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Review – Prostate Cancer

Comparative Survival in Metastatic Hormone-sensitive Prostate Cancer by Volume of Disease and Timing of Metastasis: A Living Network Meta-analysis

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Abstract

Background and objective: We aimed to assess the comparative effectiveness of contemporary systemic treatment options across patients with metastatic hormone-sensitive prostate cancer (mHSPC) across clinically relevant prognostic subgroups (synchronous high [SHV] and low [SLV] volume, and metachronous high [MHV] and low [MLV] volume).

Methods: This living network meta-analysis was conducted using the living interactive evidence (LIvE) synthesis framework. Phase 3 randomized controlled trials assessing treatment intensification with androgen receptor pathway inhibitors (ARPIs), docetaxel (D), or both were included. Mixed treatment comparisons were conducted for overall population and for each prognostic subgroup (SHV, SLV, MHV, and MLV). Overall survival (OS) and progression-free survival were assessed.

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Triplet therapy
Living interactive meta-analysis
Metastatic hormone-sensitive prostate cancer
Volume of disease
Personalized medicine

Key findings and limitations: The current report of a living systematic review includes a total of 11 trials (12 668 patients and 12 unique treatments). In the overall population, the results were consistent with those of a previous report. An analysis of OS by prespecified subgroups included nine clinical trials (8990 patients and eight unique treatments). In the SHV subgroup (*N* = 5171; 57%), ARPI + D + androgen deprivation therapy (ADT) led to a statistically significant improvement in OS compared with D + ADT (hazard ratio: 0.72; 95% confidence interval: 0.62–0.83) and ARPI + ADT (0.71; 0.53–0.97). In the SLV subgroup (*N* = 2455; 27%), ARPI + ADT led to a statistically significant improvement compared with ADT alone (0.65; 0.52–0.80). There was no statistically significant difference between ARPI + D + ADT and ARPI + ADT (1.08; 0.65–1.79). In the MHV subgroup (*N* = 589; 6.5%), no statistically significant improvement was observed with ARPI + D + ADT compared with ARPI + ADT (0.89; 0.43–1.85) and D + ADT (0.90; 0.60–1.36). There was no statistically significant difference between ARPI + ADT and D + ADT (1.02; 0.45–2.28). In the MLV subgroup (*N* = 775; 8.5%), ARPI + ADT led to a statistically significant improvement compared with ADT alone (0.43; 0.29–0.64) and D + ADT (0.41; 0.24–0.70). There was no statistically significant difference between ARPI + D + ADT and ARPI + ADT (1.56; 0.40–6.25). Inherent limitations of this analysis include the inability to account for all relevant variables such as the patient- and cancer-related factors that likely influenced the decision of physicians to offer docetaxel to patients.

Conclusions and clinical implications: Current evidence suggests that triplet systemic therapy is preferred for patients with SHV mHSPC who are fit for docetaxel. Androgen receptor pathway doublet therapy is preferred for all other patient subgroups compared with ADT alone. There is no role of docetaxel doublet in patients with access to ARPI therapy and if they are able to receive it.

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What does this study add?

This living network meta-analysis investigates the role of systemic treatment intensification in metastatic hormone-sensitive prostate cancer (mHSPC) by stratifying outcomes by disease volume and timing of metastasis. The findings support the use of triplet therapy exclusively in fit patients with synchronous high-volume disease, in whom it yields a significant survival benefit compared with other treatment options. In all other subgroups, the combination of androgen receptor pathway inhibitors and androgen deprivation therapy remains the preferred option, with no added value from docetaxel. The use of a living interactive evidence platform (living evidence) allows clinicians to continuously access the latest treatment comparisons, supporting dynamic, evidence-based decision-making for mHSPC patients as new data emerge.

Clinical Relevance

This living network meta-analysis uniquely integrates data from 11 phase III randomized trials to provide the most comprehensive comparative assessment of systemic therapies for patients with metastatic hormone-sensitive prostate cancer, stratified by disease volume and timing of metastasis development. The findings establish triplet therapy (androgen deprivation therapy combined with docetaxel and an ARPI) as the optimal strategy for chemofit patients with synchronous high-volume disease, while confirming androgen deprivation therapy combined with an ARPI as the preferred approach for all other subgroups. Importantly, the former standard of care, androgen deprivation therapy combined with docetaxel, is no longer an option when an ARPI is available. For uro-oncologists, these results help refine patient selection for treatment intensification and support evidence-based, personalized care in daily practice. Associate Editor: Gianluca Giannarini, MD.

Patient Summary

For patients with metastatic hormone-sensitive prostate cancer, treatment depends on disease severity and overall health. For patients with high-volume and advanced disease at presentation who can tolerate chemotherapy, a combination of hormonal therapy (androgen receptor pathway inhibitors [ARPIs]) and chemotherapy (docetaxel), in addition to androgen deprivation therapy (ADT), offers the best survival benefit. For other patients, the combination of an ARPI and ADT is the preferred treatment. Docetaxel is not beneficial if ARPIs present an option.

1. Introduction

The treatment landscape for patients diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC) has evolved rapidly over the past 5 yr with the emergence of triplet systemic regimens and disease prognostication by volume of disease [1]. Now, patients have several life-prolonging options such as novel androgen receptor pathway inhibitor (ARPI) doublet therapy [2–7], docetaxel doublet therapy, and triplet systemic therapy [8–10], with the addition of both ARPIs and docetaxel to androgen deprivation therapy (ADT), as well as consideration of radiation to the prostate [11–13].

Results from the Chemo Hormonal Therapy vs Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trials [14–16] demonstrated that patients with mHSPC could derive survival benefits by adding docetaxel to ADT. Subgroup analyses in the CHAARTED and GETUG-15 trials, but not in STAMPEDE, suggested that this was driven by benefit in the synchronous high-volume (SHV) subgroup, with smaller benefits in patients with synchronous low-volume (SLV) disease. Quantitative evidence from a recent individual patient data (IPD) meta-analysis of the three main docetaxel trials (GETUG 15, CHAARTED, and STAMPEDE arm C) confirmed the differential efficacy of docetaxel by timing of metastases and disease volume [17]. Similarly, in early 2023, the initial report from our living interactive systematic review (LISR), which was based on a primary analysis of the PEACE-1 and ARASENS trials [8,9], suggested an overall survival (OS) benefit for triplet therapy over docetaxel plus ADT (D + ADT) and ARPI plus ADT (ARPI + ADT) only in patients with SHV disease [1].

