REVIEWS IN UROLOGY

Darolutamide for Metastatic Hormone-Sensitive Prostate Cancer: An Overview of Meta-Analyses and Indirect Treatment Comparisons

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KEYWORDS:
Prostatic neoplasms; network meta-analysis; overall survival; adverse events

Abstract

Background: We evaluated the numerous published indirect treatment comparisons (ITCs) and meta-analyses of the efficacy and safety of treatments in metastatic hormone-sensitive prostate cancer (mHSPC), which include the ARASENS study of darolutamide triple therapy, to identify limitations of the evidence and to suggest methodological improvements.

Methods: MEDLINE, Embase, and Cochrane databases were searched through February 12, 2024. Indirect treatment comparisons and meta-analyses were included of patients with mHSPC who received docetaxel, novel hormonal therapies plus androgen-deprivation therapy, standard of care, or developmental agents. Outcomes included overall survival, progression-free survival, and adverse events of grade 3 or higher.

Results: Fifteen ITCs (including 2 ITCs of pooled androgen receptor axis–targeted triple therapy) and 8 meta-analyses of novel hormonal therapies were identified, with variation in included trials and analytical methods. Eleven ITCs ranked darolutamide triple therapy highest in providing benefits in overall survival, using data from ARASENS. Evidence for progression-free survival was sparse across trials. For darolutamide triple therapy, ITCs reported a lower risk of adverse events than for abiraterone triple therapy (1 ITC, relative risk, 0.86; 1 ITC, odds ratio, 0.73) and a similar safety profile to docetaxel plus androgen-deprivation therapy (4 ITCs). Compared with androgen receptor axis–targeted doublet therapy, adverse events occurred with darolutamide triple therapy (6 ITCs).

Conclusion: Despite methodological variability and imprecision in results, ITCs consistently ranked darolutamide triple therapy higher for overall survival than other treatment options. Standardized methodology is needed for

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progression-free survival and safety end points to ensure robustness and interpretability of findings and to optimize treatment decision-making.

Introduction

The therapeutic landscape for men with metastatic hormone-sensitive prostate cancer (mHSPC) has evolved in recent years. First-line standard of care now consists of systemic therapy with docetaxel and androgen-deprivation therapy (ADT), doublet therapy that includes androgen receptor axis–targeted therapies (ARATs) (eg, abiraterone acetate plus prednisolone [AAP], enzalutamide, or apalutamide [APA]) with ADT), or triple therapy consisting of an ARAT agent, docetaxel, and ADT combination treatment. More recently, darolutamide triple therapy has been approved for the treatment of adult men with mHSPC by the US Food and Drug Administration,[1] the European Medicines Agency,[2] and multiple health authorities. Evidence from the Darolutamide in Addition to Standard Androgen Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer (ARASENS) phase 3 trial (ClinicalTrials.gov identifier NCT02799602) showed a significant improvement in overall survival (OS) with darolutamide triple therapy compared with docetaxel plus ADT.[3]

Indirect treatment comparisons (ITCs) allow treatments to be compared in the absence of or owing to insufficient evidence from head-to-head trials and are often conducted using network meta-analysis. The validity of ITCs depends on the studies on which they are based because of basic assumptions about homogeneity. Many ITCs have compared the efficacy and safety of treatment alternatives in mHSPC that have not been compared in head-to-head trials.[4] Fisher et al[4] highlighted variations in eligibility criteria, including data and statistical methodologies, and reported inadequacies across trials in the treatment of advanced prostate cancer. Given the variety and increasing number of publications in this field, we systematically identified and summarized the findings of published meta-analyses (including ITCs) that include findings for darolutamide triple therapy from the ARASENS trial.[3] We aimed to determine whether findings from these studies were consistent, and we discuss both limitations and possible improvements.

KEY POINTS

- The article reviews and compares published ITCs and meta-analyses in the treatment of patients with mHSPC that include darolutamide triple therapy, identifying inconsistencies and discussing limitations in the process.
- We assessed published evidence and described differences in trials as well as the need to standardize methodology for PFS and safety end points to ensure robustness and interpretability of findings.
- Indirect treatment comparisons showed a higher ranking with darolutamide triple therapy in terms of OS compared with other treatment options despite methodological variability and imprecise results.

ABBREVIATIONS

AAP, abiraterone acetate plus prednisone

ADT, androgen-deprivation therapy

AE, adverse event

APA, apalutamide

ARASENS, Darolutamide in Addition to Standard Androgen Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer

ARAT, androgen receptor axis–targeted therapy

CINeMA, Confidence in Network Meta-Analysis

ENZAMET, Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cance

GRADE, Grading of Recommendations Assessment, Development and Evaluation

HR, hazard ratio

HRQOL, health-related quality of life

IPD, individual patient data

ITC, indirect treatment comparison

mHSPC, metastatic hormone-sensitive prostate cancer

OS, overall survival

PFS, progression-free survival

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PS, performance score

STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

Methods

The study protocol was prospectively registered with PROSPERO (CRD42023429478).

