Apalutamide-induced prostate-specific antigen response and its association with clinical outcomes in metastatic castration sensitive prostate cancer (Review)

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Abstract. Prostate-specific antigen (PSA) kinetics in metastatic castration-sensitive prostate cancer (mCSPC) have been evaluated as prognostic markers in relation to clinical outcomes under apalutamide plus androgen deprivation therapy (ADT). A literature search was conducted via PubMed, Scopus and Google Scholar. Randomized controlled trials, post hoc analyses, and real-world and retrospective cohort studies were included. Early and deep PSA responses (for example, PSA50, PSA90, PSA ≤0.2 ng/ml, ultralow PSA) were found to be induced more frequently and more rapidly when apalutamide + ADT were used. Such PSA responses at 3-6 months were correlated with prolonged radiographic progression-free survival, overall survival, and delayed progression to castration-resistant prostate cancer (CRPC). Comparative analyses demonstrated that PSA90 or ultralow PSA thresholds were reached sooner and in more patients with apalutamide than with abiraterone or enzalutamide, resulting in lower mortality at 24 months in real-world data. It is concluded that rapid, deep PSA suppression under apalutamide + ADT is associated with improved clinical outcomes in mCSPC. PSA response metrics are proposed to be considered as early surrogate endpoints for guiding treatment decisions but are recommended to be used in conjunction with imaging and clinical assessment.

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Key words: apalutamide, castration-sensitive prostate cancer, prostate-specific antigen response, deep prostate-specific antigen suppression, prognostic biomarkers

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1. Introduction

Prostate cancer (PC) is the second most common cancer diagnosed in men worldwide, with nearly 1.4 million new cases reported in 2022 (1). National Cancer Registry Program in India found that PC ranks second among men over 65 years of age and third among all cancers (2). Metastatic castration-sensitive PC (mCSPC) may be either a *de novo* condition or as a recurrence following local treatment for PC that has spread locally. Prostate-specific antigen (PSA) is a biomarker used for prognosis and to determine oncological outcomes in patients with PC. A decline in PSA is a well-established indicator of disease control in both early and advanced stages of PC (3). Combining androgen deprivation therapy (ADT) with androgen receptor (AR) signaling inhibitors (ARSIs) has been shown to significantly improve oncological outcomes in patients and influence PSA dynamics with mCSPC. In the last several years, there have been significant advancements in the management of mCSPC, with studies showing that when compared with ADT alone, new ARSIs significantly improve overall survival (OS) (4). A total of four hormonal therapies

including abiraterone, apalutamide, darolutamide and enzalutamide have been given approval for management of mCSPC when paired along with ADT.

According to 2025 National Comprehensive Cancer Network guidelines, apalutamide, darolutamide, enzalutamide or abiraterone is recommended along with ADT for low and high volume synchronous and metachronous metastases CSPC (5). Similarly, the American Urology Association guidelines strongly recommend that 'for patients with mCSPC, ADT should be offered by clinicians in combination with either androgen pathway-directed therapy (abiraterone, apalutamide, enzalutamide) or chemotherapy (docetaxel) (6). Japanese guidelines also align on combining ADT with ARSIs (abiraterone, apalutamide, enzalutamide, or darolutamide) in mCSPC, favoring them over chemotherapy for their superior efficacy and safety profile (7). The 2025 Canadian guidelines recommend combining ADT with ARSIs (abiraterone, apalutamide, enzalutamide, or darolutamide) in mCSPC, with apalutamide recommended regardless of disease volume based on strong evidence of efficacy in both high- and low-volume settings (8).

The present review focuses on apalutamide because, among the approved ARSIs, it offers a distinct clinical profile and robust evidence of PSA suppression in mCSPC yet remains relatively underexplored in terms of detailed PSA response correlations with long-term outcomes. Through the present review, it was aimed to provide a comprehensive overview of the implications of PSA dynamics in the context of apalutamide therapy.