Since our first report, the data for triplet therapy with darolutamide and docetaxel from the ARASENS trial [18] have been updated with subset analyses according to risk/volume of disease and timing of metastases, and have shown consistent benefits with triplet therapy in all prognostic subgroups, with the most significant benefit for SHV disease. Likewise, the Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer (ENZAMET) trial [6] showed that ADT with standard nonsteroidal antiandrogen (NSAA) alone was suboptimal, while the addition of enzalutamide, docetaxel, or both (E + ADT, D + ADT, or E + D + ADT) demonstrated similar overall efficacy. Although E + D + ADT showed some early benefit in SHV disease, survival curves converged over time, and the triple combination was associated with increased toxicity. Results from the ARCHES (enzalutamide) [3,19] and Targeted Investigational Treatment Analysis of Novel Anti-androgen (TITAN; apalutamide) [20] trials further confirmed the consistent OS benefits regardless of disease volume and timing of metastases. Recently, results from the ARANOTE trial showed a significant improvement in progression-free survival (PFS) with the addition of darolutamide to ADT [21]. Hence, it has now become crucial to reassess how these systemic therapies compare with each other and which patients may benefit from these options using the recently available data. The need for robust indirect analyses is further apparent in the absence of any trials directly comparing ARPI plus docetaxel and ADT (ARPI + D + ADT) with ARPI + ADT, as well as the need for data to guide patients and physicians.

Collating disease volume and metastasis timing creates four prognostic groups that may help guide systemic therapy in the absence of validated biomarkers. Therefore, in this report, we present the updated results from our LISR and network meta-analysis assessing the comparative effectiveness of contemporary systemic treatment options by disease volume and timing of metastatic presentation in patients diagnosed with mHSPC. Future reports will incorporate the data published on radiation to the prostate from the PEACE-1 trial (NCT01957436).

2. Methods

This LISR is conducted using the living interactive evidence (LIvE) synthesis framework [22]. Detailed methods were published with the initial report and are provided in the Supplementary material [1]. It is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for systematic reviews, incorporating network meta-analyses for health care interventions (Supplementary material) [23]. The original living systematic review was registered at the open science framework (OSF: https://osf.io/e2q3w) and is live on a website (living evidence).

2.1. Literature search and study selection

The *Watcher* module performs automated weekly searches using EMBASE and Ovid MEDLINE to identify new or updated reports of eligible criteria. The detailed *living* search strategy and methods are provided in the Supplementary material.

All phase 3 randomized controlled trials assessing contemporary systemic treatment options in patients diagnosed with mHSPC were eligible. Prespecified subgroups of interest (a priori for this report) included the following categories: synchronous (de novo) high volume (SHV), synchronous (de novo) low volume (SLV), metachronous (recurrent) high volume (MHV), and metachronous (recurrent) low volume disease (MLV), using the CHAARTED criteria for volume assessment [14,15].

2.2. Data extraction and quality assessment

The main outcome of interest included OS and PFS. When eligible trials had multiple reports, data from the most recent follow-up were included in the analysis. The quality of included trials was assessed using the Cochrane Risk of Bias tool version 2. This process of data extraction and quality assessment was carried out by two independent reviewers (S.A.A.N. and I.B.R.). Any discrepancies were resolved by consensus and input from a senior reviewer (A.H.B.).

2.3. Data analysis

Precomputed hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were pooled using an inverse variance approach following logarithmic transformation. A

DerSimonian and Laird random-effect meta-analysis was conducted to make *updated* direct (pairwise) comparisons. A *p* value of interaction was computed to assess differences by choice of doublet therapy (ARPI vs docetaxel), volume of disease, and timing of metastatic presentation. A *p* value of <0.1 was considered statistically significant for subgroup differences. Cochran's Q statistical test described statistically significant heterogeneity not explained by chance.

A trial-level network meta-analysis [24,25] using both direct and indirect evidence was conducted within the frequentist framework. Mixed treatment comparisons were *updated* and were made for prespecified subgroups of interest (SHV, MHV, SLV, and MLV). Analyses that grouped each treatment regimen into triplet, ARPI doublet, or docetaxel doublet therapy were conducted to assess comparative effectiveness among treatment class groups (ARPI + D + ADT, ARPI + ADT, and D + ADT).

Both fixed- and random-effect models were fitted, and the final choice of model was made based on the network geometry and sparsity of direct evidence. The fixed-effect model was used if the network was open and sparse, given that the common between-study heterogeneity cannot be estimated reliably in such networks [26]. P scores were computed to assess relative treatment rankings for OS. A higher P score indicated potentially better survival for a given treatment compared with other treatment options. Treatment rankings were interpreted in congruency with the pairwise estimates.

All statistical analyses were conducted using the *Analyzer* module enabled on the R project for statistical computing (version 4.1.1). Pairwise and network meta-analyses were carried out using meta (version 5.1-1) and netmeta (version 2.0-1), respectively.

2.4. Summary of findings

The relative effect estimates along with their 95% CIs pushed from the analysis module to the *Tabulator* module are translated into intervention risk, and absolute risk differences using relative estimates and assumed baseline event risk. The absolute risk difference per 1000 patients using HR is calculated as follows:

$$RR = \frac{(1 - e^{HR \times \ln(1 - baseline\ \ risk)})}{baseline\ \ risk}$$

$$ARD = 1000 \times baseline\ \ event\ \ risk \times (RR - 1)$$

3. Results

The updated report of a living systematic review includes data from 11 clinical trials published as of February 1, 2025. The study selection process is shown in the PRISMA flowchart (Supplementary Fig. 1). Results are available on an online interactive website (living evidence) [27].

3.1. Baseline trial and population characteristics

3.1.1. Overall population

The current report of this LISR includes a total of 11 trials with 12 668 patients and 12 unique treatments. All eligible trials followed a phase 3 randomized design; six trials (PEACE-1, STAMPEDE, CHAARTED, GETUG-AFU15, ENZAMET, and SWOG 1216) were open label, while five (ARASENS, LATITUDE, TITAN, ARCHES, and ARANOTE) were double blinded. Triplet regimens, including the combinations of E + D + ADT, darolutamide with docetaxel plus ADT (DARO + D + ADT), abiraterone acetate-prednisone with docetaxel plus ADT (AAP + D + ADT), and enzalutamide with abiraterone plus ADT (E + AAP + ADT), were assessed in one trial each. Among doublet regimens—in terms of chemotherapy doublet—D + ADT was assessed in three trials. In terms of ARPI doublet therapy, abiraterone acetate-prednisone plus ADT (AAP + ADT) was assessed in two, enzalutamide plus ADT in two, apalutamide plus ADT (APA + ADT) in one, and darolutamide plus ADT (DARO + ADT) in one trial. The overall risk of bias for OS was low, with some concerns for PFS due to the open-label design in some trials (Supplementary Table 1). Detailed baseline characteristics are provided in Supplementary Table 2 and are also available on an online interactive website (living evidence).

3.1.2. Prespecified subgroups by volume of disease and timing of metastatic presentation

An analysis by prespecified subgroups for this report included a total of 8990 patients and eight unique treatment options from nine clinical trials [3,9,15,18,20,28–31]. Three trials (STAMPEDE arm C, SWOG 1216, and ARANOTE) did not report analyzable estimates for any of four prespecified subgroups and hence were excluded from the respective analyses. PEACE-1 [9] reported data for both the overall population and the patients who received docetaxel; however, only data for patients who received docetaxel were used for the analysis since data by subgroups for patients who did not receive docetaxel were reported inconsistently.

