most effective approach in this high-risk population. However, significant gaps remain, particularly regarding the biological heterogeneity of VD, the potential role of molecular profiling in treatment selection, and the absence of IPD. Future research should focus on addressing these knowledge gaps through prospective studies, real-world evidence, and biomarker-driven trials to further refine the management of mHSPC patients with VD.

Author contributions: Luigi Formisano 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: Neola, Flauto, Caso, Formisano.
Acquisition of data: Neola, Flauto, Caso.
Analysis and interpretation of data: Neola, Flauto, Caso, Formisano.
Drafting of the manuscript: Neola, Flauto, Caso, Signori, Fornarini, Scagliarini, Rossetti, Crocetto, Grillone, Di Costanzo, Rescigno, Conteduca, Banna, Caffo, Maruzzo, Iacovelli, Castro, Bianco, Servetto, Formisano.
Critical revision of the manuscript for important intellectual content: Signori, Fornarini, Scagliarini, Rossetti, Crocetto, Grillone, Di Costanzo, Rescigno, Conteduca, Banna, Caffo, Maruzzo, Iacovelli, Castro, Bianco, Servetto, Formisano.
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Obtaining funding: Bianco, Servetto, Formisano.
Administrative, technical, or material support: Neola, Flauto, Caso, Formisano.
Supervision: Signori, Fornarini, Scagliarini, Rossetti, Crocetto, Grillone, Di Costanzo, Rescigno, Conteduca, Banna, Caffo, Maruzzo, Iacovelli, Castro, Bianco, Servetto, Formisano.
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Appendix A. Supplementary material

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References

[1] Rawla P. Epidemiology of prostate cancer. World J Oncol 2019;10:63–89.
[2] James ND, Tannock I, N'Dow J, et al. The lancet commission on prostate cancer: planning for the surge in cases. Lancet 2024;403:1683–722.
[3] 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;10:811044.
[4] Litwin MS, Tan H. The diagnosis and treatment of prostate cancer: a review. JAMA 2017;317:2532–42.
[5] Yekedüz E, McKay RR, Gillessen S, Choueiri TK, Ürün Y. Visceral metastasis predicts response to new hormonal agents in metastatic castration-sensitive prostate cancer. Oncologist 2023;28:596–603.
[6] Akfirat C, Zhang X, Ventura A, et al. Tumour cell survival mechanisms in lethal metastatic prostate cancer differ between bone and soft tissue metastases. J Pathol 2013;230:291–7.
[7] Morrissey C, True LD, Roudier MP, et al. Differential expression of angiogenesis associated genes in prostate cancer bone, liver and lymph node metastases. Clin Exp Metastasis 2008;25:377–88.
[8] Rycaj K, Tang DG. Molecular determinants of prostate cancer metastasis. Oncotarget 2017;8:88211–31.
[9] Gandaglia G, Karakiewicz PI, Briganti A, et al. Impact of the site of metastases on survival in patients with metastatic prostate cancer. Eur Urolo 2015;68:325–34.
[10] Klaassen Z, Chandrasekar T, Goldberg H, Hamilton R, Fleshner N, Kulkarni G. Predictors of early disease specific mortality among patients with prostate adenocarcinoma bone metastasis at diagnosis. J Urol 2017;197(4S_Suppl):e170.
[11] Armstrong AJ, Shore ND, Szmulewitz RZ, et al. Efficacy of enzalutamide plus androgen deprivation therapy in metastatic hormone-sensitive prostate cancer by pattern of metastatic spread: ARCHES post hoc analyses. J Urol 2021;205:1361–71.
[12] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
[13] 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.
[14] 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.
[15] Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13–24.
[16] Armstrong AJ, Szmulewitz RZ, Petrylak DP, 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.
[17] 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.
[18] Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med 2022;386:1132–42.
[19] Fizazi K, Foulon S, Carles J, 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 2×2 factorial design. Lancet 2022;399:1695–707.
[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] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan - a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
[22] Sterne JAC, Savovi ÄJ, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
[23] Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. PLoS Med 2020;17:e1003082.
[24] Xie CX, Machado GC. Clinimetrics: grading of recommendations, assessment, development and evaluation (GRADE). J Physiother 2021;67:66.
[25] Shim SR, Kim SJ, Lee J, Rücker G. Network meta-analysis: application and practice using R software. Epidemiol Health 2019;41:e2019013.
[26] Drake CG. Visceral metastases and prostate cancer treatment: 'die hard,' 'tough neighborhoods,' or 'evil humors'? Oncology (Williston Park) 2014;28:974–80.
[27] Fujita K, Nonomura N. Role of androgen receptor in prostate cancer: a review. World J Mens Health 2019;37:288–95.
[28] Cussenot O, Timms KM, Perrot E, et al. Tumour-based mutational profiles predict visceral metastasis outcome and early death in prostate cancer patients. Eur Urol Oncol 2024;7:597–604.
[29] Sharifi MN, Feng E, Rydzewski NR, et al. Adverse prognosis gene expression patterns in metastatic castration-resistant prostate cancer. Mol Oncol. In press. https://doi.org/10.1002/1878-0261.70001.
[30] Lee JK, Phillips JW, Smith BA, et al. N-Myc drives neuroendocrine prostate cancer initiated from human prostate epithelial cells. Cancer Cell 2016;29:536–47.
[31] Ni X, Wei Y, Li X, et al. From biology to the clinic - exploring liver metastasis in prostate cancer. Nat Rev Urol 2024;21:593–614.

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[32] Thakur A, Roy A, Ghosh A, Chhabra M, Banerjee S. Abiraterone acetate in the treatment of prostate cancer. Biomed Pharmacother 2018;101:211–8.
[33] Pond GR, Sonpavde G, de Wit R, Eisenberger MA, Tannock IF, Armstrong AJ. The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. Eur Urol 2014;65:3–6.
[34] Caffo O, Veccia A, Russo L, Galligioni E. Brain metastases from prostate cancer: an emerging clinical problem with implications for the future therapeutic scenario. Future Oncol 2012;8:1585–95.
[35] Baciarello G, Özgüroğlu M, Mundle S, et al. Impact of abiraterone acetate plus prednisone in patients with castration-sensitive prostate cancer and visceral metastases over four years of follow-up: a post-hoc exploratory analysis of the LATITUDE study. Eur J Cancer 2022;162:56–64.
[36] Roviello G, Petrioli R, Villari D, D'Angelo A. Treating de novo metastatic castration-sensitive prostate cancer with visceral metastases: an evolving issue. Clin Genitourin Cancer 2021;19:83–6.
[37] Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. J Clin Oncol 2016;34:1652–9.
[38] Morris MJ, Castellano D, Herrmann K, et al. 177Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. Lancet 2024;404:1227–39.
[39] Kuo PH, Morris MJ, Hesterman J, et al. Quantitative 68Ga-PSMA-11 PET and clinical outcomes in metastatic castration-resistant prostate cancer following 177Lu-PSMA-617 (VISION trial). Radiology 2024;312:e233460.

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