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Review – Prostate Cancer

Androgen Receptor Pathway Inhibitor Monotherapy in Prostate Cancer: Safety, Oncologic Outcomes, and Quality of Life—A Systematic Review and Meta-analysis

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Abstract

Background and objective: Androgen receptor pathway inhibitors (ARPIs) as monotherapy are studied increasingly across prostate cancer disease states. We aimed to evaluate the safety, oncologic efficacy, and quality of life (QoL) of ARPI monotherapy as compared with ARPI + androgen deprivation therapy (ADT) and ADT alone.

Methods: PubMed/Medline, Embase, and Cochrane/Central were queried through June 2024 for clinical trials. The primary outcomes were the rates of adverse events (AEs) presented as risk ratios (RRs); the secondary outcomes included efficacy and QoL.

Key findings and limitations: We synthesized data from 2015 men, retrieved from 17 studies. The incidence of any AEs was similar between patients on ARPIs, ARPI + ADT

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Apalutamide
Androgen deprivation therapy
Androgens
Testosterone

(RR: 1.01, 95% confidence interval [CI]: 1–1.02, $p = 0.08$), and ADT (RR: 1.01, 95% CI: 0.98–1.04, $p = 0.3$). The incidence of grade ≥3 AEs was higher in patients on ARPI monotherapy than in those on ADT (RR: 1.18, 95% CI: 1.11–1.24, $p < 0.01$), driven mainly by fatigue and cardiovascular toxicity. There was no statistically significant difference in grade ≥3 AEs between patients treated with ARPIs and ARPI + ADT (RR: 1.07, 95% CI: 0.87–1.3, $p = 0.4$). ARPI monotherapy led to a lower incidence of hot flushes (RR: 0.4, 95% CI: 0.18–0.89, $p = 0.03$) but higher incidences of breast pain (RR: 6.03, 95% CI: 3.34–10.88, $p < 0.01$) and gynecomastia (RR: 5.73, 95% CI: 3.79–8.66, $p < 0.01$) than treatment with ARPI + ADT. ARPIs demonstrated promising oncologic efficacy for patients with biochemical recurrence, while maintaining favorable overall and sexual QoL.

Conclusions and clinical implications: ARPI monotherapy results in overall similar toxicities for ARPI + ADT and ADT alone. The specific AE pattern of each combination can serve as a basis to tailor therapy to each patient's needs and wishes.

ADVANCING PRACTICE

What does this study add?

This study summarizes all clinical trials published up to November 2024 on the safety, oncologic efficacy, and quality of life associated with androgen receptor pathway inhibitor (ARPI) monotherapy in prostate cancer treatment. It highlights the comparable overall toxicity of ARPI monotherapy to that of androgen deprivation therapy (ADT) alone and ARPI + ADT combination, but with distinct adverse event patterns. Notably, the use of ARPI monotherapy was associated with a higher incidence of grade ≥3 adverse events, driven mainly by fatigue and cardiovascular toxicity, as compared with ADT monotherapy. Moreover, it reduced the rate of hot flushes, but increased the rate of breast-related adverse events, as compared with both ARPI + ADT and ADT alone. The findings emphasize the oncologic efficacy of ARPI monotherapy in the setting of biochemical recurrence after curative treatment, while maintaining favorable quality of life, particularly in terms of sexual function. These data support the potential for personalized treatment approaches based on individual patient preferences and specific adverse event profiles.

Clinical Relevance

This systematic review and meta-analysis shows that ARPI monotherapy offers overall similar toxicities compared to ARPI +ADT combination therapy and ADT monotherapy, while demonstrating significant oncologicefficacy in patients with BCR. The findings support its selective use in patients prioritizing sexual function, while highlighting the need to weigh potential risks. Associate Editor: Derya Tilki, M.D.

Patient Summary

In this report, we examined the safety, oncologic efficacy, and quality of life with new-generation androgen receptor pathway inhibitors administered as monotherapies. We found that these agents have promising antitumor activity and an overall similar safety profile to their combination with androgen deprivation therapy. However, their use led to a higher rate of breast-related adverse events, while lowering the rate of hut flushes. We conclude that androgen receptor pathway inhibitor monotherapy can help tailor therapy to each patient's needs and wishes.

1. Introduction

The combination of new-generation androgen receptor pathway inhibitors (ARPIs), including abiraterone acetate, apalutamide, darolutamide, and enzalutamide, with androgen deprivation therapy (ADT) transformed the therapeutic landscape of advanced prostate cancer (PCa) and currently represents the standard of care therapy for patients with metastatic disease [1,2]. ARPIs are increasingly being utilized as treatment intensification in earlier disease states such as high-risk locally advanced PCa and high-risk biochemical recurrence (BCR) following local treatment with curative intent [1]. These agents are, however, associated with non-negligible short- and long-term toxicities, which can impact quality of life (QoL) as well as mortality [3]. ADT results in testosterone suppression and impairs cardiovascular, metabolic, bone, sexual, and mental health [4]. In contrast, ARPIs directly inhibit the androgen receptor, leading to distinct endocrine changes: elevated testosterone levels and, as a result of the conversion of excess testosterone by peripheral aromatase, elevated progesterone levels, contributing to the potentially more favorable metabolic and sexual health–related side effect profile of ARPI monotherapy [5,6]. Consequently, there has been a growing

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trend toward ARPI monotherapy, with several studies investigating its oncologic efficacy across various PCa disease states, demonstrating durable antitumor activity. Furthermore, based on the results of the EMBARK trial, enzalutamide became the first ARPI to gain approval as a monotherapy for PCa, as it surpassed ADT in terms of metastasis-free survival (MFS) in patients with high-risk BCR [7]. However, what seem to distinguish ARPIs from ADT even more are the type and severity of adverse events (AEs), potentially allowing for AE-driven personalized treatment selection.

In the setting of a rapidly evolving body of literature addressing the utility of ARPI monotherapy in PCa care, there is a need to synthesize the most up-to-date evidence to inform clinical practice and guide future research endeavors. To address this unmet need, in this systematic review and meta-analysis, we aimed to summarize the currently available literature on the effect of ARPI monotherapy on safety, oncologic efficacy, and QoL, and compared it with that of ADT monotherapy and ARPI + ADT combination therapy.

2. Methods

This systematic review and meta-analysis is reported according to the recommendations of the *Cochrane Handbook* and the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guidelines (Supplementary Table 1) [8,9]. The study protocol was registered on PROSPERO (registration number: CRD42024538769).

2.1. Study eligibility and outcomes

We used the PICO framework to formulate the research question and inclusion criteria [10]. We included studies of men with PCa of any stage (population), who received ARPI monotherapy (intervention) and were compared with men treated with the combination of ARPI + ADT or ADT alone (comparison). The coprimary endpoints were any grade and grade $\geq$3 AEs (outcome). The secondary endpoints included all reported specific AEs, as defined by the Common Terminology Criteria for Adverse Events (CTCAE), metabolic changes, oncologic efficacy, and QoL outcomes [11]. This meta-analysis was restricted to randomized controlled trials (RCTs) or single-arm trials.

2.2. Search strategy, study selection, and data collection

The MEDLINE (via PubMed), Embase, and Cochrane/Central databases were queried on November 25, 2024 (Supplementary material). After selection by two independent review authors, the following data were extracted: details of the intervention and comparator, AEs, QoL, and main findings regarding oncologic efficacy (for more details, see the Supplementary material).

2.3. Statistical analyses

Quantitative data synthesis was carried out with the R statistical software. Based on the likely heterogeneity of the studies, we utilized random-effect models [12]. To assess and compare the incidences of AEs of ARPIs, ARPI + ADT, and ADT, we calculated pooled event rates using the generalized mixed-effect approach, and risk ratios (RRs) with 95% confidence intervals (CIs) using the random-effect variant of the Mantel-Haenszel method (for more details, see the Supplementary material) [13]. To evaluate the moderator effect of different ARPIs (abiraterone, apalutamide, darolutamide, and enzalutamide), disease state (perioperative, active surveillance [AS], BCR, metastatic castration-resistant PCa [mCRPC], or any stage if ADT indicated), and length of treatment (<1 vs $\geq$1 yr), we performed subgroup analyses. We restricted testing for subgroup difference to subgroups with at least three studies. Heterogeneity was assessed by calculating the Cochran's Q and I^2 measure and its CI. We utilized forest plots to visualize event rates and effect measures. To test the robustness of our analyses and to rule out any reporting bias, we performed sensitivity analyses based on the reporting of AE type (AE vs treatment-emergent AE [TEAE]).

2.4. Risk of bias

For randomized and single-arm trials, the risk of bias (RoB) was evaluated by two reviewers according to the Cochrane Collaboration's RoB assessment (version 2.0) and the RoB in nonrandomized studies of interventions (ROBINS-I) tool, respectively [14,15]. Disagreements were resolved via consensus with coauthors.

3. Results

3.1. Study selection and baseline characteristics

Following systematic search and selection (Fig. 1), 22 reports comprising 17 studies (n = 2015) were included. Baseline characteristics of the studies are summarized in Table 1 and Supplementary Table 5. We found seven single-arm trials [16–25], nine phase 2 RCTs [26–34], and one phase 3 RCT [7,35]. Abiraterone acetate (n = 73), apalutamide (n = 178), darolutamide (n = 32), and enzalutamide (n = 745) monotherapy were utilized in two [27,34], six [18,23–26,32], one [28], and eight [7,16,17,20,29–31,33] studies, respectively. In addition to ARPI monotherapy, six studies reported data on ARPI + ADT (n = 528) [7,26,27,30,32,34], while four reported on ADT monotherapy (n = 459) [7,26–28]. Moreover, we identified one study utilizing dutasteride in combination with enzalutamide + ADT [30]. Hormonal treatment was administered regardless of tumor stage (n = 212) [20,28,32], during AS (n = 146) [23,24,33], as neoadjuvant treatment before radical prostatectomy (RP; n = 127) [18,25,30], in combination with primary radiotherapy (RT; n = 120) [16,17], for BCR (n = 1342) [7,26,27,29,31], and in the metastatic castration-resistant disease stage (n = 68) [34]. The length of hormonal treatment ranged from 3 mo to more than a year. All but one study [30] used CTCAE version 4.0 or 4.03 for the reporting of AEs. As for measures of oncologic efficacy, prostate-specific antigen (PSA)-based outcomes were the primary endpoints in the majority of the studies [16,17,20,26–29,31,32], while pathologic [18,23,25,30,33] and radiographic [7,24,34] outcomes were applied in five and three studies, respectively. Among QoL questionnaires, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 [17,19,20,24,26,28], EORTC QLQ—Prostate 25