Of the total population in the trials eligible for an analysis by prognostic subgroups, approximately 5171 (57%) patients had SHV, 2455 (27%) had SLV, 589 (6.5%) had MHV, and 775 (8.5%) had MLV disease. Detailed results are shown in Table 1, and Supplementary Tables 3 and 4.

3.2. Direct pairwise comparisons

Pairwise comparisons, using new data from ARANOTE trial, to assess differences by choice of doublet therapy (ARPI vs docetaxel), volume of disease (high vs low), and timing of metastatic presentation (synchronous vs metachronous) were consistent with those of a previous report [1]. Detailed pairwise results are available on an online interactive website (living evidence).

3.3. Mixed treatment comparisons

A total of 11 trials contributed to the network in the overall population (Supplementary Fig. 2). Eight trials contributed to the network for the SHV subgroup, nine for the SLV subgroup, and five for both the MHV and the MLV subgroup (Supplementary Fig. 3). Results of the fixed-effect network meta-analysis are reported here and available in Figures 1–3 and Supplementary Figures 4–7. The random-effect

Table 1 – Baseline trial and population characteristics of the studies included in the analysis for prespecified subgroups of interests

Study	Treatment arms		Total participants	Median age (yr)	Median follow up (mo)	Prognostic subgroups, *N* (%)				Docetaxel (%)	Median OS (mo)[a]
(year)	Experimental	Control				SHV	SLV	MHV	MLV		
CHAARTED (2018)	D + ADT	ADT	790	Rx: 64 Control: 63	54	421 (53)	154 (20)	91 (12)	123 (16)	100	Rx: 57.6 Control: 47.2
GETUG-AFU15 (2018)	D + ADT	ADT	385	Rx: 63 Control: 64	84	153 (40)	119 (31)	29 (7.6)	79 (21)	100	Rx: 62.1 Control: 48.6
LATITUDE (2019)	AAP + ADT	ADT	1199	Rx: 68 Control: 67	52	955 (80)[b]	243 (20)[b]	0 (0)		0	Rx: 53.3 Control: 36.5
STAMPEDE arm G (2019)	AAP + ADT	ADT	901	Rx: 67 Control: 67	96	486 (54)	373 (41)	13 (1.4)	29 (3.2)	0	Rx: 79.0[c] Control: 46.0[c]
ARCHES (2022)	E + ADT	ADT	1150	Rx: 70 Control: 70	45	606 (53)[d]	284 (25)[d]	116 (10)[d]	130 (11)[d]	18	Rx: NR Control: NR
PEACE-1 (2022)	AAP + D + ADT	D + ADT	1172	Rx: 67 Control: 66	46	667 (57)[b]	505 (43)[b]	0 (0)		61	Rx: 68.4 Control: 56.4
ARASENS (2023)	DARO + D + ADT	D + ADT	1305	Rx: 67 Control: 67	~44	877 (68)[d]	247 (19)[d]	117 (9.1) [d]	51 (3.9)[d]	100	Rx: NR Control: 48.9
ENZAMET (2023)	E + ADT	NSAA + ADT	622	Rx: 69 Control: 69	68	169 (27)	153 (25)	74 (12)	227 (36)	0	Rx: NR Control: NR
	E + D + ADT	NSAA + D + ADT	503			270 (54)	92 (18)	89 (18)	52 (10)	100	Rx: NR Control: ~62[e]
TITAN (2023)	APA + ADT	ADT	1052	Rx: 69 Control; 68	44	567 (54)[d]	285 (27)[d]	60 (5.7)[d]	84 (7.9)[d]	11	Rx: NR Control: 52.2

AAP = abiraterone acetate and prednisone; ADT = androgen deprivation therapy; APA = apalutamide; CHAARTED = Chemo Hormonal Therapy vs Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; D = docetaxel; DARO = darolutamide; E = enzalutamide; ENZAMET = Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer; MHV = metachronous high-volume disease; MLV = metachronous low-volume disease; NR = not reached; NSAA = nonsteroidal antiandrogen; OS = overall survival; Rx = treatment; SHV = synchronous high-volume disease; SLV = synchronous low-volume disease; STAMPEDE = Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; TITAN = Targeted Investigational Treatment Analysis of Novel Anti-androgen.

[a] Outlines the median overall survival in the overall patient population.

[b] LATITUDE, and PEACE-1 did not include patients with metachronous metastases, and GETUG-AGU15 and ARASENS did not provide analyzable estimates for timing of metastasis in high-volume patients and metachronous low-volume disease patients, respectively.

[c] Estimates for median overall survival were extracted from the 5-yr follow-up analysis of STAMPEDE arm G.

[d] The relative percentages of patients in prognostic subgroups in ARASENS, ARCHES, and TITAN do not add up to 100. A total of 13 patients in ARASENS, 14 in ARCHES, and 56 in TITAN had missing scans, and unknown or undetermined status of metastatic presentation at initial diagnosis. Therefore, a total of 8990 patients were included in the current analysis.

[e] Approximated using Kaplan-Meier curves.