SEARCH STRATEGY

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. A search was conducted of the MEDLINE, Embase, and Cochrane databases to identify ITCs and meta-analyses published through February 12, 2024 (Supplementary Table 1). Although no restrictions to search dates were applied, only ITCs and meta-analyses that included the ARASENS trial results were considered. This review therefore focuses on the latest trial results in mHSPC. Studies that met the eligibility criteria but that were published before 2022 or did not include the ARASENS trial findings were tagged and captured within the PRISMA flowchart (Figure 1).

STUDY SELECTION

Abstracts were screened in a double-blind manner against predefined inclusion and exclusion criteria, with discrepancies resolved by a third reviewer. Full texts were reviewed to confirm their eligibility in a single-blind manner, and uncertainties were resolved by a senior reviewer. Patients with mHSPC met inclusion criteria if they had received docetaxel or ARATs (eg, AAP, enzalutamide, APA, or darolutamide) in any

Table 1. Summary of Included Trials in Each Indirect Treatment Comparison

	Indirect treatment comparison												
Trial	Cao 2023	Chen 2023	Dou 2023	Jian 2022	Lee 2023	Mandel 2023	Menges 2022	Rajwa 2023	Riaz 2023	Sathianathen 2023	Wang 2023	Yanagisawa 2022	Zhou 2023
N	16 815	9488	11 058	2836	13 509	9702	9064	9183	11 043	10 065	12 298	7679	6708
ARASENS	■	■	■	■	■	■	■	■	■	■	■	■	■
ARCHES	■	■	■	■	■	■	■	■	■	■	■	■	■
CHART					■								
CHAARTED			■			■	■	■	■	■	■	■	■
ENZAMET			■	■	■	■	■	■	■	■	■	■	■
HORRAD											■		
GETUG-AFU15			■			■	■	■	■	■	■	■	■
LATITUDE	■		■	■	■	■	■	■	■	■	■	■	■
NCT02058706[a]					■		■						
PEACE1			■	■	■	■		■	■	■	■	■	■
STAMPEDE (Arms)			C+G		C+G	C+G	C+G	B C,G+E	C+G	C+G	C G+H	B C,G+E	C+G
SWOG1216									■				
TITAN			■	■	■	■	■	■	■	■	■	■	■
Others					[a]		[b]						

Shaded boxes indicate that the trial was included in the indirect treatment comparison.
[a] "Other" included trials as reported in Lee et al (2023): Akaza, Usami, Tyrrell, Schellhammer, Eisenberger, Alghandour (MANSMED), Reijke, Agarwal, and Palmbos.[12]
[b] Vaishampayan et al (2021).[42]