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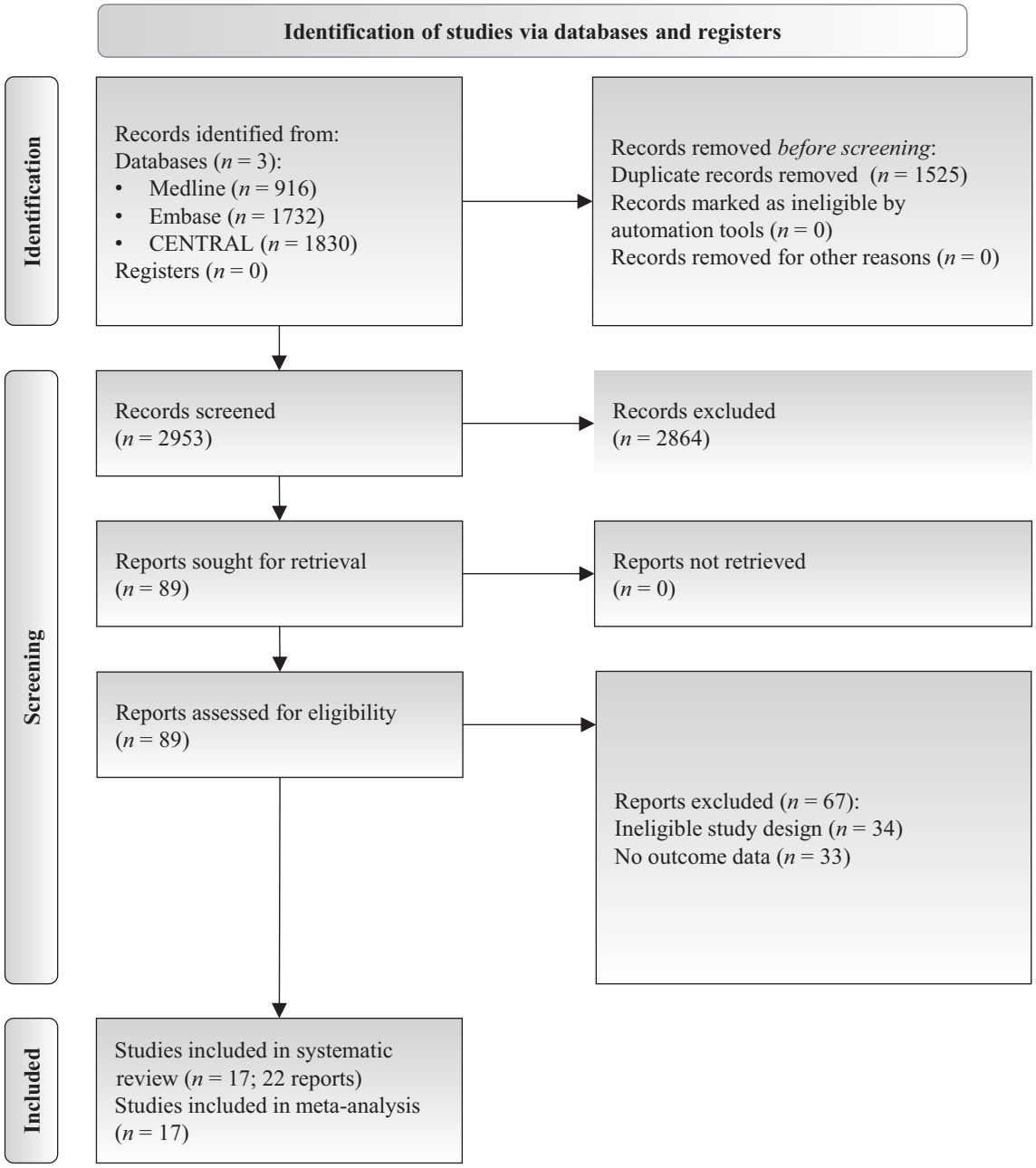

Fig. 1 – PRISMA flowchart of the selection process. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

[17,19,20,26,28,35], and the Functional Assessment of Cancer Therapy—Prostate (FACT-P) [23,26,32,35] were the most frequently utilized ones.

3.2. *Safety profile*

A detailed overview of the pooled AE incidences of ARPI monotherapy and ARPI + ADT can be found in Table 2, while data for ADT alone are presented in Supplementary Table 6. The pooled incidences of any grade and grade ≥3 AEs of ARPIs were 97% (89–99%) and 18% (7.2–37%), respectively. ARPI monotherapy was associated with a similar incidence of any AEs to ARPI + ADT (RR: 1.01, CI: 1–1.02, p = 0.08) and ADT alone (RR: 1.01, 95% CI: 0.98–1.04, p = 0.3). However, a higher incidence of grade ≥3 AEs was observed with ARPIs than with ADT alone (RR: 1.18, 95% CI: 1.11–1.24, p < 0.01), while no statistically significant difference was found compared with ARPI + ADT (RR: 1.07, 95% CI: 0.87–1.3, p = 0.4; Fig. 2 and 3). To further explore the difference in grade ≥3 AEs between ARPIs and ADT alone, we investigated specific AEs, and found fatigue (RR: 2.26, 95% CI: 0.78–6.6, p = 0.09; Fig. 3) and ischemic heart disease (5.9% for ARPIs vs 3.1% for ADT, as reported in the EMBARK trial) as possible contributors to the difference observed. A higher incidence of dose reduction (RR: 2.13, 95% CI: 1.09–4.16, p = 0.04) but a lower incidence of treatment discontinuation (RR: 0.83, 95% CI: 0.83–0.9, p < 0.01) were observed with ARPI monotherapy than with ARPI + ADT.

Among specific AEs of any grade with ARPI monotherapy, fatigue (50%, 95% CI: 36–64%), gynecomastia (41%, 95% CI:

Table 1 – Characteristics of the included studies

Author (year) Study	Study design	Disease setting	Length of treatment	ARPI monotherapy			ARPI + ADT			ADT monotherapy			Adverse event		Oncologic efficacy outcomes	Quality of life questionnaire used
				Compound	*N*	Age [a]	Compound	*N*	Age [a]	Compound	*N*	Age [a]	CTCAE version	Minimum incidence to report (% patients)		
Aggarwal (2022) [26] ARN-509-002	Phase 2 RCT open label	High-risk BCR after primary radical prostatectomy or radiotherapy	12 mo	Apalutamide (240 mg/d)	29	66 (55–79)	Apalutamide (240 mg/d) + LHRH agonist	31	67 (54–78)	LHRH agonist	30	69 (46–80)	4.03	>25%	1. PSA response rate (PSA <0.2 ng/ml) at 7 mo. Time to PSA progression	FACT-P (baseline to 12 mo), [b] EORTC QLQ-C30, EORTC QLQ-PR25, SHIM
Autio (2021) [27,36] NCT01751451	Phase 2 RCT open label	High-risk BCR after primary radical prostatectomy	8 mo	Abiraterone acetate (1000 mg/d) + prednisone (2 × 5 mg)	39	64 (43–83)	Abiraterone acetate (1000 mg/d) + prednisone (2 × 5 mg) + degarelix (80 mg/mo after 240 mg initial loading dose)	41	65 (53–74)	Degarelix (80 mg/mo after 240 mg initial loading dose)	42	66 (46–78)	4.0	>5%	1. PSA response rate (undetectable) at 18 mo (with testosterone >150 ng/dl) [b] 2. PSA response rate at 8 mo (undetectable)	PRO-CTCAE
Kaplan (2021) [16] NCT02028988	Phase 2 single-arm open label	Primary radiation therapy (NCCN intermediate-risk localized disease)	6 mo (EBRT 7–10 wk after enzalutamide initiation)	Enzalutamide (160 mg/d) + EBRT (79.2 Gy in 1.8 Gy fractions)	64	NR	NA	NA	NA	NA	NA	NA	4.0	NR	1. PSA response rate (≤0.2 ng/ml) [b] 2. PSA nonresponse rate (>0.5 ng/ml)	NA
Lara (2022) [17]ENZART	Phase 2 single-arm open label	Primary radiation therapy (NCCN intermediate-risk localized disease)	6 mo (hypo-EBRT 8–12 wk after enzalutamide initiation)	Enzalutamide (160 mg/d) + EBRT (75 Gy in 2.5 Gy fractions)	56	NR	NA	NA	NA	NA	NA	NA	4.0	NR	PSA response rate at 25th week (≥80% decrease) [b]	EORTC QLQ-C30, EORTC QLQ-PR25
Lee (2022) [18], Yang (2022) [19]NEAR	Phase 2 single-arm open label	Neoadjuvant therapy (D'Amico intermediate- and high-risk localized disease)	12 wk	Apalutamide (240 mg/d)	30	69 (65–71) [c]	NA	NA	NA	NA	NA	NA	4.0	NR	1. Pathologic complete response rate [b] 2. PSA response rate (<0.03 ng/ml) at 24 wk 3. Pathologic response rate (described by the change in tumor burden) 4. Biochemical relapse-free survival	EORTC QLQ-C30, EORTC QLQ-PR25, SHIM
Ohlmann (2022) [24]SPARE	Phase 2 RCT open label	Metastatic castration-resistant disease	Median treatment duration ∼12 mo [d]	Abiraterone acetate (1000 mg/d) + prednisone (2 × 5 mg/d)	34 [e]	76 (60–86)	Abiraterone acetate (1000 mg/d) + prednisone (2 × 5 mg) + LHRH analog	34 [f]	74 (60–83)	NA	NA	NA	4.0	NR	1. rPFS at 12 mo [b] 2. PSA response rate (≥50% decrease) 3. Time to PSA progression (PCWG2)4. Objective response rate (RECIST)	NA
Tombal (2024) [28]EORTC-GUCG 1532	Phase 2 noncomparative RCT open label	Any stage [g]	At least 24 wk [h]	Darolutamide (1200 mg/d)	32	72 (64–78) [c]	NA	NA	NA	LHRH analog	29	74 (68–76) [c]	4.03	≥10%	1. PSA response rate at week 24 (≥80% decrease) [b] 2. PSA complete response rate at week 24 (≥90% decrease)	EORTC QLQ-C30, EORTC QLQ-PR25, AMS

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Table 1 (*continued*)