2. Methodology

The present article is a narrative review that synthesizes evidence on PSA dynamics and clinical outcomes in patients with mCSPC treated with apalutamide plus ADT. A literature search was conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.sciencedirect.com) and Google Scholar (https://scholar.google.com/) from database inception to February 2025 using combinations of the following terms: 'apalutamide', 'metastatic castration-sensitive PC', 'mCSPC', 'PSA response', 'PSA50', 'PSA90', 'PSA ≤0.2 ng/ml', 'ultralow PSA', 'PSA kinetics', and 'real-world'. Randomized controlled trials (RCTs) and post-hoc analyses, as well as observational cohort and real-world database studies were included, that evaluated apalutamide plus ADT in adult patients with mCSPC and quantitative PSA outcomes (for example PSA50, PSA90, PSA ≤0.2 ng/ml or ultralow PSA) and/or clinical endpoints such as radiographic progression-free survival (PFS), OS, or time to castration resistance were reported. Case reports, small series (fewer than ~20 patients), non-English articles, conference abstracts without sufficient numerical data, and studies not reporting PSA outcomes of interest were excluded. Because this was a narrative rather than a formal systematic review, a structured risk-of-bias assessment was not performed; instead, post-hoc analyses of phase III randomized trials and larger multicenter real-world studies were prioritized when summarizing the evidence.

3. PSA decline as a prognostic indicator

PC is accompanied by the release of various biomarkers into the bloodstream, with PSA and PSA-phosphatase (PSAP) being most clinically relevant. These markers are used for screening, monitoring treatment response, and providing diagnostic insight. The free form of PSA is particularly helpful for detecting PC for males whose total PSA levels fall between 4 and 10 μg/l (9). PSA90 response, characterized by a decrease of 90% PSA or more is an early predictor of better or extended rPFS and OS among patients with mCSPC undergoing next-generation ARSI therapy (10). Achieving a PSA50 (≥50% decline in PSA) early in treatment is strongly associated with improved OS in mCSPC. A deep and rapid PSA response, a decline >90% from baseline, improves survival in mCSPC and also positively influences prognosis in subsequent CRPC therapy (11).

Decline in PSA is a powerful prognostic marker in mCSPC. A total of five RCTs were recently the subject of a systematic review and Bayesian meta-analysis. PEACE-1, ARASENS, CHAARTED, LATITUDE and TITAN, including 2,533 patients, demonstrated that deep PSA response following intensified therapy (either doublet or triplet regimens) was achieved in ~49.45% of patients (95% CI: 37.75-61.18). Importantly, patients who achieved a deep PSA response experienced notably superior OS with a pooled hazard ratio (HR) of 0.39 (95% CI: 0.30-0.50) in comparison to individuals who were not affected. These findings, consistent across sensitivity analyses, suggest that early deep PSA decline may serve not only as a surrogate for improved survival but also as a potential biomarker to inform future treatment de-escalation strategies in selected patients with mCSPC (12).

4. Apalutamide

Mechanism of action. Apalutamide is a nonsteroidal AR inhibitor that binds directly to the androgen ligand binding-domain of the AR. This action inhibits AR nuclear translocation, DNA binding and AR-mediated transcription (13) (Fig. 1).

Key clinical trials and real-world evidence with apalutamide. Table I summarizes evidence from randomized clinical trials, post hoc analyses, and real-world studies evaluating PSA response outcomes with apalutamide-based therapy in patients with mCSPC. Comparative real-world analyses further suggest that apalutamide may achieve faster and deeper PSA responses than enzalutamide or abiraterone in mCSPC populations (Table I).

PSA decline with apalutamide and its correlation with clinical outcomes. The combination of apalutamide with ADT has been extensively evaluated for its impact on PSA responses in patients with mCSPC. Clinical trials and retrospective studies have consistently demonstrated that this therapeutic regimen leads to significant reductions in PSA levels, including deep (≥90% decline from baseline) and ultra-low (≤0.02 ng/ml) PSA responses. These findings underscore the efficacy of apalutamide plus ADT in achieving substantial PSA declines in the mCSPC patient population.

PSA kinetics are validated early prognostic biomarkers in mCSPC. In the phase III TITAN trial, treatment with apalutamide plus ADT resulted in higher rates of deep PSA declines, including PSA50, PSA90 and PSA reduction to ≤0.2 ng/ml, compared with ADT alone, supporting PSA decline as a marker of treatment response (24).