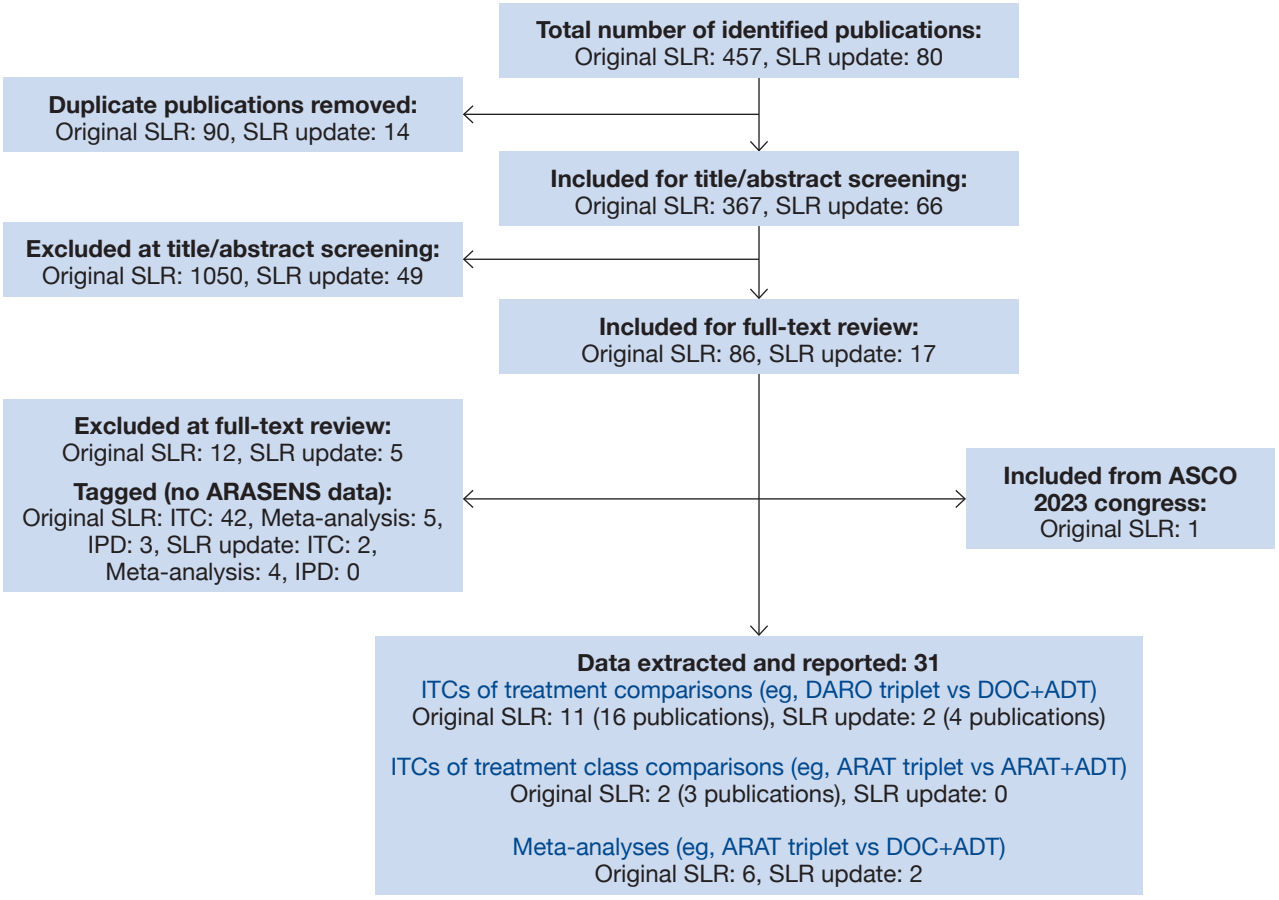

Figure 1. PRISMA flowchart

Abbreviations: ADT, androgen-deprivation therapy; ARAT, androgen receptor axis–targeted therapy; ASCO, American Society of Clinical Oncology; DARO, darolutamide; DOC, docetaxel; ITC, indirect treatment comparison; IPD, individual patient data; SLR, systematic literature review.

combination with ADT, radiation therapy, or standard of care for low-volume or developmental agents. Outcomes included OS, progression-free survival (PFS), adverse events (AEs), health-related quality of life (HRQOL), and other secondary end points. Eligible study designs included full publications and congress abstracts. Studies published in languages other than English were excluded.

To present the most up-to-date evidence, this review summarizes the meta-analyses (and ITCs), including the ARASENS trial results; publications not including the ARASENS trial are listed in Supplementary Table 2.

DATA EXTRACTION

Data were extracted into prespecified data-extraction tables by 1 reviewer and checked for quality by a second reviewer. Data were extracted based on methodology, outcomes (efficacy and AEs, including subgroup or secondary analyses), and treatment ranking (for ITCs only). Efficacy outcomes were extracted as hazard ratios (HRs) and safety outcomes as odds ratios, risk ratios, or HRs, with corresponding 95% CIs or credible intervals as reported in the publication.

Assessments from each ITC evaluating risk of bias (eg, Cochrane Risk of Bias 2) and rating the

confidence and certainty of the results of a network meta-analysis were extracted, including the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[5] and Confidence in Network Meta-Analysis (CINeMA)[6] approaches. Risk of bias and quality assessments were also extracted for each meta-analysis (without ITC).

DATA ANALYSIS

Data were summarized from meta-analyses (and ITCs) in tables and schematics, with a narrative summary. Credible intervals and CIs were assumed to be the same for ease of interpretation, and it was acknowledged that some studies used bayesian analysis, whereas others used frequentist statistical frameworks. This review of meta-analyses (and ITCs) compares included trials, treatment regimens, statistical methods, network inconsistency and heterogeneity tests, adjustment for trial-level factors, and estimated effect sizes and precision, as reported by each publication. A benefit was defined as an HR less than 1, and imprecision was described separately (where the 95% CI crossed the line of no effect).

Results

INCLUDED STUDY POPULATION AND CHARACTERISTICS

Thirty-one articles published through February 12, 2024, were included, as shown in the PRISMA flowchart (Figure 1). The identified publications included 13 ITCs (20 publications; Supplementary Table 3) of specific treatments (eg, darolutamide triple therapy vs docetaxel + ADT), 2 ITCs (3 publications) of treatment classes (eg, pooled ARAT triple therapy vs ARAT plus ADT or docetaxel plus ADT), and 8 meta-analyses (direct pairwise comparisons) of treatments (eg, ARAT triple therapy vs docetaxel plus ADT).

