A systematic literature review of comparative efficacy measures in randomized controlled trials of Darolutamide treatment in metastatic hormone-sensitive prostate cancer

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Background and Objectives

- Prostate cancer incidence in China has been showing an upward trend over the years, with an average annual growth rate of approximately 2.75%[1,2]. The mortality-to-incidence ratio (MIR) is high[3], indicating relatively lower survival rates. Among newly diagnosed prostate cancer patients in China, 54% have already experienced distant metastasis, indicating a more severe situation in terms of prevention and control.
- Metastatic hormone-sensitive prostate cancer (mHSPC) is a pivotal stage in the progression of prostate cancer, and progression to metastatic castration-resistant prostate cancer (mCRPC) leads to a 40% increase in annual all-cause mortality[4]. Additionally, patients experience a 2.4-fold increase in disease-related economic burden[5], causing significant health threats and imposing a heavy disease burden on patients.
- mHSPC presents various unmet clinical treatment needs, including low patient survival rates, short time to progression to CRPC, and poor quality of life for patients.
- Darolutamide is an orally administered androgen receptor inhibitor (ARi) that represents an innovative drug with significant therapeutic advantages. The ARASENS trial has demonstrated the various benefits of Darolutamide in patients with mHSPC, including prolonged survival, delayed disease progression, and improved quality of life.
- By conducting a systematic literature review of Darolutamide, its clinical value in treating mHSPC cancer has been evaluated.

Methods

- A systematic literature review (SLR) was conducted by searching Embase, Medline and Cochrane from database inception to June 2, 2023. Following the appropriate search strategy, an initial search yielded 57 relevant literature reviews and systematic reviews (Figure 1).

-- Using the corresponding search strategy, we initially retrieved 57 relevant systematic reviews and meta-analyses.

-- After removing duplicate publications and screening titles and abstracts for ineligible studies, we finally included 14 studies (12 NMA studies and 2 meta-analyses) in our analysis.

- Additionally, duplicate publications were removed, and the titles and abstracts of the remaining literature were reviewed to exclude studies that did not meet the selection criteria. In the end, a total of 14 studies were included, comprising 12 network meta-analyses (NMA) and 2 meta-analyses (Table 1).

Figure 1. Flow diagram

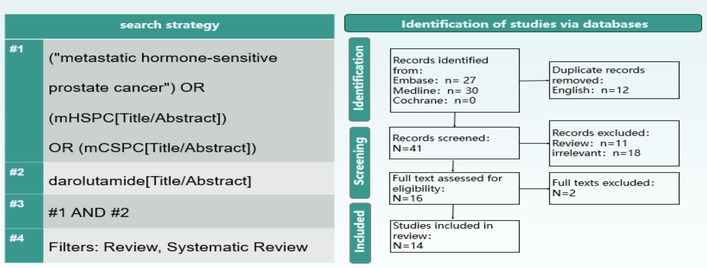

Table 1. Description of included studies

Sources	Authors	Types	Search time	Trails	Subgroups
8	Jian TT, et al.	NMA	~2022.11	12 RCTs	HVD, LVD；the risk of any AEs or grade ≥3 AEs；Gleason score
9	Chen XY, et al.	NMA	2000.1~2022.12	7 RCTs	/
10	Wang L, et al.	NMA	~2022.7	10 RCTs	HVD, LVD; visceral metastases
11	Dou MY, et al.	NMA	~2022.7	9 RCTs	ECOG；Gleason
12	Riaz IB, et al.	NMA	~2022.7	10 RCTs	HVD, LVD
13	Hoeh B, et al.	NMA	~2023	10 RCTs	HVD, LVD
14	Mandel P, et al.	NMA	~2022.4	10 RCTs	HVD, LVD
15	Yanagisawa T, et al.	NMA	~2022.4	11 RCTs	HVD, LVD
16	Soumyajit R, et al.	NMA	~2022.3	11 RCTs	/
17	Menges D, et al.	NMA	~2022.3	10 RCTs	HVD, LVD
18	Jian TT, et al.	NMA	~2022.4	5 RCTs	/
19	Niranjan JS	NMA	~2022.4	10 RCTs	HVD, LVD; visceral metastases
20	Chiara C et al.	Meta	~2022.2	5 RCTs	/
21	Maiorano BA et al.	Meta	~2022.4	5 RCTs	/