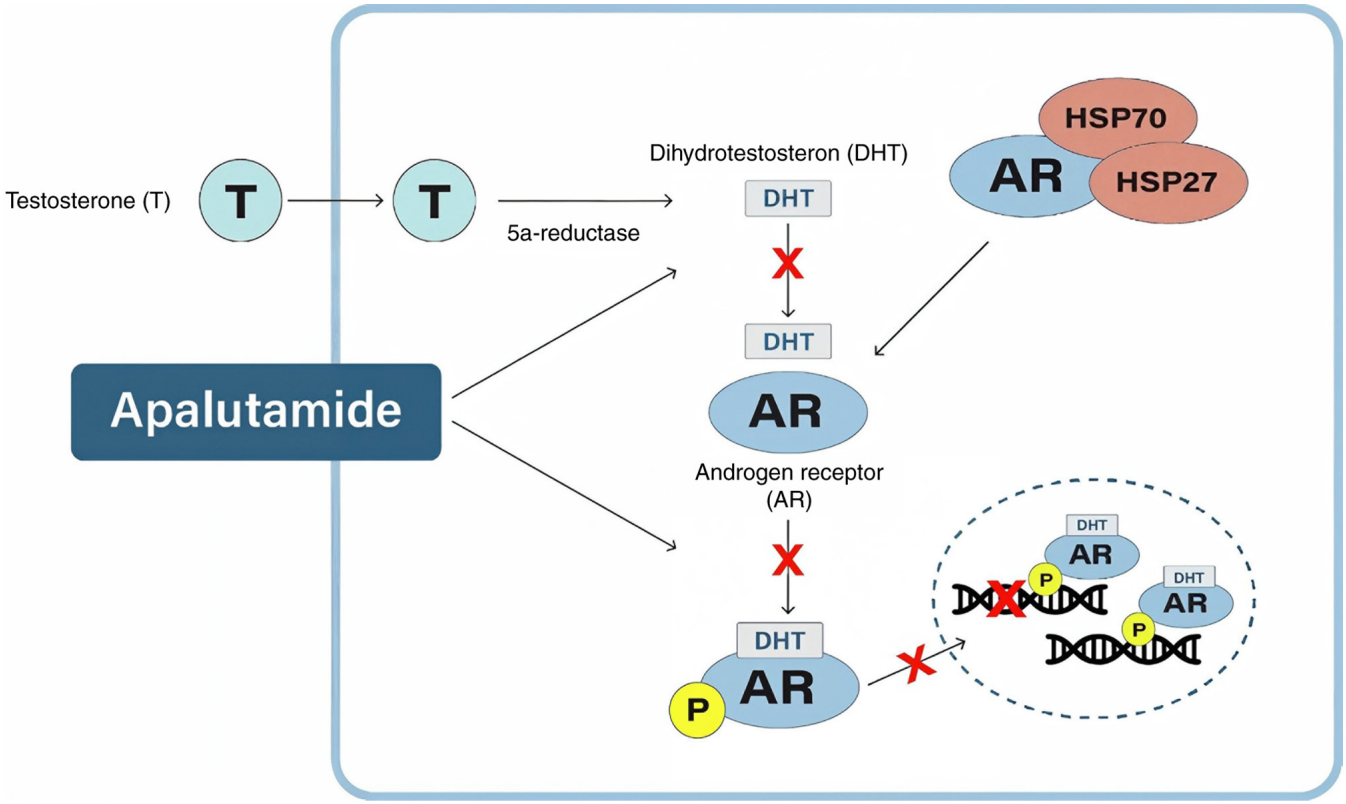

Figure 1. Mechanism of action of apalutamide.

Post-hoc analyses of TITAN further demonstrated that early achievement of PSA90 and lower PSA nadir levels were independently associated with improved OS, radiographic PFS (rPFS), delayed time to castration resistance, and delayed PSA progression, establishing the prognostic value of both depth and timing of PSA decline (15,24). Consistent with randomized trial data, real-world evidence shows that patients with mCSPC treated with apalutamide plus ADT achieve PSA90 more frequently and with a shorter median time to PSA90 compared with other AR pathway inhibitors, reinforcing the clinical utility of PSA kinetics as dynamic prognostic markers in routine practice (10).