METHODOLOGY OF INCLUDED ITCS AND META-ANALYSES

Among the ITCs, there was variation in the number of trials included in each analysis (range, 2-17) (Table 1) and in statistical methods used (frequentist or bayesian network meta-analyses, random or fixed effects). Few ITCs reported the justification of the analysis model, with only Mandel et al[7] and the living network meta-analysis from Riaz et al[8] providing a rationale. Two ITCs described consideration of treatment effect modifiers,[9,10] and few detailed tests were used to assess network inconsistency.[10,11] Menges et al[10] reported having assessed inconsistency according to epidemiologic criteria and the presence of potential effect modifiers; however, no further details are given. Wang et al[11] described the assessment of inconsistency via a node-splitting model ($P < .05$ was considered statistically significant). A minority of ITCs performed quality and certainty assessments for network outcomes (eg, GRADE or CINeMA).[8-11] There were also differences across the identified meta-analyses, with variation in the number of trials per analysis (range, 5-10) and differences in the analytical models used. No ITCs considered variation in HRs over time using, for example, fractional polynomial models.

The majority of studies focused on the analysis of OS, with PFS (including the reconstituted or proxy end point ARASENS trial data) reported by 3 ITCs[12-14] and 3 meta-analyses.[15-17] Adverse events were reported in 8 ITCs and 4 meta-analyses. No ITCs or meta-analyses reported HRQOL outcomes.

TREATMENT VS TREATMENT COMPARISON

Indirect treatment comparisons consistently showed a significant benefit in OS with darolutamide triple therapy compared with ADT (4 ITCs) and docetaxel plus ADT (8 ITCs in line with ARASENS trial results; Supplementary Table 4). Darolutamide triple therapy demonstrated a benefit in OS compared with ARAT doublet therapies (AAP plus ADT, enzalutamide plus ADT, or APA plus ADT), but the confidence in this effect estimate is uncertain owing to imprecision (wide CIs) (Figure 2A-2C). Three ITCs reported the comparison of darolutamide triple therapy vs AAP triple therapy. The ITCs reported an HR that indicated a trend toward reduced risk of death with darolutamide triple therapy; however, the CI includes 1 (HR, 0.91

[95% CI, 0.68-1.22] [2 ITCs] and HR, 0.91 [95% CI, 0.61-1.34] [1 ITC]) with low certainty (GRADE) or very low confidence (CINeMA) (Figure 2D). Darolutamide triple therapy was consistently ranked highest for OS in 11 of 12 ITCs that reported ranking analyses, above ARAT doublet and triple therapies, except for Lee et al.[12] Sathianathen et al[14] included darolutamide or AAP triple therapy as a pooled treatment in their ranking analysis, which was ranked highest for OS. See Table 2 for a summary of the ranking of darolutamide triple therapy in each ITC.

One ITC included time to castration-resistant prostate cancer within their PFS analysis network, as evaluated in the ARASENS trial. The ITC reported darolutamide triple therapy compared with docetaxel plus ADT for this end point (HR, 0.47 [95% CI, 0.20-1.10]).[14] Other ITCs included PFS but without ARASENS data owing to inconsistency in end point definitions among studies.

Of the ITCs that included ARASENS trial data, 8 studies reported AE analyses. The risk of grade 3 or higher AEs was greater with darolutamide triple therapy than with ARAT doublet therapies across 6 ITCs (GRADE, low to moderate certainty of evidence; CINeMA, very low confidence; Supplementary Table 5). There was a similar risk of grade 3 or higher AEs with darolutamide triple therapy and with docetaxel plus ADT across 4 ITCs, but the confidence in this result was rated as having low to moderate certainty with GRADE and very low confidence with CINeMA. Indirect treatment comparisons of AEs across triple therapies showed a lower risk of grade 3 or higher AEs for darolutamide triple therapy than for AAP triple therapy across 2 ITCs (GRADE, low certainty; CINeMA, very low confidence) (Table 3).[8,11] Four ITCs ranked darolutamide triple therapy as the third to seventh treatment, and it was consistently ranked higher than AAP plus docetaxel plus ADT with respect to the incidence of grade 3 or higher AEs.[8,11,18,19] Androgen-deprivation therapy alone was consistently ranked first, showing a favorable safety profile.[8,11,18,19]

TREATMENT CLASS VS TREATMENT CLASS COMPARISON IN AN ITC

Two ITCs across 3 publications reported OS for pooled ARAT triple therapies (including data from the ARASENS trial) compared with pooled ARAT doublet therapies. Naqvi et al[20] showed increased OS with ARAT plus docetaxel plus ADT compared with docetaxel plus ADT (HR, 0.74 [95% CI, 0.66-0.84]).[20] Androgen receptor axis–targeted therapy plus ADT in 2 ITCs[21,22] reported an HR less than 1.0 for OS (Naqvi et al, HR, 0.97 [95% CI, 0.78-1.20]; Roy et al, HR, 0.89 [95% CI, 0.68-1.16]), but wide CIs indicated no evidence of a difference.[21,22] Progression-free survival and AE outcomes were not reported for these 2 pooled analyses (ARASENS not included in networks).