Results

- Compared to placebo in combination with docetaxel and androgen deprivation therapy (ADT), Darolutamide in combination with docetaxel and ADT further reduces the risk of death by 32%[6, 7], and all relevant NMAs indicate that the Darolutamide regimen provides the greatest survival benefit[10-11, 15 17, 19] (Figure 2, 3).
- Compared to ARAT in combination with ADT, the Darolutamide regimen in combination with docetaxel and ADT also demonstrates the highest OS benefit. In high volume disease （HVD） populations, only the Darolutamide regimen shows significant benefit[13,14] (Figure 4, 5).
- Compared to placebo in combination with docetaxel and ADT, Darolutamide in combination with docetaxel and ADT significantly reduces the risk of pain progression, delays time to initiation of subsequent systemic antineoplastic therapy and other clinical endpoints[6, 22] (Table 2).
- Darolutamide has minimal drug interactions with commonly co-administered medications, making it a reassuring choice for long-term use[6, 23].

Figure 2. All relevant NMAs demonstrate the survival benefit of the Darolutamide regimen

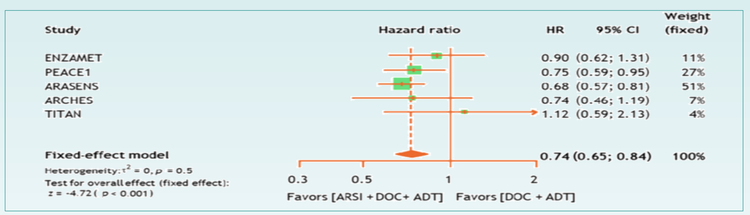

Figure 3. Summary of Overall Survival Benefit of Darolutamide vs. Apalutamide in the Treatment of mHSPC

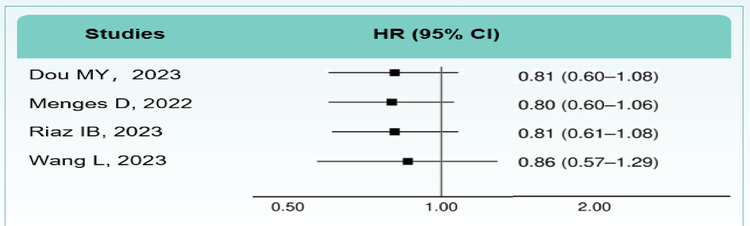

Figure 4. OS benefit results of Darolutamide triple therapy compared to second-generation ARis in combination with ADT in overall population

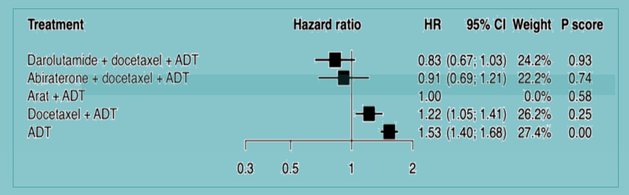

Figure 5. OS benefit results of Darolutamide triple therapy compared to ARAT in combination with ADT in HVD population

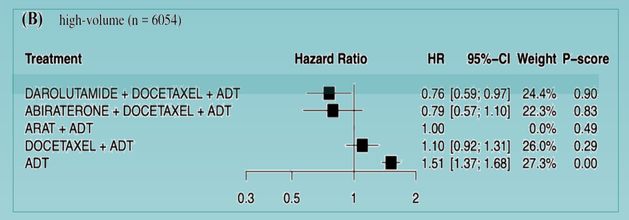

Table 2. Description of other clinical endpoint study results for Darolutamide

Second endpoints	HR(95%CI)	Risk reduction
Time to pain progression[6]	0.79 (0.66–0.95), $p < 0.05$	21%
Time to initiation of subsequent systemic antineoplastic therapy[6]	0.39 (0.33–0.46), $p < 0.05$	61%
Symptomatic skeletal event–free survival (SSE-FS) [6]	0.61 (0.52–0.72), $p < 0.05$	39%
Time to a first symptomatic skeletal event (SSE) [6]	0.71 (0.54–0.94), $p < 0.05$	29%
Time to PSA progression [22]	0.26 (0.21-0.31), $p < 0.05$	74%

Conclusions

Compared to similar medications, Darolutamide improves patient prognosis in terms of prolonging overall survival, delaying progression to CRPC, delaying time to pain progression, and ensuring safety, thereby enhancing patients' quality of life. Darolutamide significantly improves clinical benefits and exhibits overall good safety, offering a clinically advantageous treatment option with multiple benefits for Chinese patients with prostate cancer at different disease stages.

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