Author (year) Study	Study design	Disease setting	Length of treatment	ARPI monotherapy			ARPI + ADT			ADT monotherapy			Adverse event		Oncologic efficacy outcomes	Quality of life questionnaire used
				Compound	*N*	Age [a]	Compound	*N*	Age [a]	Compound	*N*	Age [a]	CTCAE version	Minimum incidence to report (% patients)		
Tombal (2014) [20], Tombal-(2015) [21], Tombal (2018) [22] NCT01302041	Phase 2 single-arm open label	Any stage [g]	24 wk [i]	Enzalutamide (160 mg/d)	67	73 (48–86)	NA	NA	NA	NA	NA	NA	4.0	NR	1. PSA response rate at week 25 (≥80% decrease) [b] 2. PSA dynamics and kinetics3. Objective response rate (PCWG2)	EORTC QLQ-C30, EORTC QLQ-PR25
Shore (2022) [33]ENACT	Phase 2 RCT open label	Active surveillance (NCCN low- or intermediate-risk localized disease)	1 yr	Enzalutamide (160 mg/d) + active surveillance	114 [j]	65 (41–87)	NA	NA	NA	NA	NA	NA	4.03	≥5%	1. Time to pathologic or therapeutic progression [b] 2. Incidence of pathologic or therapeutic progression at 1 and 2 yr 3. Incidence of negative biopsy results at 1 and 2 yr 4. Percentage of cancer positive cores at 1 and 2 yr 5. Time to PSA progression 6. Incidence of a secondary rise in serum PSA levels at 1 and 2 yr	Brief Fatigue Inventory, 12-item Short Form, EPIC, Memorial Anxiety Scale for Prostate Cancer
Tran (2023) [29]SALV-ENZA	Phase 2 placebo-controlled RCT double blind	BCR after primary radical prostatectomy	6 mo (salvage radiation therapy: from day 61 to 120)	Enzalutamide (160 mg/d) + salvage radiation (66.6–70.2 Gy/1.8 Gy)	43	69 (51–82)	NA	NA	NA	NA	NA	NA	4.0	NR	1. PSA PFS [b] 2. Local recurrence within the radiation field (confirmed via pathology) 3. Metastasis-free survival rate	EPIC
Montgomery (2017) [30] NCT01547299	Phase 2 RCT open label	Neoadjuvant therapy (intermediate- or high-risk disease)	6 mo	Enzalutamide (160 mg/d)	27	61 (47–57)	Enzalutamide (160 mg/d) + leuprolide (22.5 mg/3 mo) + dutasteride (0.5 mg/d)	25	60 (46–74)	NA	NA	NA	NR	>20%	1. Pathologic complete response rate [b] 2. Rate of ≤3 mm tumor on final pathology 3. Positive surgical margin rate 4. Nodal involvement rate	NA

Table 1 (*continued*)

Author (year) Study	Study design	Disease setting	Length of treatment	ARPI monotherapy			ARPI + ADT			ADT monotherapy			Adverse event		Oncologic efficacy outcomes	Quality of life questionnaire used
				Compound	*N*	Age [a]	Compound	*N*	Age [a]	Compound	*N*	Age [a]	CTCAE version	Minimum incidence to report (% patients)		
Freedland (2023) [7,35] EMBARK	Phase 3 RCT [k]	High-risk BCR after primary radical prostatectomy	At least 37 wk (option of intermittent treatment) [l]	Enzalutamide (160 mg/d)	355	69 (49–93)	Enzalutamide (160 mg/d) + leuprolide (22.5 mg/3 mo)	355	69 (51–87)	Placebo + leuprolide (22.5 mg/3 mo)	358	70 (50–92)	4.03	≥10%	1. Metastasis-free survival [b] 2. Time to PSA progression 3. Time to use of new antineoplastic therapy 4. Overall survival 5. Time to distant metastasis 6. Time to castration resistance 7. Time to symptomatic progression 8. Time to first symptomatic skeletal event	BPI-SF, FACT-P, EORTC QLQ-PR25, EQ-5D-5L
Madan (2021) [31] NCT01875250	Phase 2 RCT open label	High-risk BCR after primary radical prostatectomy or radiation therapy	84 d [m]	Enzalutamide (160 mg/d)	19	68 (54–87)	NA	NA	NA	NA	NA	NA	4.0	NR	1. PSA recovery kinetics at 7 mo [b] 2. PSA kinetics after short-course enzalutamide	NA
Maluf (2021) [32]LACOG 0415	Phase 2 RCT open label	Locally advanced node-positive disease/high-risk BCR/metastatic hormone-sensitive disease	25 wk [n]	Apalutamide (240 mg/d)	42	70 (53–88)	Abiraterone acetate (1000 mg/d) + prednisone (10 mg/d) + goserelin (10.8 mg/3 mo)	42	69 (51–85)	NA	NA	NA	4.0	NR	1. PSA response rate at week 25 (≤0.2 ng/ml)) [b] 2. PSA response rate at week 25 (≥50% and ≥80% decrease) 3. Maximum PSA decline 4. Overall PSA change at weeks 25 and 52 5. rPFS at week 256. PSA progression	FACT-P
Schweizer (2023) [23] NCT02721979	Phase 2 single-arm open label	Active surveillance (NCCN very-low-, low-, and low- to intermediate-risk disease)	90 d	Apalutamide (240 mg/d)	23	67 (45–76)	NA	NA	NA	NA	NA	NA	4.03	≥5%	1. Negative repeat biopsy at 3 mo [b] 2. Negative repeat biopsies at 1 and 2 yr 3. Exit from AS due to pathologic progression or otherwise at 2 yr4. Receipt of local treatment	FACT-P, 36-Item Short Form
Barrett-(2022) [24]TAPS01	Phase 2 single-arm open label	Active surveillance (low-risk or favorable intermediate-risk disease; Cambridge prognostic groups 1 and 2)	90 d	Apalutamide (240 mg/d)	9	NR	NA	NA	NA	NA	NA	NA	4.03	NA	Physiologic response [b,o]	EORTC QLQ-C30, EQ-5D-5L, VAS

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Author (year) Study	Study design	Disease setting	Length of treatment	ARPI monotherapy			ARPI + ADT			ADT monotherapy			Adverse event		Oncologic efficacy outcomes	Quality of life questionnaire used
				Compound	*N*	Age [a]	Compound	*N*	Age [a]	Compound	*N*	Age [a]	CTCAE version	Minimum incidence to report (% patients)		
Hahn (2024) [25] NCT03412396	Phase 2 single-arm open label	Neoadjuvant therapy (NCCN intermediate-risk localized disease)	6 mo	Apalutamide (240 mg/d)	45	60 (57–67) [c]	NA	NA	NA	NA	NA	NA	4.0	NR	1. Adverse surgical pathology feature rate [b,p] 2. 3–5-yr BCR rate	NA

ADT = androgen deprivation therapy; AMS = Aging Male Symptoms; ARPI = androgen receptor pathway inhibitor; BCR = biochemical recurrence; BPI-SF = Brief Pain Inventory—Short Form; CTCAE = Common Terminology Criteria for Adverse Events; EBRT = external beam radiation therapy; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Prostate 25; EPIC = Expanded Prostate Cancer Index Composite; EQ-5D-5L = EuroQol 5-Dimension 5-Level; FACT-P = Functional Assessment of Cancer Therapy—Prostate; IQR = interquartile range; LHRH = luteinizing hormone-releasing hormone; mpMRI = multiparametric magnetic resonance imaging; NA = not available or not applicable; NCCN = National Comprehensive Cancer Network; NR = not reported; PCWG2 = Prostate Cancer Working Group 2; PFS = progression-free survival; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; SHIM = Sexual Health Inventory for Men.

[a] Reported as median (range) in years.

[b] Primary outcome.

[c] Reported as median (IQR).

[d] Treatment until radiographic progression or unequivocal clinical progression. Median duration of treatment: arm A = 358 d; arm B = 394 d.

[e] Safety population: 33.

[f] Safety population: 32.

[g] When continuous ADT is indicated for a minimum of 24 wk.

[h] Until initial treatment plan/progressive disease/patient's decision. Of the patients, 93.5% continued beyond 6 mo; median treatment duration: 29.1 mo.

[i] Continued beyond until objective or clinical disease progression or occurrence of an unacceptable safety or tolerability issue.

[j] Safety population: 112.

[k] Enzalutamide monotherapy arm: open label. Enzalutamide + leuprolide arm and placebo + leuprolide arm: double blind.

[l] Intermittent treatment (treatment holiday) was indicated if the PSA level was <0.2 ng/ml and treatment was restarted when the PSA level was at least 5.0 ng/ml (if the patient had not undergone radical prostatectomy previously) or at least 2.0 ng/ml (if the patient had previously undergone radical prostatectomy). Patients continued to receive their assigned treatments until imaging-based disease progression (confirmed by a central review), an unacceptable adverse event, seizure, or death occurred; nonadherence due to protocol violation was documented; or the patient or physician decided to discontinue the regimen. The median duration of treatment was 32.4 mo for enzalutamide plus leuprolide, 35.4 mo for leuprolide alone, and 45.9 mo for enzalutamide monotherapy.

[m] Option of second 84-d course (if PSA recovery to baseline beyond 7 mo, and no metastatic disease diagnosed).

[n] Treatment beyond week 25 allowed in case of patient benefit.

[o] Defined as achieving tumor volume downsizing in at least 50% of the cohort population, as determined via mpMRI at 90 d from the start of treatment.

[p] Defined as pathologic T3a, T3b stage, N1 and/or PSM.

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32–50%), hypertension (27%, 95% CI: 8.3–60%), breast pain (26%, 95% CI: 15–41%), erectile dysfunction (23%, 95% CI: 9.4–46%), and rash (22%, 95% CI: 12–36%) were reported most frequently. Grade ≥3 AEs were generally rare, with the pooled incidence ranging between 0% and 4.1%. For the majority of the AEs, we found similar incidences with ARPIs and ARPI + ADT; however, higher incidences of gynecomastia (RR: 5.73, 95% CI: 3.79 8.66, $p < 0.01$), breast pain (RR: 6.03, 95% CI: 3.34–10.88, $p < 0.01$), and alanine aminotransferase elevation (RR: 1.19, 95% CI: 1.01–1.41, $p = 0.04$), but lower incidence of hot flashes (RR: 0.4, 95% CI: 0.18–0.89, $p = 0.03$) were detected during ARPI monotherapy (Fig. 2). Similarly, ARPI monotherapy led to higher incidences of gynecomastia (RR: 4.97, 95% CI: 3.54–6.97, $p < 0.01$) and breast pain (RR: 13.41, 95% CI: 6.85–26.22, $p < 0.01$), but a lower incidence of hot flashes (RR: 0.45, 95% CI: 0.26–0.76, $p = 0.02$) than ADT (Fig. 3).

