

# Overall survival with second-generation androgen-receptor signaling inhibitors in patients with metastatic castration resistant prostate cancer

## An Umbrella Review

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### Introduction

- Prostate cancer is a frequently diagnosed malignancy among men and a leading cause of cancer-related mortality worldwide.<sup>1</sup> Despite initial control with hormone therapy, prostate cancer often progresses to mCRPC, a stage linked with poor outcomes and prognosis.<sup>2,3</sup>
- mCRPC is an aggressive disease, with five-year survival under 30% and a significant impact on health-related quality of life (HRQoL).<sup>4,5</sup>
- Second-generation androgen-receptor inhibitors (SGARI) have been approved in mCRPC patients and were assessed in multiple systematic reviews (SLRs) but often remain inconclusive due to inconsistent methodology and quality.

### Objectives

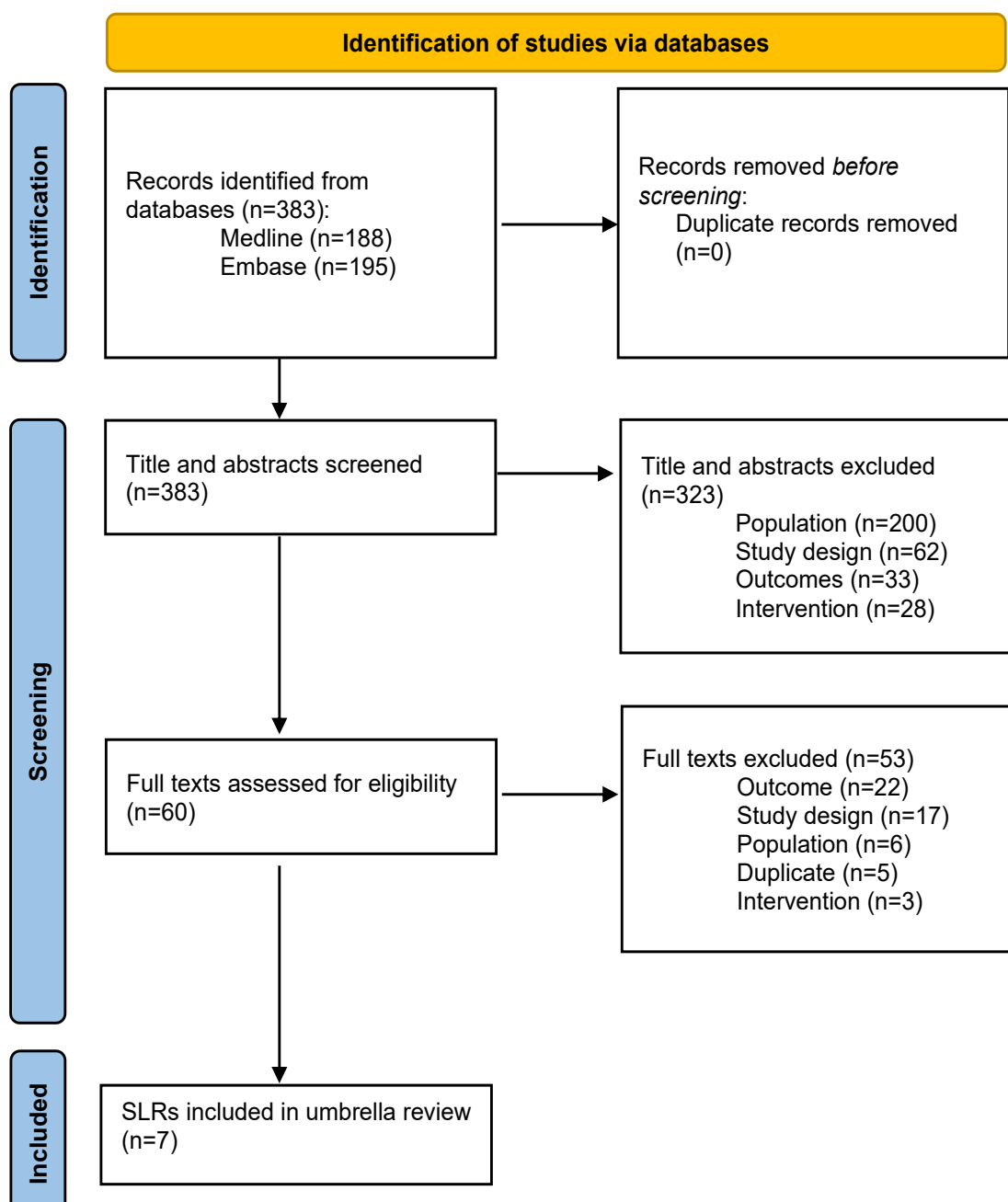
This umbrella review aimed to synthesize evidence on the overall survival (OS), radiographic progression free survival (rPFS) and HRQoL in mCRPC patients receiving second-generation androgen-receptor inhibitors (SGARI) in combination or alone.