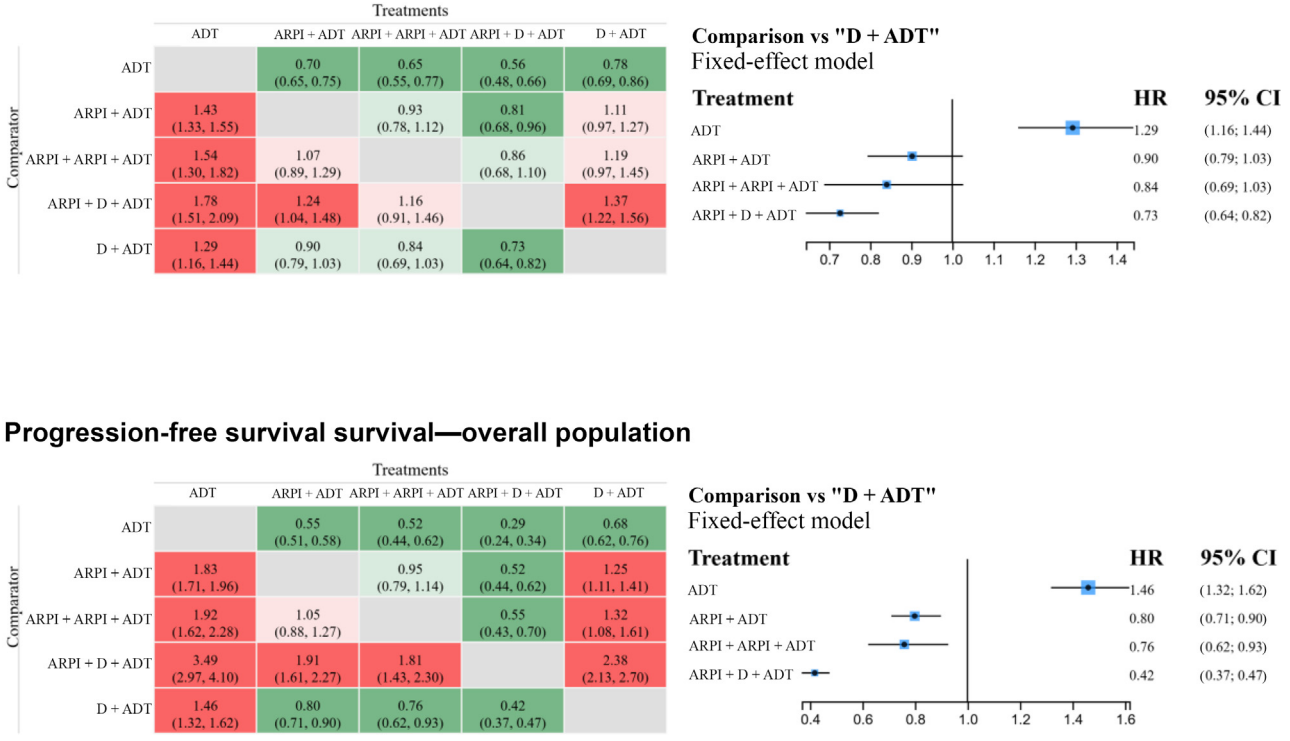

Fig. 1 – Mixed treatment comparisons for OS and PFS in overall population by treatment class. League tables are provided in the left and forest plots in the right. In league tables, the values in each cell represent the relative treatment effect (and 95% CI) of the treatment on the top, compared with the treatment on the left. Green color suggests relative treatment benefit: light green suggests nonsignificant benefit and dark green suggests significant benefit. Red color suggests relative treatment harm: light red suggests nonsignificant harm and dark red suggests significant harm. The "ARPI + D + ADT" triplet refers specifically to regimens with concurrent administration of androgen deprivation therapy, androgen receptor pathway inhibitor, and docetaxel. At this time, apalutamide is not included in this category due to the lack of published data on concurrent dosing with ADT and docetaxel. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; CI = confidence interval; D = docetaxel; HR = hazard ratio.

network meta-analysis showed consistent results, which are reported in Supplementary Figures 8–12. Updated analyses by clinically relevant subgroups are available on an online interactive website (living evidence).

3.3.1. Overall population

When analyzed by treatment class, the combination of ARPI + D + ADT led to a statistically significant improvement in OS when compared with ARPI + ADT (HR: 0.81; 95% CI: 0.68–0.96), D + ADT (HR: 0.73; 95% CI: 0.64–0.82), and ADT alone (HR: 0.56; 95% CI: 0.48–0.66). The combination of ARPI + ARPI + ADT led to a statistically significant improvement in OS only when compared with ADT alone (HR: 0.65; 95% CI: 0.55–0.77). There were no statistically significant differences between ARPI + D + ADT and ARPI + ARPI + ADT, and between ARPI + A DT and D + ADT, as shown in Figure 1.

When analyzed by treatment regimen, the pattern of results for OS was consistent with the analysis by treatment class (Fig. 2). Similar results were observed for PFS.

3.3.2. Analyses by prespecified prognostic subgroups

OS was analyzed and is reported here; PFS was not consistently reported across the eligible trials by prespecified prognostic subgroups. Three trials (STAMPEDE arm C, SWOG 1216, and ARANOTE) did not report analyzable estimates of OS for any of the four prespecified subgroups and hence were excluded from the following subset analyses.

3.3.2.1. SHV disease. When analyzed by treatment class, ARPI + D + ADT (P score: 0.99) was ranked as the potentially most efficacious treatment with regard to OS improvement (Fig. 3 and Table 2). The combination of ARPI + D + ADT led to a statistically significant improvement in OS when compared with ARPI + ADT (HR: 0.71; 95% CI: 0.53–0.97) and D + ADT (HR: 0.72; 95% CI: 0.62–0.83). There was no statistically significant difference between ARPI + ADT and D + ADT (HR: 1.01; 95% CI: 0.76–1.32).

When analyzed by treatment regimen, DARO + D + ADT led to a statistically significant improvement in OS when compared with D + ADT (HR: 0.69; 95% CI: 0.57–0.85), E + ADT (HR: 0.67; 95% CI: 0.46–0.99), and APA + ADT (HR: 0.65; 95% CI: 0.43–0.96). There was no statistically significant difference between DARO + D + ADT and AAP + ADT (HR: 0.72; 95% CI: 0.51–1.02). The combination of AAP + D + ADT led to a statistically significant improvement in OS when compared with D + ADT (HR: 0.72; 95% CI: 0.55–0.95) and ADT alone (HR: 0.45; 95% CI: 0.31–0.66), but not compared with ARPI doublet regimens. The combination of E + D + ADT led to a statistically significant improvement