The preplanned subgroup and sensitivity analyses did not reveal meaningful differences for most AEs. Longer treatment was associated with a higher incidence of dose reduction (15.4% vs 0.8%, $p = 0.014$; Supplementary material). Moreover, in studies enrolling patients regardless of disease status, we observed a lower incidence of any grade breast pain (8.6% vs 32.1% [BCR] vs 40.8% [perioperative], $p < 0.001$; Supplementary material), fatigue (23.7% vs 60.9% [BCR] vs 54.2% [perioperative], $p < 0.001$; Supplementary material), and hypertension (8.6% vs 18.8% [BCR], $p = 0.005$; Supplementary material).

Four studies evaluated metabolic changes during ARPI monotherapy (Table 3) [16,17,20–22,26]. Bone mineral density remained unchanged during short-course (<1 yr) treatment; however, a slight reduction in femoral neck (–2.4%) and trochanter (–2.7%) density was noted with prolonged treatment [17,22,26]. Similarly, body fat composition did not change in two studies utilizing 6-mo treatment [16,17]; however, Tombal et al [22] demonstrated a progressive decrease in lean body mass (–6.5%) and an increase in fat mass (+17%) during 3 yr of treatment. Concerning serum lipids, Lara et al [17] found cholesterol and triglyceride levels unchanged at 6 mo; however, Tombal et al [22] detected impaired lipid profiles at 2 yr, but not at 3 yr [21]. Interestingly, all the studies reported a modest elevation in high-density lipoprotein cholesterol levels [17,20,21]. Notably, while serum fasting glucose and glycated hemoglobin (HbA1c) levels remained stable, fasting insulin levels and insulin resistance index increased moderately, although the generalizability of these findings is limited by the high variability observed within the studies [17,20–22].

3.3. Oncologic efficacy

3.3.1. Any disease state

Three studies enrolled patients regardless of tumor state, whenever ADT was indicated (eg, locally advanced node-positive disease/high-risk BCR/metastatic hormone-sensitive PCa) [20,28,32]. The first study to assess ARPI monotherapy for PCa utilized a 24-wk course of enzalutamide in 67 hormone-naive patients (M0 52%, M1 15%, and Mx 33%) [20]. Notably treatment continuation was permitted until objective or clinical disease progression or unacceptable safety issue, with 81%, 67%, and 63% of the patients remaining on treatment beyond 1, 2, and 3 yr, respectively [20–22]. Enzalutamide monotherapy exhibited significant PSA responses: the rates of undetectable PSA (≤0.1 ng/ml) were 45% at 25 wk and 72% during the 3-yr study period [20,22]. A reduction of ≥80% in PSA level (PSA80) was achieved in 93% at 25 wk, 81% at 1 yr, 67% at 2 yr, and 57% at 3 yr [20–22]. Based on the radiographic response, 18 of the 26 metastatic patients at baseline benefited from the treatment (Table 3) [22]. Similarly, in the EORTC-GUCG 1532 study by Tombal et al [28], a short course of darolutamide demonstrated significant PSA response rates (PSA80: 100%; PSA90: 100%) at 24 wk in 32 patients with hormone-naive PCa (M0 56%, M1a 13%, 3.4% M1b 19%, and M1c 3.1%). Although the study was noncomparative, the use of ADT was associated with nominally lower response rates (PSA80: 86%; PSA90: 81%) [28]. In contrast, Maluf et al [32] reported lower biochemical response rates with apalutamide (PSA nadir ≤2 ng/ml: 60%; PSA80: 90%) in patients with advanced castration-sensitive PCa.

3.3.2. Active surveillance

Two small single-arm trials reported meaningful responses of apalutamide monotherapy during AS [23,24]. In the study by Schweizer et al [23], the 3-, 12-, and 18-mo negative repeat biopsy rates were 59%, 33%, and 21%, respectively. Similarly, Barrett et al [24] found durable reductions in tumor volume at 3 mo (–52%), 6 mo (–30%), and 18 mo (–20%). In the only randomized trial comparing ARPI + AS ($n = 114$) and AS ($n = 113$) to date (ENACT trial), enzalutamide reduced the risk of pathologic or therapeutic progression (hazard ratio [HR]: 0.54; CI: 0.33–0.89, $p = 0.02$) in low- and intermediate-risk PCa patients [33]. Notably, while enzalutamide was superior in terms of the incidence of pathologic or therapeutic PCa progression (odds ratio [OR]: 0.3, CI: 0.11–0.60, $p < 0.01$), none of the benefits, such as negative biopsies (OR: 3.5, CI: 1.76–6.92, $p < 0.001$), secondary rise in serum PSA level (OR: 0.1, CI: 0.08–0.26, $p < 0.001$), and mean percentage of cancer-positive cores at 1 yr ($p < 0.001$), were present at 2 yr during the follow-up, suggesting its limited long-term utility during AS (Table 3) [33].

3.3.3. Neoadjuvant setting

Three studies assessed ARPI monotherapy as neoadjuvant treatment before RP for intermediate- and high-risk PCa patients [18,25,30]. In the study by Lee et al [18] assessing apalutamide, the median tumor volume reduction was 42% (interquartile range: 33–60%); however, none of the patients achieved a pathologic complete response. Similarly, Montgomery et al [30] reported a 0% pathologic complete response rate after enzalutamide monotherapy, whereas the combination of enzalutamide + ADT + dutasteride was associated with a higher minimal residual disease rate and a lower residual cancer burden, but a higher rate of lymph node involvement than enzalutamide alone. Furthermore, Hahn et al [25] found no benefit of apalutamide, in terms of the incidence of adverse pathologic features on RP, in 40 intermediate-risk PCa patients. Notably, despite 70% of the patients achieving PSA90 prior to RP, 21% of them experienced BCR at 3 yr [25].

3.3.4. Combination with primary prostate RT

Two studies assessed the combination of ARPI monotherapy and primary RT in intermediate-risk PCa patients [16,17]. In

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Table 2 – Proportion pools of adverse events of ARPI monotherapy and the combination of ARPI and ADT

Adverse event	Grade	ARPI monotherapy			ARPI + ADT		
		Pooled incidence (95% CI)	*N*	I^2	Pooled incidence (95% CI)	*N*	I^2
Any	Any	97% (89–99%)	770	74%	97% (94–99%)	483	0%
	≥3	18% (7.2–37%)	788	91%	40.3% (22–62%)	483	79%
Dose reduction	NA	2.1% (0.3–12%)	689	0%	6.2% (3.4–11%)	451	0%
Dose interruption	NA	3.9% (0.7–18%)	167	0%	NA	NA	NA
Treatment discontinuation	NA	2.6% (0.8–8.3%)	846	49%	1.9% (0–64%)	451	44%
Fatigue	Any	50% (36–64%)	955	85%	43% (22–66%)	524	84%
	≥3	1.6% (6.0–4.2%)	883	0%	0.5% (0–70%)	499	0%
Gynecomastia	Any	41% (32–50%)	890	68%	5.1% (1.3–18%)	492	0%
	≥3	0.4% (0.1–1.3%)	946	0%	0% [a]	436	NA
Hypertension	Any	27% (8.3–60%)	857	90%	31% (9.6–65%)	468	88%
	≥3	2.1% (0.3–14%)	849	77%	7.2% (1.1–36%)	499	89%
Breast pain	Any	26% (15–41%)	880	86%	2.6% (1.2–5.6%)	492	0%
	≥3	0% [a]	824	NA	0% [a]	436	NA
Erectile dysfunction	Any	23% (9.4–46%)	219	70%	NA	NA	NA
	≥3	0.5% (0–26%)	219	0%	NA	NA	NA
Rash	Any	22% (12–36%)	236	63%	NA	NA	NA
	≥3	2.9% (0.4–20%)	191	0%	NA	NA	NA
ALT-AST elevation	Any	17% (5.7–40%)	119	35%	NA	NA	NA
Thyroid dysfunction	Any	16% (1–80%)	97	79%	NA	NA	NA
Hot flashes	Any	16% (9.9–25%)	936	78%	64% (17–94%)	524	89%
	≥3	0.1% (0–1%)	880	0%	0.4% (0–3.9%)	468	0%
Arthralgia-myalgia	Any	16% (7.8–30%)	522	63%	17% (2.6–62%)	426	74%
	≥3	0.2% (0–3.2%)	493	0%	NA	395	NA
Dry skin	Any	15% (2.5–54%)	176	90%	NA	NA	NA
	≥3	0% [a]	176	NA	NA	NA	NA
Diarrhea	Any	14% (7.1–24%)	709	79%	14% (8.4–23%)	420	0
	≥3	0% [a]	682	NA	NA	NA	NA
Decreased libido	Any	13% (6.9–24%)	300	68%	NA	NA	NA
ALT elevation	Any	13% (0.2–93%)	97	0%	12% (0.3–86%)	98	0
	≥3	4.1% (0.5–28%)	97	0%	4.1% (0.5–28%)	98	0
Dizziness	Any	12% (7–21%)	428	0%	NA	NA	NA
	≥3	0.2% (72%)	428	0%	NA	NA	NA
Back pain	Any	12% (3.4–36%)	463	0%	NA	NA	NA
	≥3	0.2% (0–14%)	463	0%	NA	NA	NA
Anorexia	Any	12% (5.2–25%)	117	0%	NA	NA	NA
	≥3	0%	117	NA	NA	NA	NA
AST elevation	Any	12% (0.4–82%)	97	0%	11% (0.5–74%)	98	0
	≥3	2.1% (0.1–31%)	97	0%	1% (0–44%)	98	0
Nausea	Any	11% (6.9–17%)	678	41%	12% (6.4–20%)	436	0%
	≥3	0.1% (0–1.7%)	678	0%	0% [a]	436	NA
Anemia	Any	10% (0.9–60%)	130	83%	7.5% (1.2–35%)	115	45%
	≥3	0.8% (0–16%)	130	0%	1.7% (0.1–28%)	115	0%
Hyperglycemia	Any	10% (1.4–47%)	286	90%	17% (1.7–72%)	115	87%
	≥3	0.4% (0.4–0.4%)	286	16%	7.7% (1.6–31%)	115	41%
Weight loss	Any	9.8% (6.4–15%)	519	11%	NA	NA	NA
	≥3	0.2% (0–16%)	407	0%	NA	NA	NA
Constipation	Any	9.7% (5.2–17%)	464	0%	NA	NA	NA
	≥3	0.2% (0–14%)	464	0%	NA	NA	NA
Edema	Any	9.1% (4.6–17%)	429	50%	8.2% (4–16%)	427	59%
	≥3	0.7% (0–44%)	429	69%	0% [a]	427	NA
Headache	Any	7.9% (3.2–18%)	507	20%	10% (5.5–19%)	436	0%
	≥3	0.2% (0–3.1%)	507	0%	0.7% (0.1–7.7%)	436	0%
Insomnia	Any	6.9% (1.6–26%)	503	60%	19% (6.1–44%)	450	84%
	≥3	0.1% (0–91%)	447	0%	NA	NA	NA
Pain in extremity	Any	6.7% (2–20%)	519	0%	NA	NA	NA
	≥3	0% [a]	519	NA	NA	NA	NA
Depression	Any	5% (1.1–20%)	160	0%	NA	NA	NA
	≥3	0% [a]	160	NA	NA	NA	NA

ADT = androgen deprivation therapy; ALT = alanine aminotransferase; ARPI = androgen receptor pathway inhibitor; AST = aspartate aminotransferase; CI = confidence interval; *N* = number of patients; NA = not applicable.