TREATMENT COMPARISONS (DIRECT PAIRWISE META-ANALYSIS ONLY)

Eight meta-analyses were identified, 4 of which reported OS for ARAT plus docetaxel plus ADT vs docetaxel plus ADT. Two of these meta-analyses reported OS for ARAT plus ADT with or without docetaxel vs ADT with or without docetaxel (Supplementary Table 6). The meta-analyses showed a consistent benefit in OS with ARAT plus docetaxel plus ADT compared with docetaxel plus ADT. Triple therapy compared with ADT alone was not reported by any of the included meta-analyses, with some noting that this comparison was not part of their objective and others noting that ADT alone does not represent current standard of care.[15,23] Progression-free survival was reported in 3 meta-analyses, with a consistent survival benefit seen with ARAT plus docetaxel plus ADT vs docetaxel plus ADT (HR, 0.41-0.43) (Supplementary Table 6).[15-17] Adverse events were reported in 4 meta-analyses of ARAT triple therapies, of which 3 reported grade 3 or higher AEs and 1 reported cardiovascular events, all favoring docetaxel plus ADT (Supplementary Table 6).[16,17,24,25]

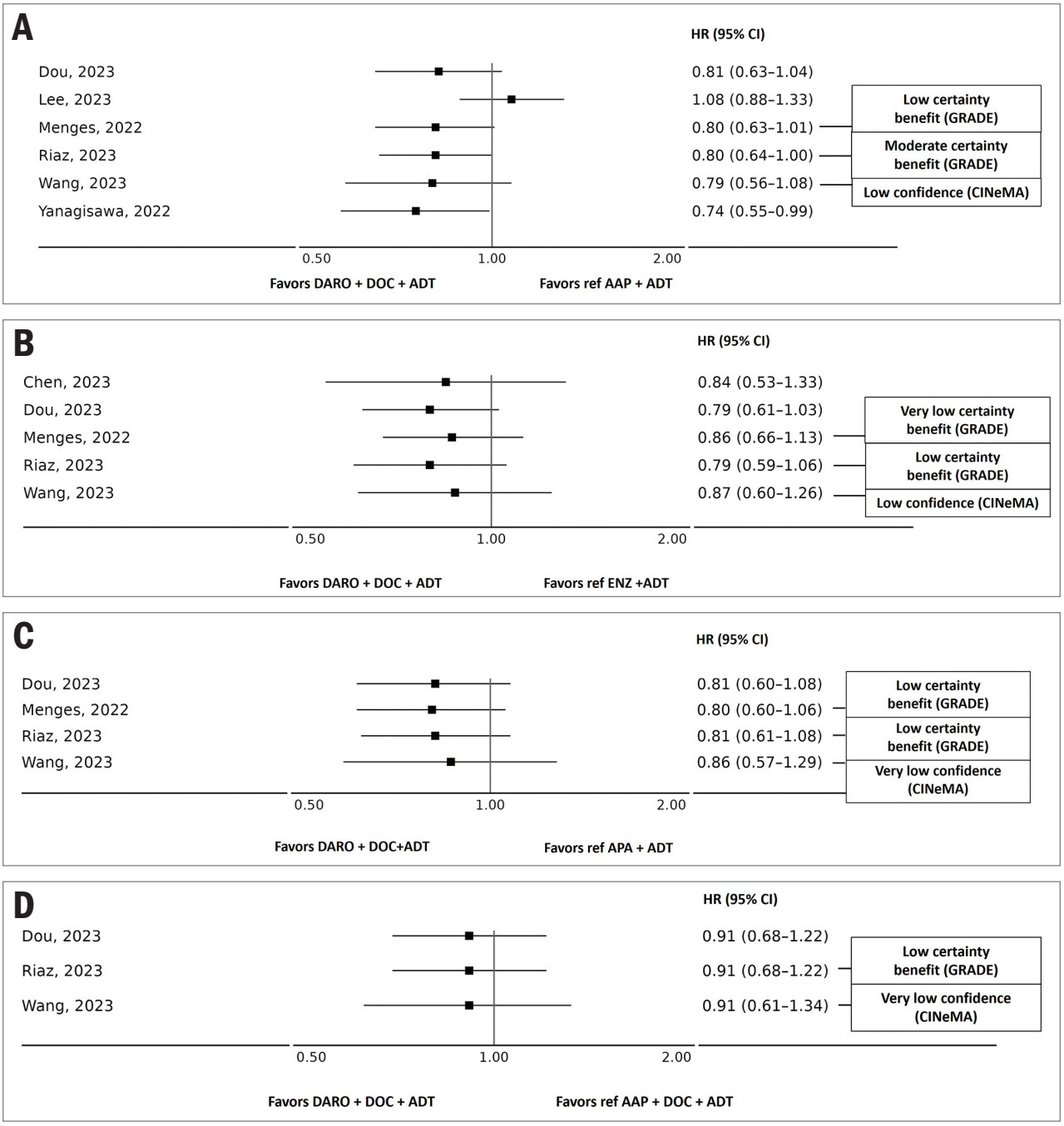

Figure 2. Overall survival rates for darolutamide triple therapy in indirect treatment comparisons are shown for (**A**) darolutamide triple therapy vs AAP and ADT; (**B**) darolutamide triple therapy vs enzalutamide and ADT; (**C**) darolutamide triple therapy vs APA and ADT; and (**D**) darolutamide triple therapy vs AAP triple therapy.

Abbreviations: AAP, abiraterone acetate and prednisone; ADT, androgen-deprivation therapy; APA, apalutamide; CINeMA, Confidence in Network Meta-Analysis; DARO, darolutamide; DOC, docetaxel; ENZ, enzalutamide; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; ref, reference.

Table 2. Ranking of Darolutamide Triple Therapy in Indirect Treatment Comparisons: Overall Survival

Indirect treatment comparison	Intervention	Measure	*P* value	Rank	No. of treatments	No. of trials
Frequentist network meta-analysis						
Sathianathen 2023	(Darolutamide or AAP) + docetaxel + ADT	Surface under the cumulative ranking curve	.96	1	7	9
Menges 2022	Darolutamide + docetaxel + ADT	*P* value	.95	1	7	9
Mandel 2023; Hoeh 2023[a]	Darolutamide + docetaxel + ADT	*P* value	.93 Low volume = .76 High volume = .92	1	5	9