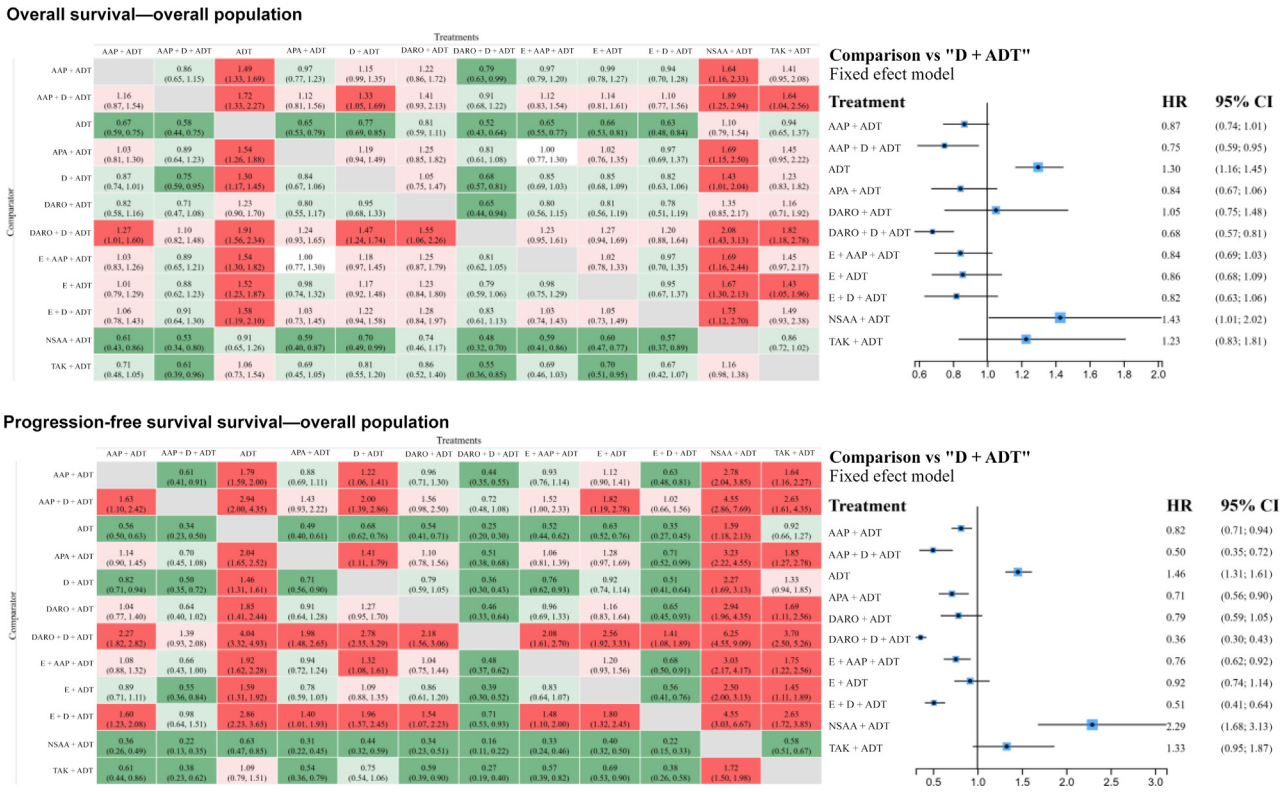

Fig. 2 – Mixed treatment comparisons for OS and PFS in overall population by treatment regimen. League tables are provided in the left and forest plots in the right. In league tables, the values in each cell represent the relative treatment effect (and 95% CI) of the treatment on the top, compared with the treatment on the left. Green color suggests relative treatment benefit: light green suggests nonsignificant benefit and dark green suggests significant benefit. Red color suggests relative treatment harm: light red suggests nonsignificant harm and dark red suggests significant harm. Sensitivity analyses limited to trials with strict radiographic progression free–survival were also conducted, and these showed a consistent pattern of results, as shown in Supplementary Figures 15–18. AAP = abiraterone acetate and prednisone; ADT = androgen deprivation therapy; APA = apalutamide; CI = confidence interval; D = docetaxel; DARO = darolutamide; E = enzalutamide; HR = hazard ratio; NSAA = nonsteroidal antiandrogen; OS = overall survival; PFS = progression-free survival.

in OS compared with ADT alone (HR: 0.50; 95% CI: 0.33–0.75), but no statistically significant differences were observed between E + D + ADT and doublet regimens. There were no statistically significant differences when triplet regimens were compared. A ranking analysis showed that triplet regimens, which included AAP + D + ADT (P score: 0.85), DARO + D + ADT (P score: 0.89), and E + D + ADT (P score: 0.73), were potentially more efficacious treatment options in terms of OS improvement than doublet regimens in patients with SHV mHSPC. The ranking analysis and detailed results are provided in Supplementary Figure 4, and Supplementary Tables 7 and 8.

3.3.2.2. SLV disease. When analyzed by treatment class (Fig. 3 and Table 2), ARPI + ADT led to a statistically significant improvement in OS compared with ADT alone (HR: 0.65; 95% CI: 0.52–0.80) but not compared with D + ADT (HR: 0.69; 95% CI: 0.47–1.01) in patients with SLV mHSPC. There was no statistically significant difference between ARPI + D + ADT and ARPI + ADT (HR: 1.08; 95% CI: 0.65–1.79).

When analyzed by treatment regimen, E + ADT (HR: 0.62; 95% CI: 0.42–0.91) and AAP + ADT (HR: 0.66; 95% CI: 0.49–0.89) led to a statistically significant improvement in OS compared with ADT. No statistically significant improvement in OS was observed for APA + ADT (HR: 0.65; 95% CI: 0.40–1.05), AAP + D + ADT (HR: 0.78; 95% CI: 0.43–1.43), DARO + D + ADT (HR: 0.71; 95% CI: 0.38–1.32), and E + D + ADT (HR: 0.53; 95% CI: 0.25–1.14) when compared with ADT alone. The ranking analysis and detailed results are provided in Supplementary Figure 5, and Supplementary Tables 7 and 8.

3.3.2.3. MHV disease. The MHV population was the smallest of the four groups (589 patients), representing 6.5% of the total population.

When analyzed by treatment class (Fig. 3 and Table 2), no statistically significant improvement in OS was observed with ARPI + D + ADT, when compared with ARPI + ADT (HR: 0.89; 95% CI: 0.36–2.22) and D + ADT (HR: 0.90; 95% CI: 0.60–1.36) in patients with MHV mHSPC.

When analyzed by treatment regimen, there was no statistically significant improvement in OS with DARO + D + ADT compared with APA + ADT (HR: 0.72; 95% CI: 0.23–2.33), E + ADT (HR: 0.67; 95% CI: 0.24–1.86), E + D + ADT (HR: 0.59; 95% CI: 0.26–1.34), and D + ADT (HR: 0.69; 95% CI: 0.39–1.23). No statistically significant differences were observed among comparisons of other treatment regimens.