### Methods

- We performed a literature search using Ovid MEDLINE, Ovid EMBASE and Cochrane Database for Systematic reviews (CDSR) for studies published from inception until 31 May 2025.
- This umbrella review included systematic literature reviews (SLRs) of randomized controlled trials (RCTs) examining OS, rPFS, and HRQoL in patients with mCRPC receiving any line of SGARI.
- Narrative descriptions of the included SLRs were synthesized for outcomes of interest. Risk of bias of included SLRs was conducted using AMSTAR-2 tool.
- The protocol for this review is registered on PROSPERO (CRD42024554056).

### Results

Figure 1. PRISMA diagram



### Results (Contd.)

Table 1: Characteristics of included systematic reviews

Author, year	Database search dates	N studies	Population	Intervention	Comparator	Outcomes reported	RoB assessment tool	Includes a meta-analysis? If yes, type of analysis method
Chen 2023 <sup>7</sup>	January 2000 - December 2022	2	mCRPC patients treated with SGARI	Enzalutamide plus ADT	Placebo plus ADT	OS and rPFS	Cochrane RoB	Yes, REM
Luo 2023 <sup>6</sup>	Up to April 27, 2023	2	mCRPC patients receiving combination therapy	Olaparib+abiraterone	Abiraterone+placebo	OS and rPFS	Cochrane RoB	Yes, REM
Nahar 2025 <sup>11</sup>	Up to July 2023	6	mCRPC patients aged 67-70 years	AKT inhibitor + ARSIs	Placebo	OS and rPFS	Cochrane RoB	No
Tan 2020 <sup>9</sup>	Up to September 2019	4	High-risk prostate cancer	AAP alone or AAP + ADT	Placebo + prednisone or ADT alone	OS and rPFS	JADAD-5-item	Yes, REM and FEM
Ternov 2021 <sup>12</sup>	Up to June 2020	8 in SLR; 4 in MA	mCRPC patients receiving 1L enzalutamide or AAP	AAP	Enzalutamide	HRQoL	Cochrane RoB	Yes, REM and FEM
Wei 2021 <sup>8</sup>	Up to December 2020	4	mCRPC patients	Enzalutamide, AAP	Placebo or placebo + prednisone	OS and rPFS	Cochrane RoB	Yes, FEM
Zhou 2014 <sup>10</sup>	Up to July 2013	10 in SLR; 2 in MA	mCRPC patients	Abiraterone + prednisone	Placebo plus prednisone	OS and rPFS	Cochrane RoB	Yes, REM

Abbreviations- AAP, abiraterone acetate prednisone; ADT, androgen deprivation therapy; AKT, AKT kinase; FEM, fixed effect model; MA, meta-analysis; mCRPC, metastatic castration resistant prostate cancer; N, number of studies; OS, overall survival; REM, random effects model; rPFS, radiographic progression-free survival; SGARI, second-generation androgen receptor inhibitors

#### Overall

- We included seven SLRs with MAs in this umbrella review (Table 1).
- All included SLRs answered the primary research objective of OS, except one SLR by Ternov 2021, which specifically provided data on HRQoL outcomes with SGARI therapies.

Table 2: OS and rPFS in included meta-analysis of systematic reviews

Study details					Overall survival	Radiographic PFS	Notes
Author, year	Intervention	Comparator	N studies	MA method	HR (95% CI); p-value I <sup>2</sup>	HR (95% CI); p-value I <sup>2</sup>	
Chen 2023 <sup>7</sup>	Enzalutamide	Placebo + ADT	2	REM	0.67 (0.59-0.76) I <sup>2</sup> =0%	0.28 (0.13-0.57) I <sup>2</sup> =96.8%	Enzalutamide improved OS and rPFS was beneficial when compared with placebo
Luo 2023 <sup>6</sup>	Olaparib + abiraterone	Abiraterone + placebo	2	REM	0.87 (0.7-1.09); 0.237 I <sup>2</sup> =0%	0.66 (0.55-0.79); <0.01 I <sup>2</sup> =0%	OS indicated no significant differences between the groups; rPFS showed improvement with no significant heterogeneity
Tan 2020 <sup>9</sup>	AAP or AAP + ADT	Placebo + prednisone or ADT alone	3	FEM for OS; REM for rPFS	0.69 (0.61-0.78); <0.0001 I <sup>2</sup> =0%	0.60 (0.48-0.75); <0.0001 I <sup>2</sup> =79%	AAP showed significant improvement of OS and rPFS in mCRPC patients; significant heterogeneity between the trials was noted for rPFS
Wei 2021 <sup>8</sup>	AAP	Placebo + prednisone	2	FEM	0.69 (0.6-0.8); <0.0001 I <sup>2</sup> =4%	0.64 (0.57-0.71); <0.0001 I <sup>2</sup> =29%	AAP and enzalutamide had significant advantages over placebo for OS and rPFS of mCRPC patients with
	Enzalutamide	Placebo	2	FEM	0.67 (0.59-0.75); <0.0001 I <sup>2</sup> =0%	0.35 (0.32-0.39); <0.0001 I <sup>2</sup> =85%	
Zhou 2014 <sup>10</sup>	AAP	Placebo + prednisone	2	REM	0.74 (0.66-0.84) I <sup>2</sup> =0%	0.59 (0.48-0.74) I <sup>2</sup> =76.2%	AAP significantly improved OS and rPFS compared with placebo. Heterogeneity was detected for rPFS
Author, year	Intervention	Comparator	N studies	MA method	OS Range; HR (90% CI)	rPFS Range; HR (90% CI)	Notes
Nahar 2025 <sup>11</sup>	AKT inhibitor + ARSI	Placebo	2	-	15.6 to 18.9 months; 0.72 (0.47-1.11)	8.18 to 19.2 months (intervention) vs. 6.37 to 16.6 months (Placebo); 0.84 (0.51-1.37)	No significant difference in OS and rPFS between groups