Dou 2023	Darolutamide + docetaxel + ADT	Surface under the cumulative ranking curve	.90	1	7	9
Jian 2022	Darolutamide + docetaxel + ADT	Surface under the cumulative ranking curve	.81	1	6	5
Chen 2023	Darolutamide + docetaxel + ADT	Rank probability	.68	1	3	2
Lee 2023	Darolutamide + docetaxel + ADT	Surface under the cumulative ranking curve	.63	5	12	18
Wang 2023	Darolutamide + docetaxel + ADT	Rank probability	.49 Visceral metastasis = .59	1	9	10
Bayesian network meta-analysis						
Riaz 2023	Darolutamide + docetaxel + ADT	*P* value	.95	1	6	10
Zhou 2023	Darolutamide + docetaxel + ADT	Surface under the cumulative ranking curve	High volume = .91	1	8	11
Rajwa 2023	Darolutamide + docetaxel + ADT	Surface under the cumulative ranking curve	Older = .89 Younger = .90	1	6	8
Yanagisawa 2022	Darolutamide + docetaxel + ADT	Surface under the cumulative ranking curve	.88 ECOG-ACRIN PS 0 = .73 ECOG-ACRIN PS ≥1 = .94 Visceral metastasis = .90 No visceral metastasis = .98	1	5	9

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen-deprivation therapy; PS, performance status.

[a] Hoeh et al (2023) reports subgroup data, by disease volume.

POPULATION SUBGROUPS

Several ITCs and meta-analyses included subgroup analyses or secondary stratified analyses in specific populations. A summary of subgroup analyses reported in ITCs for OS is given in Supplementary Figure 1, including by disease volume (low or high), age (older [≥65 or ≥70 years] or younger patients [≤65 or ≤70 years]), presence of visceral metastasis, ECOG-ACRIN performance status (PS) (0 or ≥1), Gleason score (≥8 or <8), and recurrent (metachronous) or de novo (synchronous) disease. Notably, Hoeh et al[26] reported a benefit in OS with ARAT triple therapy compared with ARAT plus ADT in patients with high-volume disease (Supplementary Figure 1A), with darolutamide triple therapy ranking first (*P* = .92), followed by AAP triple therapy (*P* = .85). The OS estimates for patients with low-volume disease are imprecise, and there is therefore uncertainty around these results.[26,27] Many subgroup analyses showed imprecise results, but

Table 3. Grade 3 or Higher AEs With Darolutamide Triple Therapy Compared With AAP Triple Therapy in Indirect Treatment Comparisons