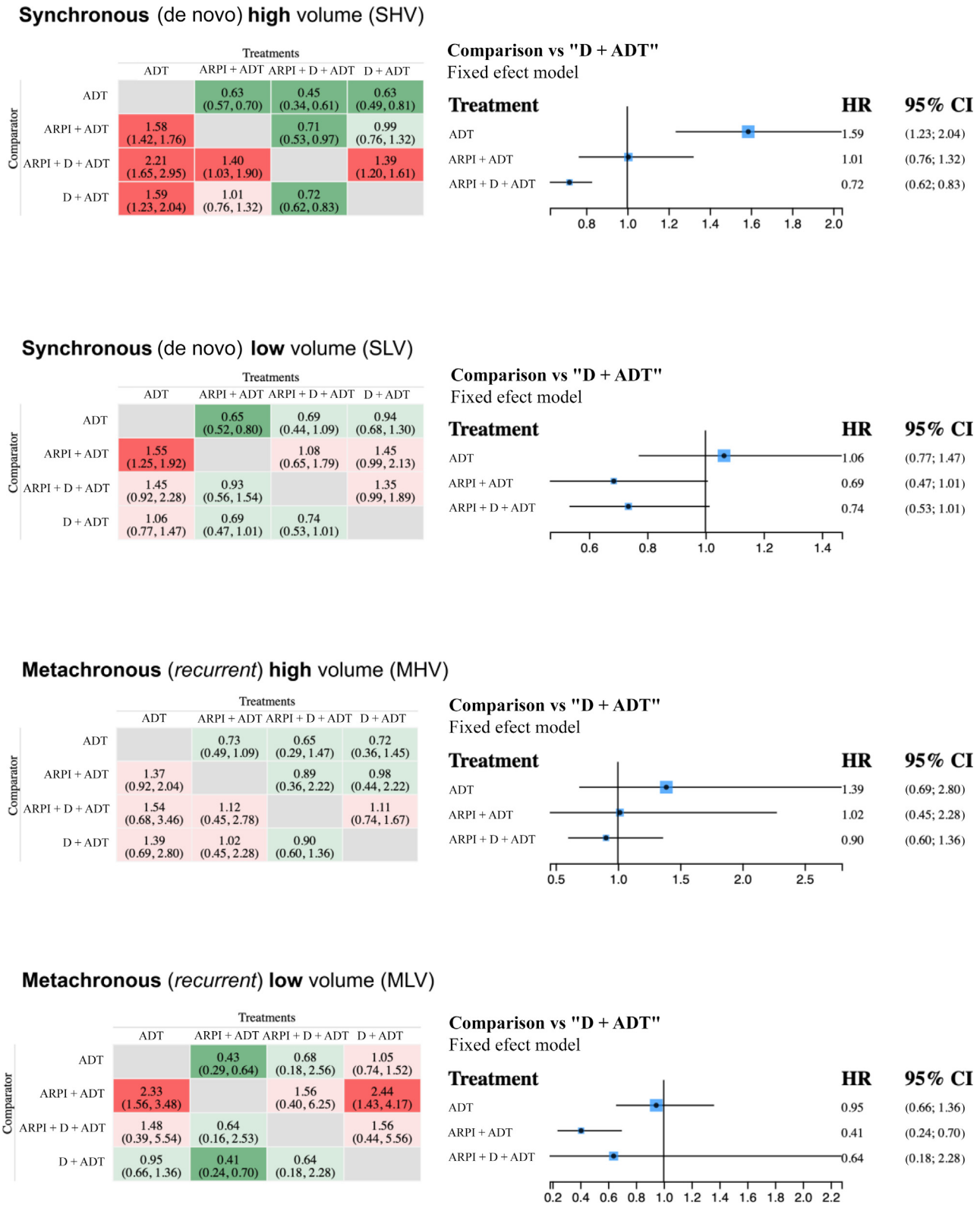

Fig. 3 – Mixed treatment comparisons by class across prognostic subgroups. League tables are provided in the left and forest plots in the right. In league tables, the values in each cell represent the relative treatment effect (and 95% CI) of the treatment on the top, compared with the treatment on the left. Green color suggests relative treatment benefit: light green suggests nonsignificant benefit and dark green suggests significant benefit. Red color suggests relative treatment harm: light red suggests nonsignificant harm and dark red suggests significant harm. The "ARPI + D + ADT" triplet refers specifically to regimens with concurrent administration of androgen deprivation therapy, an androgen receptor pathway inhibitor, and docetaxel. At this time, apalutamide is not included in this category due to the lack of published data on concurrent dosing with ADT and docetaxel. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitors; CI = confidence interval; D = docetaxel; HR = hazard ratio.

Table 2 – Summary of findings outlining absolute risk differences for overall survival by class[a]

Comparators	Triplet therapy			
	Synchronous high volume	Synchronous low volume	Metachronous high volume	Metachronous low volume
Androgen receptor pathway inhibitor doublet SHV: 463 deaths per 1000 SLV: 225 deaths per 1000 MHV: 317 deaths per 1000 MLV: 209 deaths per 1000	101 fewer deaths per 1000 (from 172 fewer to 10 fewer)	18 more deaths per 1000 (from 83 fewer to 158 more)	33 fewer deaths per 1000 (from 222 fewer to 274 more)	78 more deaths per 1000 (from 93 fewer to 504 more)
	HR: 0.71 (0.53–0.97)	HR: 1.08 (0.65–1.79)	HR: 0.89 (0.36–2.22)	HR: 1.56 (0.40–6.25)
	2164 patients (7 RCTs)	1055 patients (7 RCTs)	357 patients (4 RCTs)	236 patients (3 RCTs)
	Rank 3	Rank 1	Rank 2	Rank 1
Docetaxel doublet SHV: 531 deaths per 1000 SLV: 340 deaths per 1000 MHV: 468 deaths per 1000 MLV: 279 deaths per 1000	97 fewer deaths per 1000 (from 135 fewer to 57 fewer)	61 fewer deaths per 1000 (from 114 fewer to 2 more)	30 fewer deaths per 1000 (from 131 fewer to 98 more)	54 fewer deaths per 1000 (from 129 fewer to 168 more)
	HR: 0.72 (0.62–0.83)	HR: 0.74 (0.53–1.01)	HR: 0.90 (0.60–1.36)	HR: 0.64 (0.18–2.28)
	1817 patients (3 RCTs)	757 patients (3 RCTs)	352 patients (2 RCTs)	111 patients (1 RCT)
	Rank 2	Rank 3	Rank 3	Rank 4
Androgen deprivation therapy SHV: 569 deaths per 1000 SLV: 334 deaths per 1000 MHV: 412 deaths per 1000 MLV: 307 deaths per 1000	206 fewer deaths per 1000 (from 255 fewer to 139 fewer)	73 fewer deaths per 1000 (from 138 fewer to 20 more)	113 fewer deaths per 1000 (from 251 fewer to 125 more)	48 fewer deaths per 1000 (from 129 fewer to 200 more)
	HR: 0.45 (0.34–0.61)	HR: 0.69 (0.44–1.09)	HR: 0.65 (0.29–1.47)	HR: 0.68 (0.18–2.56)
	2404 patients (8 RCTs)	1139 patients (9 RCTs)	403 patients (5 RCTs)	295 patients (3 RCTs)
	Rank 4	Rank 4	Rank 4	Rank 3
	Androgen receptor pathway inhibitor doublet			
Triplet therapy SHV: 428 deaths per 1000 SLV: 264 deaths per 1000 MHV: 380 deaths per 1000 MLV: 160 deaths per 1000	118 more deaths per 1000 (from 10 more to 230 more)	14 fewer deaths per 1000 (from 92 fewer to 100 more)	31 more deaths per 1000 (from 159 fewer to 337 more)	70 fewer deaths per 1000 (from 172 fewer to 238 more)
	HR: 1.40 (1.03–1.90)	HR: 0.93 (0.56–1.54)	HR: 1.12 (0.45–2.78)	HR: 0.64 (0.16–2.53)
	2164 patients (7 RCTs)	1055 patients (7 RCTs)	352 patients (4 RCTs)	236 patients (3 RCTs)
	Rank 1	Rank 2	Rank 1	Rank 2
Docetaxel doublet SHV: 531 deaths per 1000 SLV: 340 deaths per 1000 MHV: 468 deaths per 1000 MLV: 279 deaths per 1000	3 more deaths per 1000 (from 86 fewer to 97 more)	64 fewer deaths per 1000 (from 112 fewer to 2 more)	5 more deaths per 1000 (from 159 fewer to 264 more)	117 fewer deaths per 1000 (from 154 fewer to 58 fewer)
	HR: 1.01 (0.76–1.32)	HR: 0.69 (0.47–1.01)	HR: 1.02 (0.45–2.28)	HR: 0.41 (0.24–0.70)
	2403 patients (6 RCTs)	1108 patients (7 RCTs)	393 patients (4 RCTs)	297 patients (5 RCTs)
	Rank 2	Rank 3	Rank 3	Rank 4
Androgen deprivation therapy SHV: 569 deaths per 1000 SLV: 334 deaths per 1000 MHV: 412 deaths per 1000 MLV: 307 deaths per 1000	139 fewer deaths per 1000 (from 165 fewer to 110 fewer)	72 fewer deaths per 1000 (from 101 fewer to 41 fewer)	74 fewer deaths per 1000 (from 147 fewer to 23 more)	113 fewer deaths per 1000 (from 143 fewer to 70 fewer)
	HR: 0.63 (0.57–0.70)	HR: 0.65 (0.52–0.80)	HR: 0.73 (0.49–1.09)	HR: 0.43 (0.29–0.64)
	2990 patients (5 RCTs)	1490 patients (5 RCTs)	444 patients (3 RCTs)	481 patients (3 RCTs)
	Rank 4	Rank 4	Rank 4	Rank 3

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; D = docetaxel; HR = hazard ratio; MHV = metachronous high volume; MLV = metachronous low volume; RCT = randomized controlled trials; SHV = synchronous high volume; SLV = synchronous low volume.