[a] Pooled proportions were not calculated due to zero events in all studies for the outcome. For further information, see Supplementary Table 3.

both studies, the addition of a 6-mo course of enzalutamide to RT demonstrated deep and durable PSA responses (nadir PSA ≤0.2 ng/ml: 79% and 100%) suggesting its utility in combination with primary RT [16,17].

3.3.5. *Biochemical recurrence*

Five studies assessed ARPI monotherapy in the setting of high-risk BCR with promising results [7,26,27,29,31]. Aggarwal et al [26] found no statistically significant difference between PSA response rates (nadir <0.2 ng/ml) of apalutamide + ADT (97%), apalutamide (89%), and ADT (89%). However, the time to PSA progression was longer with apalutamide + ADT than with apalutamide (HR: 0.40, CI: 0.17–0.98, $p = 0.038$), and similar between apalutamide and ADT (HR: 1.09, CI: 0.49–2.43, $p = 0.8$) after a median follow-up of 30 mo [26]. In the study by Autio et al [27], after 8-mo-long treatment, the undetectable PSA levels among patients with testosterone recovery at 18 mo were comparable between

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Adverse event	ARPI (*N*)	ARPI + ADT (*N*)	Pooled RR (95% CI)	I^2
Any				
Any grade	475/485	469/483	1.01 (1.0–1.02)	0%
Grade ≥3	222/485	215/483	1.07 (0.87–1.3)	20%
Treatment modification				
Dose reduction *	59/452	28/451	2.13 (1.09–4.16)	0%
Treatment discontinuation *	64/452	74/451	0.86 (0.83–0.9)	0%
Fatigue				
Any grade	236/522	222/524	1.05 (0.94–1.18)	0%
Grade ≥3	16/495	12/499	1.27 (0.84–1.91)	0%
Gynecomastia				
Any grade *	215/489	34/492	5.73 (3.79–8.66)	0%
Grade ≥3	1/433	0/436	1.64 (0.34–7.95)	0%
Hot flashes				
Any grade *	121/522	343/524	0.4 (0.18–0.89)	83%
Grade ≥3	1/466	2/468	0.73 (0.38–1.42)	0%
Arthralgia-myalgia				
Any grade	94/425	106/426	0.95 (0.4–2.24)	16%
Hypertension				
Any grade	97/466	121/468	0.84 (0.58–1.22)	16%
Grade ≥3	18/466	25/468	0.64 (0.14–2.89)	31%
ALT elevation				
Any grade *	20/97	17/98	1.19 (1.01–1.41)	0%
Grade ≥3	4/97	4/98	1.02 (0.82–1.27)	0%
Hyperglicemia				
Any grade	22/112	22/115	0.66 (0.05–8.16)	52%
Grade ≥3	6/112	9/115	0.67 (0.06–7.64)	0%
Breast pain				
Any grade *	95/489	13/492	6.03 (3.34–10.88)	0%
Grade ≥3	0/433	0/436	1.03 (0.89–1.2)	0%
AST elevation				
Any grade	16/97	14/98	1.16 (0.42–3.2)	0%
Grade ≥3	2/97	1/98	1.47 (0.33–6.48)	0%
Anemia				
Any grade	16/112	9/115	1.37 (0.09–19.74)	36%
Grade ≥3	1/112	2/115	0.71 (0.03–19.59)	0%
Nausea				
Any grade	61/433	50/436	1.23 (0.83–1.82)	0%
Grade ≥3	1/433	0/436	1.64 (0.34–7.95)	0%
Diarrhea				
Any grade	53/423	60/420	0.88 (0.5–1.55)	0%
Headache				
Any grade	46/433	45/436	1.03 (0.55–1.91)	0%
Grade ≥3	1/433	3/436	0.53 (0.09–2.95)	0%
Edema				
Any grade	39/429	35/427	1.09 (0.04–31.41)	64%
Grade ≥3	3/429	0/427	2.8 (0.43–18.15)	0%
Insomnia				
Any grade	38/447	64/450	0.63 (0.25–1.61)	55%

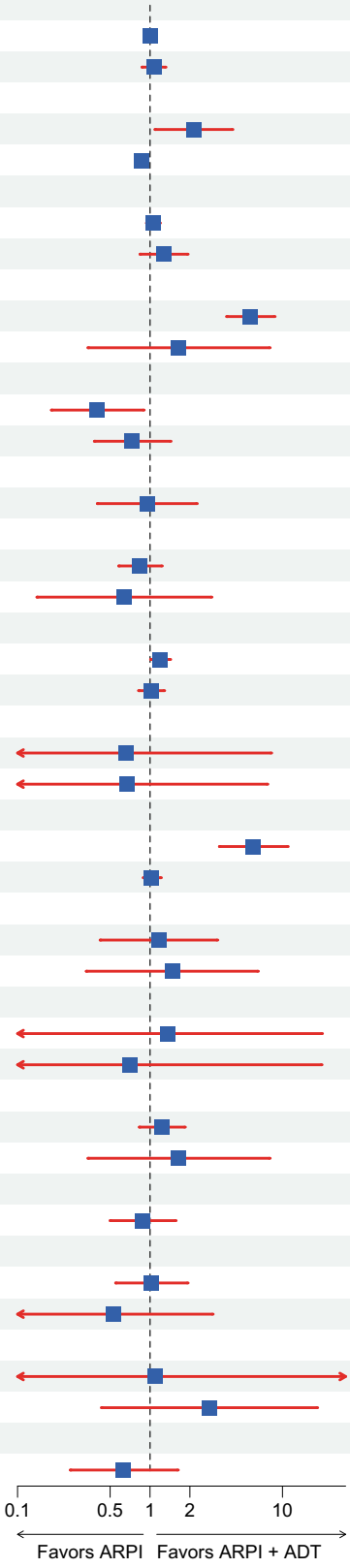

Fig. 2 – Summary plot of the comparison of the side-effect profile of androgen receptor pathway inhibitors and their combination with androgen deprivation therapy. Statistically significant results are marked with *. ADT = androgen deprivation therapy; ALT = alanine aminotransferase; ARPI = androgen receptor pathway inhibitor; AST = aspartate aminotransferase; CI = confidence interval; RR = risk ratio.

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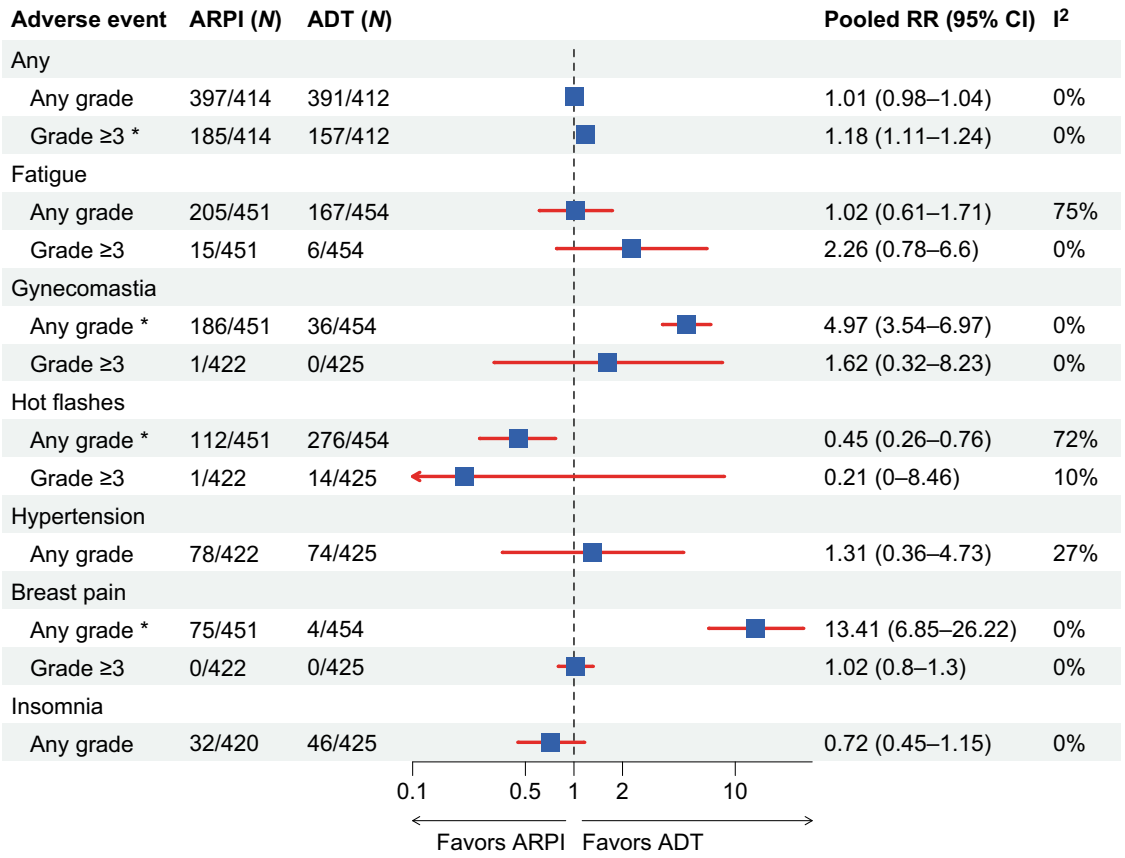

Fig. 3 – Summary plot of the comparison of the side-effect profile of androgen receptor pathway inhibitors and androgen deprivation therapy. Statistically significant results are marked with *. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; CI = confidence interval; RR = risk ratio.