Abbreviations- AAP, abiraterone acetate prednisone; ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor; CI, confidence interval; FEM, fixed effect model; HR, hazard ratio; MA, meta-analysis; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival; REM, random effects model; rPFS, radiographic progression-free survival I<sup>2</sup>, Heterogeneity

Figure 2. AMSTAR-2 ratings

Included SLRs	PICO components	Protocol	Study design explanation	Comprehensive search strategy	Duplicate study selection	Duplicate data extraction	Details of excluded studies	Description of included studies	Risk of bias (RoB) (RCTs)	Funding sources	Appropriate methods for statistical analyses	RoB accounted for interpretation of results	Heterogeneity	Publication bias	Reports conflicts of interest	Overall rating
Chen 2023	✓	✓	✓	✓	✓	✓	⚠	✓	✓	✓	✓	✓	✓	✗	✓	Moderate
Luo 2023	✓	✓	✓	✓	✓	✓	⚠	✓	✓	✓	✓	✓	✓	✗	✓	Moderate
Nahar 2025	✓	✓	✓	✓	✓	✓	⚠	✓	✓	✗	✓	✓	✓	✓	✓	Moderate
Tan 2020	✓	✓	✓	✓	✓	✓	⚠	✓	✓	✓	✓	✓	✓	✗	✓	Moderate
Ternov 2021	✓	✓	✓	✓	✓	✓	⚠	✓	✓	✓	✓	✓	✓	✗	✓	Moderate
Wei 2021	✓	✓	✓	✓	✓	✓	⚠	✓	✓	✓	✓	✓	✓	✗	✗	Moderate
Zhou 2014	✓	✓	✓	✓	✓	✓	⚠	✓	✓	✗	✓	✓	✓	✗	✗	Moderate

Indicators- ✓ Yes ⚠ Partial Yes ✗ No

#### AMSTAR-2

- Risk of bias of the included SLRs was assessed using AMSTAR-2 for various domains (Figure 2).
- All included SLRs were rated to be of moderate quality due to weakness in one of the non-critical domains.
- Only one SLR explicitly assessed publication bias, while others did not assess the bias. It is worthwhile to note that all SLRs included less than ten studies.

### Results (Contd.)

#### OS

- Four reviews (with MAs) reported significant prolonging of OS with abiraterone (with or without prednisone) and enzalutamide compared with placebo, with limited to no heterogeneity.<sup>7,8,9,10</sup>
- In one SLR each, the combination of abiraterone plus olaparib and AKT inhibitor plus SGARI did not show a significant improvement in OS compared with abiraterone alone or placebo, respectively.<sup>6</sup>

#### rPFS

- Four reviews (with MAs) reported significant prolonging of rPFS with abiraterone (with or without prednisone) and enzalutamide compared with placebo, but with considerable to high heterogeneity.<sup>7,8,9,10</sup>
  - Heterogeneity reportedly stemmed due to differences in eligibility criteria, follow-up period and patient characteristics including number of prior chemotherapies in the primary included RCTs of SGARIs.
  - Use of enzalutamide before chemotherapy yielded more favorable rPFS.<sup>7</sup>
  - Combination of olaparib plus abiraterone also showed significant improvement in rPFS compared with abiraterone alone, with no heterogeneity.<sup>6</sup>
- #### HRQoL
- Better Functional Assessment of Cancer Therapy-Prostate (FACT-P) scores were reported with enzalutamide and abiraterone, compared with placebo.<sup>12</sup>

### Conclusion

Majority of the included reviews reported favorable OS and rPFS with SGARIs (alone or in combination). More research is needed to validate the current findings.

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