[a] This table outlines relative and absolute risk estimates of death with triplet therapy and androgen receptor pathway inhibitors. The comparison is directed as treatment (in column) versus comparators (in rows). Each subcolumn represents the subgroup (synchronous high volume, synchronous low volume, metachronous high volume, and metachronous low volume). The relative effect estimates along with their 95% confidence intervals are translated into corresponding intervention risks. The assumed baseline risk of death for each comparator by subgroups is computed as a mean of the risk of death within the study follow-up period from the included trials. The absolute risk difference is calculated as the absolute risk difference between corresponding intervention risks and assumed comparator risks. Treatment ranks provided in the cells reflect the rankings of each comparator in a given comparison for a given subgroup. For example, in a comparison between triplet therapy and androgen receptor pathway inhibitor doublet therapy in the synchronous high-volume subgroup, rank 3 indicates the relative treatment ranking for androgen receptor pathway inhibitor doublet therapy. The "ARPI + D + ADT" triplet therapy refers specifically to regimens with concurrent administration of androgen deprivation therapy, an androgen receptor pathway inhibitor, and docetaxel. At this time, apalutamide is not included in this category due to the lack of published data on concurrent dosing with ADT and docetaxel.

The PEACE-1 and LATITUDE trials did not include patients with metachronous metastases, and STAMPEDE arm G did not report analyzable estimates. Hence, these were excluded from the network for this subgroup. The ranking analysis and detailed results are provided in Supplementary Figure 6, and Supplementary Tables 7 and 8.

3.3.2.4. MLV disease. When analyzed by treatment class, ARPI + ADT (P score: 0.91) was ranked potentially as a more efficacious treatment option than D + ADT and ADT alone with regard to OS improvement in patients with MLV mHSPC (Fig. 3 and Table 2). The combination of an ARPI and ADT led to a statistically significant improvement in OS when compared with ADT alone (HR: 0.43; 95% CI: 0.29–0.64) and D + ADT (HR: 0.41; 95% CI: 0.24–0.70). However, there was no statistically significant difference between ARPI + D + ADT and ARPI + ADT (HR: 1.56; 95% CI: 0.40–6.25)

When analyzed by treatment regimen, E + ADT led to a statistically significant improvement in OS when compared with ADT alone (HR: 0.51; 95% CI: 0.32–0.79) and D + ADT (HR: 0.48; 95% CI: 0.27–0.85). The combination of APA + ADT led to a statistically significant improvement in OS when compared with ADT alone (HR: 0.22; 95% CI: 0.09–0.54) and D + ADT (HR: 0.21; 95% CI: 0.08–0.55). No statistically significant differences were observed among comparisons of other treatments. A ranking analysis showed that ARPI doublet regimens were potentially more efficacious than docetaxel doublet and ADT. Detailed results are provided in Supplementary Figure 7, and Supplementary Tables 7 and 8.

As indicated above, the PEACE-1 and LATITUDE trials did not include patients with metachronous metastases, while the STAMPEDE arm G and ARASENS trials did not report analyzable estimates; hence, these trials were excluded from the network for this subgroup.

Results of the trial assessing triplet therapy and summary of findings across the four prognostic subgroups by treatment regimen are available in Supplementary Tables 9 and 10.

4. Discussion

This LISR provides a comprehensive and up-to-date assessment of the comparative effectiveness of contemporary systemic therapies in patients diagnosed with mHSPC, including the new data from the recently published ARANOTE trial [21]. It outlines relative and absolute benefits in overall population and in the context of prognostic groups defined by volume of disease and timing of metastasis [27]. Prior evidence has suggested that patients across these prognostic subgroups have variable survival on ADT alone, with the longest median survival of ~3 yr in patients with SHV disease, ~4.5 yr in patients with either SLV or MHV disease, and ~8 yr in patients with MLV disease [17,32].

In patients with SHV mHSPC, our analysis indicates evidence of an OS benefit with triplet therapy with the combination of ARPIs, docetaxel, and ADT over doublets with either docetaxel or ARPI therapy. There were no statistically significant differences among different triplet regimens with respect to OS improvement, indicating that the findings are a "class effect" with drugs with similar mechanisms of action. These findings are reassuring and reinforce the efficacy of triplet therapy in patients with the worst prognosis, having high volume and initial presentation with distant metastases, and who are fit for docetaxel [9,18,33]. It should also be noted that the improved efficacy observed with triplet therapy occurs at the expense of increased toxicity, and global health-related quality of life is expected to decrease during active docetaxel treatment [1,34,35]. However, overall quality of life tends to improve with longer follow-up and after completion of chemotherapy [34]. Patient-specific factors such as age, fitness for chemotherapy [33], overall general physical health, and patient preferences should also be weighed in when making an informed decision about triplet therapy [36]. However, it should be noted that there appears to be no clear definition for docetaxel (chemotherapy) fitness [37]. Assessment of patient-important outcomes, such as the net clinical benefit in future clinical trials, may provide a clear picture of tradeoffs between treatment benefit and harm [38]. As such, current evidence suggests that docetaxel doublet therapy may be considered in SHV mHSPC patients only when access to an ARPI is not possible or absolute contraindications to ARPI doublet therapies exist [9,18]. If a patient is not fit for docetaxel [33], an ARPI doublet regimen may be preferred [1], as suggested by the improved OS for patients with SHV disease in the ENZAMET study who were not treated with docetaxel and had a median age of 74 yr, versus 66 yr for those treated with docetaxel [28].

In patients with SLV mHSPC, ARPI doublet or triplet therapy may be an effective treatment option. However, it is important to note that most mixed treatment comparisons for this subgroup precluded statistical significance due to the limited sample size. As a result, the absence of a clear survival benefit for triplet therapy over ARPI doublets raises questions about its utility in this setting, particularly given the added toxicity burden associated with triplet therapy. In the ENZAMET trial, docetaxel use was at the physician's discretion before randomization, with stratification based on planned docetaxel use. Consequently, patients with SLV mHSPC receiving concurrent docetaxel may have had more aggressive disease, as reflected by worse prostate-specific antigen (PSA) progression and prostate cancer–specific survival compared with those not receiving docetaxel. Longer-term follow-up of the PEACE-1 trial is expected to clarify whether the combination of abiraterone acetate, docetaxel, and ADT improves survival in men with SLV mHSPC.