the abiraterone (5.1%, 95% CI: 1–17%), abiraterone + ADT (17%, 95% CI: 7–32%), and ADT (12%, 95% CI: 7–26%) groups. However, the median time to PSA progression was the shortest with abiraterone (37.5 wk), followed by ADT (54.9 wk) and abiraterone + ADT (64.4 wk) [27]. In the SALV-ENZA trial, the addition of enzalutamide to salvage RT improved PSA PFS (HR: 0.42, CI: 0.19–0.92, $p = 0.031$), especially in patients with pT3 (HR: 0.22, CI: 0.07–0.69) and R1 (HR: 0.14, CI: 0.03–0.64) disease [29]. Madan et al [31] compared enzalutamide with its combination with PROSTVAC. Although PSA recovery kinetics, the primary endpoint of the trial, was not met, a short course of enzalutamide demonstrated a deep (median PSA reduction: >99%) but temporary (median time to first PSA rise after treatment cessation: 28 d) PSA response [31]. To date, the only phase 3 trial assessing ARPI monotherapy for PCa patients is EMBARK, which randomized patients with high-risk BCR (PSA doubling time ≤9 mo) to enzalutamide + ADT, enzalutamide, or ADT [7]. Intermittent treatment was allowed in case of PSA nadir ≤0.2 ng/ml at week 37 and was restarted upon PSA progression [7]. Enzalutamide monotherapy outperformed ADT in terms of MFS (HR: 0.63, CI: 0.46–0.87; $p = 0.005$), biochemical PFS (HR: 0.33, CI: 0.23–0.49; $p < 0.001$), and the time to first use of new antineoplastic therapy (HR: 0.54, CI: 0.41–0.71; $p < 0.001$); however, it did not surpass the antitumor efficacy of enzalutamide + ADT (Table 3) [7]. The interim analysis of OS data showed benefit for enzalutamide + ADT (HR: 0.59, 95% CI: 0.38–0.91; $p = 0.02$) but not for enzalutamide monotherapy (HR: 0.78, 95% CI: 0.52–1.17; $p = 0.2$) compared with ADT alone, although longer follow-up is warranted [7].

3.3.6. *Metastatic castration-resistant PCa*

We identified one RCT, the SPARE trial ($n = 68$), assessing the utility of treatment de-escalation to abiraterone monotherapy in the mCRPC stage [34]. Compared with abiraterone + ADT, abiraterone resulted in similar 1-yr radiographic PFS (89% vs 84%, $p = 0.6$), PSA progression (49% vs 49%, $p = 0.4$), overall response (40% vs 40%, no p value provided), and PSA50 response rates (74% vs 65%, no p value provided) [34].

3.4. *Quality of life*

Eleven studies assessed patient-reported QoL outcomes; the main findings are shown in Table 3 [17,19–24,26,28,32,33,35,36]. Short-term (<1 yr) use of ARPIs was associated with maintained QoL and no significant impairment in most domains [19,20,23,24,26,32,33,36]. Clinically meaningful QoL deterioration was observed in domains related to fatigue [19,20,23], physical function [17,19,24,33], and sexual function and activity [19,28,33]. Notably, most changes resolved after treatment cessation [17,23,24,33]. In the two studies comparing QoL with ARPIs,

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Table 3 – Summary of oncologic efficacy and quality of life findings

Disease setting	Author (year) Study	Oncologic efficacy	Metabolic toxicity	Quality of life
Any disease state	Tombal (2014) [20], Tombal (2015) [21], Tombal (2018) [22] NCT01302041	PSA response rate (≥80% reduction): 25th week: 93% (62/67) 1 yr: 81% (54/67) 2 yr: 67% (45/67) 3 yr: 57% (38/67) Proportion of patients on treatment at: 1 yr: 81% (54/67) 2 yr: 67% (45/67) 3 yr: 63% (42/67) Median maximum PSA decline (25th week): 99% (IQR: −100 to −98%) Rate of undetectable PSA (≤0.1 ng/ml): 25th week: 45% (30/67) 3 yr: 72% (48/67) Radiographic response rates: 16/26 metastatic patients had measurable disease at baseline Objective complete response: 25th week: 19% (3/16) 3 yr: 54% (14/26) Objective partial response: 25th week: 31% (5/16) 3 yr: 12% (3/26) Stable disease: 25th week: 19% (3/16) 3 yr: 4% (1/26)	Bone mineral density: 25th week: unchanged 2 yr: stable total, spine and forearm, small decrease in femoral neck (−2.2%) and trochanter (−2.2%) 3 yr: stable total, spine and forearm, small decrease in femoral neck (−2.4%) and trochanter (−2.7%) Body mass: 25th week: decreased lean body mass (−4.1%), increased fat mass (+6.9%) 2 yr: decreased lean body mass (−5.3%), increased fat mass (+11%) 3 yr: decreased lean body mass (−6.5%), increased fat mass (+17%) Lipid profile: 25th week: elevated fasting serum triglycerides (+6.5%), HDL cholesterol (+6.2%), and LDL cholesterol (+7.3%) 1 year: elevated fasting serum triglycerides (+9%), HDL cholesterol (+6%), and LDL cholesterol (+9%) 3 yr: elevated fasting serum triglycerides (+4.1%), decreased HDL cholesterol (−1.4%), and LDL cholesterol (−5.2%) Glucose homeostasis: 25th week: elevated fasting plasma insulin (+39%) and HOMA-IR (+45%), unchanged fasting plasma glucose (−0.1%), and hemoglobin A1C (−2%) 1 yr: elevated fasting plasma insulin (+21%) and HOMA-IR (+20%), stable fasting plasma glucose (−1%), and hemoglobin A1C (−4%) 3 yr: elevated fasting plasma insulin (+5.1%) and HOMA-IR (+30%), stable fasting plasma glucose (+3.5%), and hemoglobin A1C (−2.5%)	1. Global health status: 25th week—stable, 3 yr—minor deterioration 2. Fatigue: clinically meaningful impairment at 25th week and 3 yr 3. Sexual activity and functioning: clinically meaningful deterioration at 25th week and 1, 2, and 3 yr. 4. Treatment-related symptoms: moderate worsening both at 25th week and 3 yr 5. Dyspnea, constipation, diarrhea: meaningful worsening at 3 yr.
	Tombal (2024) [28] EORTC-GUCG 1532	PSA response rate (≥80% reduction): Darolutamide: 100% (23/23) ADT 86% (18/21) PSA response rate (≥90% reduction): Darolutamide: 100% (23/23) ADT 81% (17/21)	NR	1. Sexual functioning: meaningful worsening (mean difference −12.5 ± 23.6) 2. Sexual activity: meaningful worsening (mean difference −9.9 ± 22.4) with darolutamide 3. Diarrhea: clinically significant worsening (mean difference 11.1 ± 21.7) with ADT 4. AMS: similar mean scores.

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Table 3 (*continued*)

Disease setting	Author (year) Study	Oncologic efficacy	Metabolic toxicity	Quality of life
	Maluf (2021) [32] LACOG 0415	PSA response rate (nadir ≤0.2 ng/ml): Abiraterone + ADT: 76% Apalutamide: 60% Apalutamide + abiraterone: 80% PSA response rate (≥50% reduction): Abiraterone + ADT: 100% Apalutamide: 93% Apalutamide + abiraterone: 100% PSA response rate (≥80% reduction): Abiraterone + ADT: 100% Apalutamide: 90% Apalutamide + abiraterone: 97%	NR	FACT-P: no significant change in mean scores within the treatment arms. No difference between the treatment arms
Active surveillance	Shore (2022) [33] ENACT	Time to pathologic or therapeutic progression: Enzalutamide vs AS (HR: 0.54, 95% CI: 0.33–0.89, $p = 0.02$) Incidence of pathologic or therapeutic progression: 1 yr: enzalutamide (8%) vs AS (23%; OR: 0.3, 95% CI: 0.11–0.6, $p < 0.01$) 2 yr: enzalutamide (16%) vs AS (16%; OR: 0.9, 95% CI: 0.36–2.24, $p = 0.8$) Incidence of negative biopsy results: 1 yr: enzalutamide (35%) vs AS (14%; OR: 3.5, 95% CI: 1.76–6.92, $p < 0.001$) 2 yr: enzalutamide (19%) vs AS (12%; OR: 1.6, 95% CI: 0.66–4, $p = 0.3$) Mean percentage of cancer-positive cores: 1 yr: lower with enzalutamide (LSM difference [SE]: −10.07 [2.4], 95% CI: −14.79 to −5.34, $p < 0.001$) 2 yr: no difference (LSM: −5.15 [3.17], 95% CI: −11.4 to 1.1, $p = 0.1$) Time to PSA progression: Enzalutamide (median 14.8 mo) vs AS (median 8.8 mo; HR: 0.71; 95% CI: 0.53–0.97, $p = 0.03$) Incidence of secondary rise in serum PSA level: 1 yr: enzalutamide (25%) vs AS (69%; OR: 0.1, 95% CI: 0.08–0.26, $p < 0.001$) 2 yr: enzalutamide (92%) vs AS (93%; OR: 1.1, 95% CI: 0.37–3.53, $p = 0.8$)	NR	No association of enzalutamide with clinically meaningful worsening of quality of life was observed, except sexual and physical function; however, these resolved by month 24 after treatment termination
	Schweizer (2023) [23] NCT02721979	Negative repeat biopsy rate: 3 mo: 59% (13/22) 1 yr: 33% (7/21) 2 yr: 21% (4/19) Median time to first positive biopsy: 364 d (95% CI: 91–742) Rate of definitive local therapy: 23% (5/22)	NR	1. Transient declines across QoL domains, which returned to baseline after treatment cessation (until day 180) 2. No meaningful changes in most scores. 3. Energy/fatigue: meaningful worsening 4. Some patients reported improvements in quality of life after end of treatment compared with baseline

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Table 3 (*continued*)