Although PSA decline represents a validated early prognostic marker in mCSPC, its clinical relevance is best interpreted alongside radiographic and clinical outcomes. In post hoc analyses of the phase III TITAN trial, deep and early PSA declines with apalutamide plus ADT, including achievement of PSA90 and low PSA nadir levels, were associated with improved rPFS, delayed time to castration resistance, and delayed PSA progression (24).

These analyses further demonstrated that patients achieving early PSA90 or very low PSA nadir experienced superior OS compared with patients without deep PSA declines, supporting a link between PSA kinetics and long term clinical outcomes in mCSPC (15). However, PSA kinetics should be interpreted in conjunction with imaging findings and clinical assessment, particularly in patients with discordant biochemical and radiographic responses. This multimodal approach is especially relevant in low PSA-producing tumors or atypical disease biology, where PSA decline alone may not fully reflect disease burden (25).

In a combined analysis of the TITAN and SPARTAN trials, adding APA to ADT led to a deep and rapid decline in PSA levels at 3 and 6 months, defined as PSA ≤0.2 ng/ml or ≥90% reduction from baseline. Patients who attained this early PSA response had a longer time to worsening of patient-reported outcomes, including physical well-being, overall HRQoL, pain and fatigue. These benefits highlight the value of early and deep PSA decline with apalutamide (16).

In a real-world study, 94.4% of patients with mCSPC treated with ADT achieved a PSA50 response. These patients had significantly longer OS compared with those who did not achieve PSA50 (56.0 vs. 14.8 months; P<0.001). Additionally, 47.9% of patients achieved a deep and rapid PSA response (PSA50 in 4 months), which correlated with longer median OS (101.0 vs. 41.9 months) and PFS (23.4 vs. 11.0 months) compared with those without PSA >50% reduction within 4 months (P<0.001).

In a retrospective multicenter study by Lopez-Abad *et al* (17) involving 193 patients with mCSPC treated with ADT plus apalutamide, patients with PSA ≤0.2 ng/ml had significantly improved OS (98.7% vs. 65.3%) and rPFS (97.4% vs. 53.7%) than those with PSA >0.2 ng/ml, at 18 months, suggesting PSA suppression as a strong prognostic marker (17).

In another analysis by the same author, 58.2% achieved PSA <0.02 ng/ml, 20.6% for PSA 0.02 and 0.2 ng/ml and 21.2% of PSA levels >0.2 ng/ml. Most patients reached PSA <0.02 ng/ml within 6 months. 18-month OS in patients with mCSPC was 100% for the ultralow PSA group (<0.02 ng/ml), 94.4% for PSA 0.02-0.2 ng/ml, and 67.7% for PSA >0.2 ng/ml. Similarly, rPFS at 18 months was 100, 93.5 and 50.7%, respectively. Cox regression confirmed ultralow PSA as a strong predictor of OS

Table I. Summary of clinical trial and real-world evidence on PSA90 and deep PSA responses with apalutamide in mCSPC.