Indirect treatment comparison	Intervention	Comparison	Effect measure	*P* value	95% CI
Riaz 2023	Darolutamide + docetaxel + ADT	AAP + docetaxel + ADT	Risk ratio	.86	0.74-1.00
Wang 2023	Darolutamide + docetaxel + ADT	AAP + docetaxel + ADT	Odds ratio	.73	0.31-1.73

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen-deprivation therapy; AE, adverse event.

there is some evidence to suggest larger benefits in OS with darolutamide triple therapy in younger patients than in older patients, and in patients with an ECOG-ACRIN PS of at least 1 than in patients with a PS of 0 (Supplementary Figure 1B and 1D). In addition, darolutamide triple therapy vs both ADT and docetaxel plus ADT demonstrated a significant benefit in OS in patients with de novo disease than in patients with recurrent disease (Supplementary Figure 1F).[8,10,11,28] Additional subgroup analyses in publications reporting meta-analyses (without ITCs) are shown in Supplementary Table 6.

Zhou et al[13] reported the time to castration-resistant prostate cancer end point as evaluated in ARASENS, within their PFS analysis network in patients with high-volume disease (HR, 0.41 [95% CI, 0.34-0.49]). No subgroup analyses were reported for AEs.

Discussion

We systematically identified ITCs and meta-analyses of darolutamide therapies in mHSPC that included the ARASENS trial, identifying 15 ITCs and 8 meta-analyses published between October 2022 and February 2024.

Indirect treatment comparisons consistently ranked darolutamide triple therapy highest among studied treatment options, including AAP doublet and triple therapies, in terms of OS benefit but with uncertainty, as indicated by wide CIs. Evidence for PFS was sparse; it was not analyzed in most ITCs because of differences in PFS definitions across trials. We note that the ARASENS trial measured castration-resistant prostate cancer–free survival, whereas other trials included clinical PFS or radiographic PFS, which rendered a comparison across these trials and end points inappropriate, as discussed in several meta-analytical reports. In terms of safety, ITCs of darolutamide triple therapy reported a lower rate of grade 3 or higher AEs compared with AAP triple therapy and reported a similar safety profile to docetaxel plus ADT. Compared with ARAT doublet therapy, the risk of grade 3 or higher AEs was higher (although imprecise) with darolutamide triple therapy. This risk is reflected in the ranking analysis, which ranked darolutamide triple therapy as the third to seventh treatment across ITCs (consistently higher than AAP triple therapy).

Two ITCs compared treatment classes and included ARASENS data. They both showed longer OS with ARAT plus docetaxel plus ADT (triple therapy) than with docetaxel plus ADT and had an OS benefit compared with ARAT plus ADT. Neither ITC reported PFS or AE outcomes that included ARASENS in its networks.

In meta-analyses (without ITCs), a consistent benefit in OS was demonstrated with ARAT triple therapy compared with docetaxel plus ADT (6 studies). The benefit in OS reported with triple therapies across ITCs in patients with mHSPC is consistent with clinical guidelines, including the National Comprehensive Cancer Network (v3.2024) (for patients with high-volume or metachronous metastases and for patients with low-volume or high-volume synchronous metastases)[29] and the European Association of Urology,[30] which recommend darolutamide or AAP triple therapy.

Subgroup analysis showed a benefit in OS for patients with high-volume disease with ARAT triple therapy compared with doublet therapy. Results for low-volume disease should be interpreted with

caution given the lower numbers of patients in the analysis and the low event rates; triple therapy may still be a valid treatment option given this uncertainty. Secondary analyses suggested that being younger (compared with being older), having an ECOG-ACRIN PS of at least 1 (compared with having a PS of 0), and having de novo disease (compared with having recurrent disease) are prognostic of improved survival, although several analyses included imprecise effect estimates.

Although the findings of the meta-analyses (including ITCs) were generally consistent, there were methodological differences. One such difference was the number of trials included in each ITC, in part because of the objective of each study. For example, Chen et al[31] focused on newer-generation ARATs and so included only second-generation ARATs (enzalutamide, APA, darolutamide) or placebo trials, whereas most other studies captured the efficacy and safety of all included trials for all available treatment options.