Disease setting	Author (year) Study	Oncologic efficacy	Metabolic toxicity	Quality of life
	Barrett (2022) [24] TAPS01	Mean change (%) in tumor volume: 3 mo (end of treatment): −52% 6 mo: −30% 18 mo: −20% Mean change (%) in gland volume: 3 mo (end of treatment): −36% 6 mo: −6% 18 mo: −2%	NR	1. Global, physical, role, and social functioning: reduced scores but all starting to recover by 6th week after treatment 2. Lower mean EQ-5D-5L scores (−0.07 points) at the end of treatment and 6 wk after treatment 3. No change in EQ VAS scores
Neoadjuvant	Lee (2022) [18], Yang (2022) [19] NEAR	Pathologic complete response rate: 0% Median tumor volume reduction: 42% (IQR: 33–60%) Pathologic stage upon radical prostatectomy: pT2 (52%), pT3a (40%), pT3b (8%), N1 (16.0%) PSA response rate (≥90% reduction) at 12th week: 90% (27/30) PSA nadir 24 wk after radical prostatectomy: 84% (21/25) 2-yr biochemical recurrence-free survival: 86% (95% CI: 71–100%)	NR	1. Statistically significant deterioration: functional ($p = 0.011$) and symptom ($p < 0.01$) scales 2. Clinically meaningful deterioration: fatigue ($p = 0.012$), cognitive functioning ($p = 0.038$), role functioning ($p = 0.025$), and SHIM scores ($p < 0.001$) 3. Global health and quality of life: no clinically meaningful impairment 4. Median daily step count: reduced (8228/d to 6001/d, $p = 0.063$)
	Montgomery (2017) [30] NCT01547299	Pathologic complete response rate: 0% enzalutamide 4% enzalutamide + dutasteride + ADT Minimal residual disease rate (≤3 mm max diameter): 0% enzalutamide 13% enzalutamide + dutasteride + ADT Median residual cancer burden: 0.41 cm^3 enzalutamide 0.06 cm^3 enzalutamide + dutasteride + ADT Proportion of patients with minimal residual disease: 36% enzalutamide 74% enzalutamide + dutasteride + ADT Proportion of lymph node involvement: 4% enzalutamide 26% enzalutamide + dutasteride + ADT	NR	NR
	Hahn (2024) [25] NCT03412396	Overall incidence of adverse pathologic features: 40% (primary endpoint not met) pT3a: 33% (13/40), pT3b: 7.5% (3/40), N+: 2.5% (1/40), PSM: 7.5% (3/40) Median tumor volume: 0.79 ml (IQR: 0.46–1.32) Rate of BCR (at 36 mo): 21% (6/29) PSA response rate: ≥50% reduction: 100% ≥90% reduction: 70%	NR	NR
Combined with primary prostate radiotherapy	Kaplan (2021) [16] NCT02028988	PSA response rate (≤0.2 ng/ml): 79% (49/62) PSA nadir (<0.1 or <0.03 ng/ml): 61% (38/62) PSA nadir (0.2 and 0.5 ng/ml): 18% (11/62) PSA nadir (>0.5 ng/ml): 3% (2/62)	No significant difference in body fat composition (baseline vs end of treatment)	NR

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Table 3 (*continued*)

Disease setting	Author (year) Study	Oncologic efficacy	Metabolic toxicity	Quality of life
	Lara (2022) [17] ENZART	PSA response rate (≥80% reduction): 100% (56/56) PSA response rate (<0.2 ng/ml): 100% (50/50) Undetectable PSA (<0.1 ng/ml): 92% (44/50) Mean post-treatment PSA levels: 0.04 ng/ml (±0.04) PSA levels remained low 6 mo after cessation of enzalutamide	1. Body weight, bone mineral density: no significant difference (based on densitometry and alkaline phosphatase levels) 2. Fasting glucose: no significant difference 3. Cholesterol, triglyceride levels: no significant difference 4. HDL cholesterol level: modest increase	1. Functioning/symptom domains: significant impairment, recovering 1 mo after treatment cessation 2. Hormonal-related symptoms: significant impairment, not recovering after treatment cessation 3. Sexual activity: no meaningful deterioration
Biochemical recurrence after curative treatment	Aggarwal (2022) [26] ARN-509-002	PSA response rates (nadir <0.2 ng/ml) at 7 mo: Apalutamide + ADT: 97% (28/29) Apalutamide: 89% (24/27) ADT: 89% (23/26; no *p* value provided) PSA progression rate (after treatment cessation): Apalutamide + ADT: 39% (12/31) Apalutamide: 48% (14/29) ADT: 40% (12/30; no *p* value provided) Time to PSA progression (median): Apalutamide + ADT: 36.1 mo Apalutamide: 25.8 mo ADT: 30.9 mo Apalutamide + ADT vs ADT: HR: 0.56, 95% CI: 0.23–1.36, $p = 0.2$ Apalutamide vs ADT: HR: 1.09, 95% CI: 0.49–2.43, $p = 0.8$ Apalutamide + ADT vs apalutamide: HR: 0.40, 95% CI: 0.17–0.98, $p = 0.038$	No relevant changes in bone mineral density at 12 mo in the study arms	No clinically relevant change in any of FACT-P, EORTC QLQ-C30, EORTC QLQ-PR25, or SHIM domains
	Autio (2021) [27,36] NCT01751451	Rate of patients with undetectable PSA with testosterone recovery at 18 mo: Abiraterone: 5.1% (95% CI: 1–17%) Abiraterone + ADT: 17% (95% CI: 7–32%) ADT: 12% (95% CI: 4–26%). Abiraterone vs ADT ($p = 0.9$) Rate of patients with undetectable PSA at 8 mo: Abiraterone: 84% Abiraterone + ADT: 88% ADT: 67% Abiraterone vs ADT ($p = 0.12$) Median time to PSA progression (among patients with testosterone recovery at 18 mo): Abiraterone: 37.5 wk (95% CI: 36.3–44) Abiraterone + ADT: 64.4 wk (95% CI: 57.9–NA) ADT: 54.9 wk (95% CI: 47.9–60.7)	NR	1. Hot flushes: more severe with abiraterone + ADT vs abiraterone ($p < 0.05$) 2. Fatigue: similar severity between treatment arms 3. Overall QoL scores were high and similar with abiraterone + ADT vs abiraterone

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Table 3 (*continued*)

Disease setting	Author (year) Study	Oncologic efficacy	Metabolic toxicity	Quality of life
	Tran (2023) [29] SALV-ENZA	PSA PFS: Enzalutamide + RT vs RT: HR: 0.42, 95% CI: 0.19–0.92, $p = 0.031$ 2-yr PSA-PFS: Enzalutamide + RT: 84% vs RT alone: 66% ($p = 0.027$) Subgroups with benefit of adding enzalutamide to salvage RT: pT3 (HR: 0.22, 95% CI: 0.07–0.69) vs pT2 (HR: 1.54, 95% CI: 0.43–5.47; P interaction = 0.019) R1 (HR: 0.14, 95% CI: 0.03–0.64) vs R0 (HR: 1.00, 95% CI: 0.36–2.76; P interaction = 0.023)	NR	NR
	Freedland (2023) [7,35] EMBARK	MFS: Enzalutamide + ADT vs ADT: HR: 0.42 (95% CI: 0.30–0.61, $p < 0.001$) Enzalutamide vs ADT: HR: 0.63 (95% CI: 0.46–0.87; $p = 0.005$) 5-year MFS rate: Enzalutamide + ADT: 87% (95% CI: 83–91) Enzalutamide: 80% (95% CI: 75–84) ADT: 71% (95% CI: 66–76) 5-yr PSA PFS rate: Enzalutamide + ADT: 97% (95% CI: 95–99) Enzalutamide: 89% (95% CI: 85–92) ADT: 70% (95% CI: 64–75) PSA PFS: Enzalutamide + ADT vs ADT: HR: 0.07 (95% CI: 0.03–0.14; $p < 0.001$) Enzalutamide vs ADT: HR: 0.33 (95% CI: 0.23–0.49; $p < 0.001$) 5-yr antineoplastic therapy–free rate: Enzalutamide + ADT: 83% (95% CI: 78–87) Enzalutamide: 76% (95% CI: 71–80) ADT: 62% (95% CI: 56–67) Time to first use of new antineoplastic therapy: Enzalutamide + ADT vs ADT: HR: 0.36 (95% CI: 0.26–0.49; $p < 0.001$) Enzalutamide vs ADT: HR: 0.54 (95% CI: 0.41–0.71; $p < 0.001$) 5-yr OS rate: Enzalutamide + ADT: 92% (95% CI: 89–95) Enzalutamide: 90% (95% CI: 86–92) ADT: 87% (95% CI: 83–90) OS: Enzalutamide + ADT vs ADT: HR: 0.59 (95% CI: 0.38–0.91; $p = 0.02$; interim efficacy boundary, $p \leq 0.0001$) Enzalutamide vs ADT: HR: 0.78 (95% CI: 0.52–1.17; $p = 0.2$)	NR	1. Patient-reported outcome scores: relatively stable longitudinally, without clinically meaningful differences between treatment arms in general 2. Treatment suspension: higher proportion with enzalutamide + ADT (91%) and enzalutamide (86%) vs ADT (68%) 3. Median duration of treatment suspension: shortest for enzalutamide (11.1 mo, 95% CI: 2.3–84.9). Enzalutamide + ADT (20.2 mo, 95% CI: 5.7–87.9), ADT (16.8 mo, 95% CI: 3.4–83) 4. Worst pain/functional status: similar median TTFD and TTCD, with no clinically meaningful longitudinal changes from baseline 5. Physical well-being: worse with both enzalutamide + ADT (median TTCD: 24.8 mo, HR: 1.41, 95% CI: 1.15–1.72) and enzalutamide (median TTCD: 27.6 mo, HR: 1.35, 95% CI: 1.11–1.65), compared with ADT (median TTCD: 49.8 mo) 6. Hormonal treatment–related symptoms: similar median TTCD with enzalutamide and ADT (HR: 1.06, 95% CI: 0.90–1.25), but worse for enzalutamide + ADT (HR: 1.19, 95% CI: 1.01–1.4) 7. Sexual activity: longer median TTCD (HR: 0.76, 95% CI: 0.62–0.94) with enzalutamide (5.55 mo) vs ADT (2.99 mo) 8. Sexual functioning: shorter (although not significantly) median TTCD (HR: 1.47, 95% CI: 0.86–2.49) with enzalutamide (44.19 mo) vs ADT (47.11 mo) 9. Sexual-activity: more favorable LSM change scores from baseline with enzalutamide (−6.85, 95% CI: −8.63 to −5.07) compared with ADT (−12.9, 95% CI: −14.8 to −11.2) 10. Urinary symptoms: better TTFD (HR: 0.83, 95% CI: 0.70–0.99) with enzalutamide (8.34 mo) vs ADT (5.62 mo)

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Table 3 (*continued*)