In patients with MHV mHSPC, no statistically significant differences were observed among comparisons of treatments. MHV mHSPC is a rare situation, given that by far most patients relapsing after local treatments have oligometastatic low-volume disease. Therefore, the proportion of patients with MHV mHSPC was small (589 patients; 6.5%), which could be a plausible explanation for the lack of statistically significant differences for treatment comparisons. The effect of docetaxel may be greater in high-volume disease. However, it is possible that the effect may also be increased with the bulkiness of primary disease, as defined

by increasing T stage, which could explain the stronger evidence of a potential benefit for patients with SHV over MHV disease [17]. Furthermore, it would be plausible to consider that SLV and MHV disease may represent a broader mix of patients in terms of their clinical characteristics and underlying biology, as they have similar median OS of ~4.5 yr on ADT alone [17,32]. Some MHV patients might have been SHV patients if their diagnosis was delayed or if they had an indolent course with rising PSA after prostatectomy before mHSPC therapy. Similarly, some SLV patients might have been SHV patients due to a delayed initial diagnosis.

In patients with MLV mHSPC, current evidence supports the use of ARPI + ADT over ADT alone with a clear clinically and statistically significant OS benefit, compared with ADT alone and D + ADT. Our results are also consistent with the STOPCAP meta-analysis [17], which showed no clinical benefit with docetaxel in patients with MLV mHSPC. This suggests that ARPI doublets are preferable treatment options in this patient population. However, it is important to note that patients with MLV disease were also rarely included in trials, which were enriched with patients with synchronous (de novo) disease, or even excluded (PEACE-1 and LATITUDE). Hence, while there was no statistically significant difference between ARPI doublet and triplet therapies, the overall sample size in this subgroup was very small (~750 patients), which could have precluded statistical significance. Overall, these findings highlight the absence of clinical evidence for a meaningful benefit with docetaxel and guide the clinical management of patients with MLV mHSPC to treatment with ARPI + ADT.

While these prognostic subgroups guide systemic treatment, these may not fully capture biological heterogeneity in mHSPC. Hence, biologically driven biomarkers are needed to better predict treatment response and prognosis. Consequently, efforts are underway to determine whether predictive molecular biomarkers such as SPOP mutations, which render superior responses to ARPI therapy [39,40], or PTEN/Tp53/RB1 [41] mutations could potentially be used to guide treatment selection in mHSPC patients. Development of predictive biomarkers for treatment intensification could personalize care, especially for intermediate-risk disease states where the benefit of therapies such as docetaxel may be more variable.

It is also noteworthy that no significant differences were detected in efficacy between ARPI agents highlighting the need for a nuanced, patient-centered approach when choosing an ARPI in doublet or triplet regimens in real-world settings. Cost effectiveness remains a critical determinant, especially in regions with variable access (Supplementary Table 11). Accessibility, including drug availability and insurance coverage, can profoundly influence regimen selection in real-world practice [42]. Furthermore, the potential for drug-drug interactions, particularly in patients with polypharmacy, and the distinct toxicity profiles of ARPIs, such as cardiovascular, hepatic, or fatigue-related adverse events, necessitate individualized risk-benefit assessments.

This iteration of a living network meta-analysis has several strengths. Compared with the prior literature, this report of the living network meta-analysis incorporates data from the ARANOTE trial evaluating comparative effectiveness of DARO + ADT and updated subgroup analyses from ARASENS by volume of disease, and extends the analysis to four clinically relevant prognostic subgroups (SHV, SLV, MHV, and MLV), as shown in Supplementary Figures 13 and 14. Unlike prior meta-analyses, which are static, cross-sectional, and unidimensional, this work is part of an ongoing living evidence program using a novel living interactive evidence synthesis framework [1,22,43]. This not only allows us to update evidence in a timely manner (as soon as new data become available), but also enables us to present evidence in a way that is accessible and meaningful to clinicians. These results are presented on a living interactive website (living evidence).

However, these results should be interpreted in the context of several limitations. First, this is a trial-level meta-analysis with sparse direct evidence and an open network, which did not allow us to formally assess incoherence for mixed treatment comparisons [24,25,44]. Network metaregression using trial-level data was also not feasible due to the limited number of included trials at the level of each mixed treatment comparison. In contrast, an IPD network meta-analysis could offer additional insights by adjusting for potential covariates across studies (Supplementary Table 11). We initially attempted to conduct an IPD network meta-analysis by gathering data from individual trials. However, restrictive data-sharing agreements limited us to perform a formal IPD network meta-analysis. Second, there are variable follow-up durations across the included trials, which could have potentially over- or underestimated relative treatment effects in mixed treatment comparisons. Third, none of the included trials were originally designed to capture treatment efficacy by volume of disease and timing of metastatic presentation. Most trials reported these subgroups as post hoc analyses without stratification and adjustment for potential confounders. Fourth, TITAN [20] and ARCHES [3] included patients who received prior docetaxel therapy and did not report survival by receipt of docetaxel in each prognostic subgroup. Although the relative proportions of such patients in these trials were small, they could overestimate the efficacy of ARPI doublet regimens in the analysis. However, numerous studies [1,45,46] have demonstrated a consistent effect even after the exclusion of patients who received prior docetaxel in these trials (Supplementary Table 12). Fifth, rankings alone may not be a reliable indicator of treatment benefit or harm and should be interpreted carefully in congruence with pairwise estimates. Sixth, there was unequal distribution of the four prognostic subgroups between trials, and patients with higher-risk disease were preferentially included in the design of some trials (Table 1). Limited sample size in other prognostic subgroups could have precluded statistical significance at the level of each pairwise comparison. Seventh, it is also important to note that volume definition in the pivotal trials was purely based on conventional imaging (computed tomography or magnetic resonance imaging and bone scintigraphy), and the use of prostate-specific membrane antigen positron emission tomography imaging may lead to a higher proportion of patients with high-volume mHSPC with a risk of potential overtreatment when using

triplet therapy. Eighth, access to metastatic castration-resistant prostate cancer therapies varied by region and over time, potentially influencing comparator arm outcomes and likely treatment rankings. For example, the median OS for SHV patients on D + ADT (with NSAA) in the ENZAMET trial was 62 mo [28], compared with 40–49 mo on D + ADT (without NSAA) for all the other trials [9,14,18,28,31,47]. Additionally, use of salvage therapy differed (Supplementary Table 13)—85% in PEACE-1 and ENZAMET versus ~76% in ARASENS—potentially underestimating OS in some control arms. Ninth, the definition of PFS varied across the included trials. We assumed that radiographic progression typically precedes symptomatic progression, initiation of new anticancer therapies, and death from other causes. Nevertheless, a sensitivity analysis restricted to trials using radiographic PFS definitions demonstrated a consistent pattern of results (Supplementary Figs. 15–18, and Supplementary Tables 14 and 15). Finally, this analysis did not adjust for patient- and cancer-related factors influencing docetaxel use in certain trials. In ENZAMET, for instance, SHV patients treated with docetaxel were younger (median age 66 vs 74 yr) and had worse prognoses, while those not given docetaxel had higher noncancer mortality, as reflected in better prostate cancer–specific survival.

5. Conclusions

Current evidence from the LIvE framework suggests that triplet systemic therapy is preferred for patients with SHV mHSPC who are fit for docetaxel. Androgen receptor pathway doublet therapy is preferred to ADT alone for all other subgroups with mHSPC. There is no role of docetaxel doublet in patients with access to ARPI therapy if they are able to receive it.

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Supplementary data

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