Lee et al[32] reported the only ITC that showed a lower ranking of triple therapies over doublet therapies for OS. They used the intention-to-treat analysis for ARASENS unlike the other included ITCs. In addition, rezvilutamide was included from the CHART trial, which included a subpopulation of Asian men with de novo, high-volume mHSPC.[32] Rezvilutamide has limited availability in the United States and the European Union, which may explain why CHART was not included in other ITCs. The ITC reported by Zhou et al[13] was the only other ITC that included the CHART trial. They reported that in patients with high-volume disease, darolutamide triple therapy ranked the highest and as the best-performing regimen in terms of OS, but they did not report ITCs of triple therapies with doublet therapies.[13]

Analytic methods varied across included studies, which complicated comparisons. Most identified ITCs did not assess inconsistencies and assumed that there were few or no treatment effect modifiers (or population heterogeneity) without formally checking or documenting these considerations. Only 1 ITC described the assessment of inconsistency and used a node-splitting model with closed-loop comparisons all suggesting $P > .111$; however, it is uncertain whether the consistency assumptions made were justified across other ITCs because there is limited information reported. Another element of uncertainty is the use of HRs that are constant over time (proportional hazard assumption) despite trials having different follow-up durations and treatments potentially having different speeds of action. In addition, the choice of the analysis model for safety end points varied; ITCs calculated either odds ratios or risk ratios, which gave wider or narrower CIs and therefore different interpretations of results across conclusions. Most of the included ITCs in this review, with the exception of the ITC reported by Menges et al,[10] did not account for the unique structure of the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) study (ClinicalTrials.gov identifier NCT00268476), which was a multiarm, multistage, adaptive trial.[33] Vale et al[33] were the first to make this adjustment, which was later incorporated into individual patient data (IPD) analysis.[34] In addition, most ITCs did not explore subgroup or sensitivity analyses other than for disease volume. More recent publications, however, are providing more of these types of analyses as updates or associated studies (eg, subanalyses according to ECOG-ACRIN PS and in patients with visceral metastasis).[35,36] There was also an absence of population-adjusted ITCs,[37] such as matching-adjusted indirect comparisons, multilevel network meta-regressions, and network meta-interpolations.[38-40] In addition, there were differences in the trials themselves; for example, 2 trials had an open-label study design (Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer [ENZAMET; ClinicalTrials.gov identifier NCT02446405] and A Phase III Study for Patients With Metastatic Hormone-naïve Prostate Cancer [PEACE1; ClinicalTrials.gov identifier NCT01957436]).

There was a lack of HRQOL outcomes identified from ITCs of darolutamide, in part owing to ARASENS using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index 17-item version instrument, which was not used across other trials, meaning that no comparisons were possible. Health-related

QOL outcomes were assessed in a minority of ITCs, despite being measured across trials. Menges et al[8] and Riaz et al[10] reported that 8 and 7 of 10 trials reported data on HRQOL, respectively. Menges et al[8] described a short-term (3-month to 6-month) decrease in HRQOL with ADT plus docetaxel and reported a potential benefit of ADT plus AAP in HRQOL at up to 24 months of follow-up compared with ADT alone. Riaz et al[10] noted that evidence is still emerging. If consistent patient-reported outcome instruments are used in future trials, comparisons of HRQOL will be possible.

This review's findings are consistent with those of Fisher et al,[4] who also examined results and methods across published ITCs in mHSPC and described variation in eligibility criteria and statistical methodology between identified ITCs. Despite this variation, the findings of Fisher et al[4] are in agreement with the similarity in results reported across ITCs in this review. Our review has broader inclusion criteria for analysis type (including meta-analyses as well as ITCs), has a unique objective in comparing analyses of darolutamide in the published literature, and is more up-to-date owing to our later search cutoff date.

Company-sponsored studies are rarely included in IPD network meta-analyses, and we note that no IPD analyses that included ARASENS data were identified in the literature. An IPD of the GETUG-AFU15, Androgen Ablation Therapy With or Without Chemotherapy in Treating Patients With Metastatic Prostate Cancer (CHAARTED; ClinicalTrials.gov identifier NCT00309985), and STAMPEDE trials has been published, describing the benefit in OS of adding docetaxel to ADT, including in treatment of patients with high-volume disease.[34] We also note the publication of the Darolutamide in Addition to ADT Versus ADT in Metastatic Hormone-sensitive Prostate Cancer (ARANOTE; ClinicalTrials.gov identifier NCT04736199) phase 3 randomized controlled trial, which reports that darolutamide plus ADT significantly improved radiographic PFS, reducing the risk of progression or death by 46% compared with placebo plus ADT, with consistent benefits across subgroups, including high-volume and low-volume disease.[41] Adverse events were similar between the darolutamide and placebo groups. This review followed a robust process to minimize the limitations of systematic reviews, with an extensive search strategy, and a protocol registered a priori in PROSPERO. We acknowledge, however, that a limitation of this review is the requirement for analyses to include ARASENS.

Conclusions

Despite methodologic variability and imprecision in results, ITCs consistently ranked darolutamide triple therapy highly for OS over other treatment options. Consistent results from ITCs of greater OS with darolutamide triple therapy compared with docetaxel plus ADT were in line with evidence from ARASENS.[3] There remains a need to standardize ITC methodology for PFS and safety end points to ensure robustness and interpretability of findings and to optimize treatment decision-making.

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