Disease setting	Author (year) Study	Oncologic efficacy	Metabolic toxicity	Quality of life
	Madan (2021) [31] NCT01875250	PSA growth rate after 7 mo: 0.031 enzalutamide vs 0.03 enzalutamide + PROSTVAC (p = 0.7; primary endpoint not met) Median PSA reduction: >99% (range: 84–99%) Median time to first PSA rise after treatment cessation: 28 d (range: 14–182 d) Median time to PSA recovery to baseline: 224 d (range: 84–1246 d)	NR	NR
Metastatic castration-resistant prostate cancer	Ohlmann (2022) [34] SPARE	rPFS rate at 12 mo: Abiraterone 89% (95% CI: 64–97) Abiraterone + ADT: 84% (95% CI: 63–94, p = 0.6) PSA response rate (≥50% reduction): Abiraterone: 74% (25/34) Abiraterone + ADT: 65% (22/34 patients) PSA progression rate at 12 mo: Abiraterone: 49% (95% CI: 29–66%) Abiraterone + ADT 49% (95% CI: 25–66%, p = 0.4) Objective response at 12 mo: Complete response: abiraterone 20% (3/15) vs abiraterone + ADT 20% (4/20) Partial response: abiraterone 20% (3/15) vs abiraterone + ADT 20% (4/20)	NR	NR

ADT = androgen deprivation therapy; AMS = Aging Male Symptoms (score); AS = active surveillance; BCR = biochemical recurrence; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC-QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer 25; EQ-5D-5L = EuroQol 5-Dimension 5-Level (Health Questionnaire); EQ VAS = EuroQol Visual Analog Scale; FACT-P = Functional Assessment of Cancer Therapy—Prostate; HDL = high-density lipoprotein; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; HR = hazard ratio; IQR = interquartile range; LDL = low-density lipoprotein; QoL = quality of life; LSM = least squares mean; MFS = metastasis-free survival; NA = not applicable; NR = not reported; OR = odds ratio; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; PSM = positive surgical margin; rPFS = radiographic progression-free survival; SE = standard error; SHIM = Sexual Health Inventory for Men; TTCD = time to confirmed deterioration; TTFD = time to first clinically meaningful deterioration.

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ARPI + ADT, and ADT, no clinically relevant differences were noted [26,36].

Two studies allowed for the evaluation of QoL with long-term (≥1 yr) ARPI monotherapy [21,22,35]. Tombal et al [22] reported generally maintained global health status at 3 yr of enzalutamide treatment, although meaningful worsening of fatigue, dyspnea, constipation, diarrhea, treatment-related symptoms, sexual activity, and function was observed. Similarly, in the EMBARK trial, enzalutamide monotherapy was associated with relatively stable QoL outcomes longitudinally, without clinically meaningful differences between treatment arms in general [35]. Nonetheless, the time to confirmed deterioration (TTCD) in terms of physical well-being was shorter with both enzalutamide + ADT (HR: 1.41, 95% CI: 1.15–1.72) and enzalutamide (HR: 1.35, 95% CI: 1.11–1.65) than with ADT [35]. However, the TTCD of hormonal treatment-related symptoms was comparable between enzalutamide and ADT (HR: 1.06, 95% CI: 0.90–1.25), but not between enzalutamide + ADT and ADT (HR: 1.19; 95% CI, 1.01–1.40) [35]. In terms of sexual QoL, enzalutamide demonstrated a longer TTCD for sexual activity (HR: 0.76, 95% CI: 0.62–0.94) but a shorter (although not significantly) TTCD for sexual functioning (HR: 1.47, 95%-CI: 0.86–2.49) than ADT [35].

3.5. RoB assessment

We identified a moderate overall RoB in the majority of the included studies (Supplementary Fig. 1 and 2), mainly due to a bias in the measurement and reporting of the AEs.

4. Discussion

We present the first systematic review and meta-analysis on the safety, oncologic efficacy, and QoL outcomes of ARPI monotherapy in PCa, with several notable and clinically relevant findings. First, these analyses suggest that ARPI monotherapy has a similar incidence of AEs to ARPI + ADT. Second, a higher incidence of grade ≥3 AEs was observed with ARPIs than with ADT alone, potentially attributable to severe fatigue and ischemic heart disease. In line with this, we found that long-term use of ARPIs leads to impairments in QoL domains related to fatigue, while offering a more favorable sexual QoL. Fourth, ARPI monotherapy exhibits a distinct AE profile, with a lower incidence of hot flashes and a higher incidence of breast-related AEs, compared with both ARPI + ADT and ADT alone. Finally, in terms of oncologic efficacy, ARPI monotherapy outperformed ADT monotherapy but did not surpass ARPI + ADT in the BCR setting.

Our findings suggest that ARPI monotherapy and ADT-based regimens have comparable toxicity; however, the higher incidence of grade ≥3 AEs with ARPIs than with ADT calls for precaution. While the addition of an ARPI to ADT is known to increase cardiovascular toxicity and fatigue further, long-term toxicity data on ARPI monotherapy are scarce [3,37]. We found that metabolic syndrome–related domains were either not impaired or only moderately impaired during long-course ARPI treatment, suggesting a more favorable cardiovascular toxicity profile of these agents. In contrast, no difference in terms of hypertonia or hyperglycemia was observed between ARPIs and ARPI + ADT; moreover, we found ischemic heart disease as a potential contributor to the higher rate of grade ≥3 AEs with ARPIs alone as compared with ADT. This suggests that ARPIs are the main drivers of cardiovascular toxicity, although these findings are limited by the lack of granular data and small sample size, and should therefore be interpreted as hypothesis generating. Therefore, large-scale observational investigations assessing the cardiovascular safety of ARPI monotherapy are being warranted in the future [38,39]. Additionally, the higher incidence of severe fatigue and more pronounced impairment in fatigue-related QoL with ARPI monotherapy than with ADT makes treatment de-escalation to ARPI monotherapy questionable [40].

We found that ARPI monotherapy exhibits a distinct AE profile compared with ADT-based treatments. Moreover, similarly to the combinations of ARPIs with ADT, AE profiles of different ARPI monotherapies were comparable in our analyses [41]. Hot flashes represent a common symptom for PCa patients treated with ADT, which can be mitigated by hormonal manipulation with medroxyprogesterone, estradiol, or estetrol, although at the cost of additional breast-related toxicity [42–45]. Based on our findings, ARPI monotherapy represents a viable option for patients experiencing bothersome hot flashes. At the same time, similar to estrogen derivatives, it leads to a higher incidence of gynecomastia and breast pain, impairing QoL. While tamoxifen and prophylactic breast irradiation have shown significant efficacy in the treatment of bicalutamide-induced gynecomastia, future studies assessing their utility during ARPI treatment are warranted [46–49].

Our findings strengthen the cumulative evidence suggesting a reasonable tradeoff between oncologic efficacy and QoL of ARPI monotherapy in various stages of PCa. In patients with high-risk BCR, ARPIs demonstrated deep and sustained PSA responses; moreover, MFS data from the EMBARK trial provided level 1 evidence for the use of enzalutamide in this context [1]. Similarly, ARPI monotherapy demonstrated promising antitumor activity in combination with primary RT, albeit longer follow-up and comparative studies are warranted in the future. In general, treatment outcomes with ARPIs were comparable with or superior to that of ADT, although not surpassing the efficacy of ARPI + ADT. While changes in overall QoL and most specific domains were similar between the different treatments, ARPI monotherapy was associated with the most favorable (although still meaningful) deterioration in sexual QoL. Notably, pharmacodynamics and kinetics of ARPI monotherapy yields more prompt hormonal changes and subsequent effects, leading to faster resolution of QoL deterioration after treatment cessation, which might explain the higher rate of treatment reduction with ARPIs than with ARPI + ADT. Balancing between tolerability, QoL, and oncologic efficacy via short-course or intermittent treatment strategies allows for patient-tailored use of these compounds, however, at the cost of less prolonged treatment effects. Overall, compared with ADT-based regimens, ARPI monotherapy offers improved sexual QoL and a more favorable toxicity profile in terms of hot flushes, however, at the cost of breast-related toxicity, and additionally a higher incidence of grade ≥3 AEs and an elevated cardiovascular risk as compared with ADT alone. These factors should be weighed carefully when discussing treatment options with patients, taking into account their individual needs and preferences.

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In contrast, we found limited or no benefit of ARPI monotherapy during AS, as neoadjuvant treatment, and in mCRPC patients. The oncologic efficacy of enzalutamide during AS was less pronounced 1 yr after treatment cessation, making its utility questionable in this setting [33]. Furthermore, the added toxicity of hormonal treatment presents a challenging tradeoff, particularly for a patient group, where preserving QoL and sexual function is a key driver of clinical decision-making [50]. Finally, although we found de-escalation of ARPI + ADT combination to ARPI monotherapy as a feasible treatment option in the mCRPC stage, the less pronounced benefits in terms of costs, safety, and unclear effect on QoL compared with omitting ARPIs may limit its future utility [40,51].

There are several limitations to this research: a relatively low number of studies were allowed for comparisons, and accordingly heterogeneity, subgroup evaluation, and publication bias assessment were limited. Moreover, owing to the large number of statistical tests performed, false significant results can be present among the analyses; however, the smaller the *p* value, the lower the likelihood that the finding is false positive. As a result of these, subgroup analyses should be interpreted as hypothesis generating. Most studies assessed enzalutamide monotherapy, limiting the wide-scale generalizability of these results. Except for EMBARK and ENACT, sample sizes were relatively low for other studies. A bias arising from the heterogeneity of the definition, detection, and reporting of AEs could not be excluded. In line with this, pooling of AEs and TEAEs together might introduce a reporting bias, although the sensitivity analysis did not show any difference between the two definitions, supporting the robustness of the analyses. Moreover, different therapeutic approaches may have varying impacts on AEs and QoL across different disease settings. Notably, baseline QoL can influence how treatment-related QoL is affected, underscoring the need for more detailed analyses in future studies. Finally, data synthesis of oncologic efficacy and QoL was limited to a qualitative analysis, with most studies using insufficient intermediate clinical outcomes [52].

5. Conclusions

ARPI monotherapy results in overall similar toxicities to ARPI + ADT combination therapy and ADT monotherapy, while also demonstrating significant oncologic efficacy in patients with BCR. The distinct AE and QoL patterns of each combination can serve as a basis to patient-tailored PCa treatment.

***Author contributions*:** Tamás Fazekas, Marcin Miszczyk, and Pawel Rajwa had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fazekas, Miszczyk, Kói, Gandaglia, Nyirády, Shariat, Rajwa.
Acquisition of data: Fazekas, Miszczyk, Giesen, Kói, Matsukawa, Zattoni, Rodriguez-Sanchez, Rajwa.
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***Data sharing statement*:** The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis. The statistical codes used in the analyses are available upon request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2025.05.006.

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