First author/s, year	Study type	Population/N	Treatment	PSA90 Response	PSA ≤0.2 ng/ml Response	Timepoint	Key clinical outcomes	(Refs.)
Chi *et al*, 2019	Clinical Trial (Phase III RCT)	1052 (APA + ADT-525; Placebo + ADT-527)	APA 240 mg or placebo (1:1), orally once daily, in addition to continuous ADT.	-	68.4% vs. 28.7%	Median follow up 22.7 months	Improved OS (HR 0.67), improved rPFS, delayed PSA progression and CRPC progression	(14)
Chowdhury *et al*, 2023	Clinical Trial (Post Hoc TITAN)	mCSPC; n=525 vs. 527	Apalutamide + ADT vs. Placebo + ADT	PSA90 achieved in 73% vs. 29%	PSA ≤0.2 ng/ml in 68% vs. 32%	44 months	Deep PSA decline associated with superior OS, rPFS, delayed PSA progression and delayed CRPC	(15)
Merseburger *et al*, 2023	Clinical Trial (Post Hoc TITAN)	mCSPC; n=525 vs. 527	Apalutamide + ADT vs. Placebo + ADT	-	UL1: 38% vs. 15%; UL2: 23% vs. 5%	3 months	UL PSA responses associated with improved OS, rPFS and delayed CRPC	(16)
Lopez-Abad *et al*, 2024	Real-World Study	mCSPC; n=193	Apalutamide + ADT	88%	82.4%	12 months	OS: 98.7% vs. 65.3%; rPFS: 97.4% vs. 53.7% in PSA ≤0.2 group	(17)
Tohi *et al*, 2024	Real-World Study	mCSPC; n=108	Apalutamide + ADT	84.3%	65.7%	16 months	PSA ≤0.2 ng/ml associated with significantly longer time to CRPC	(18)
Santoni *et al*, 2024	Real-World Study	mCSPC; n=531	Apalutamide + ADT	87%	69%	18 months	2-year OS: 93% vs. 70% for PSA90 achievers; 95% vs. 80% for PSA ≤0.2 achievers	(19)
Encarnación Navarro *et al*, 2025	Real-World Study	mCSPC; n=432	Apalutamide + ADT	88.2%	81.7%	12 months	rPFS: 95.1% vs. 62% in PSA ≤0.2 ng/ml responders	(20)
Lopez-Abad *et al*, 2024	Real-World Study	mCSPC; n=193	Apalutamide + ADT	-	PSA <0.02 ng/ml: 58.2%	6 months	18-month OS: 100% vs. 67.7%; rPFS: 100% vs. 50.7%	(21)
Lowentritt *et al*, 2023	Comparative Real-World Study	mCSPC	Apalutamide vs. Enzalutamide	72.3% vs. 61.6%	81% vs. 63%	12 months	Faster median time to PSA90 with apalutamide (3.1 vs. 5.2 months)	(22)
	Comparative Real-World Study	mCSPC	Apalutamide vs. Abiraterone	72.3% vs. 54.7%	81% vs. 58%	12 months	Greater probability and earlier achievement of PSA90 with apalutamide	
Maughan *et al*, 2024	Comparative Real-World Study	mCSPC	Apalutamide vs. Enzalutamide vs. Abiraterone	66% vs. 61% vs. 57%	74% vs. 61% vs. 58%	12 months	Lower progression to CRPC and improved OS with apalutamide	(23)

ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; PSA90, ≥90% decline in PSA from baseline; rPFS, radiographic progression-free survival; UL, ultra-low PSA; PSA, prostate-specific antigen.

(HR=8.256) and rPFS (HR=0.085), reinforcing the prognostic significance of deep PSA suppression (21). PSA <0.2 ng/ml and a full initial dose of apalutamide were significantly associated with a longer time to CRPC according to Tohi *et al* (18). Median OS was significantly longer for patients with PSA90 response or PSA <0.2 ng/ml than for subjects lacking these responses in ARON 3 study (19).

PSA response metrics have been proposed as early indicators of treatment activity in mCSPC, as changes in PSA often precede radiographic or clinical progression (26,27). However, PSA responses do not consistently reflect disease burden or progression at the individual-patient level. Discordance between biochemical response and radiographic progression has been well described, particularly under modern systemic therapies (27-29). Therefore, current evidence and expert opinion support interpreting PSA kinetics in conjunction with serial imaging and clinical evaluation, rather than relying on PSA alone as a surrogate endpoint to guide treatment decisions (30,31).

Comparing PSA response and clinical outcomes with apalutamide vs. enzalutamide and abiraterone. For numerous years, ADT was the sole systemic treatment for mCSPC. However, clinicians now have access to several life-prolonging therapies that can be used alongside ADT, including docetaxel, abiraterone acetate, enzalutamide, apalutamide and darolutamide. All these offer significant survival benefits compared with ADT alone. A retrospective observational cohort study using real-world data comparing apalutamide and abiraterone acetate in patients with mCSPC found that by 6 months, patients were 53% more likely to achieve PSA (PSA90) reduction of ≥90% compared with those on abiraterone acetate (P=0.016). At 9, and 12 months, similar findings have been noted (P<0.019). For the apalutamide group, the median time to reach PSA90 was 3.5 months. In contrast to the abiraterone acetate group, where the median was not achieved (32).

A real-world study comparing apalutamide and enzalutamide found that by the sixth month, patients starting apalutamide received a 56% greater probability of achieving a ≥90% decrease in PSA in contrast to those starting enzalutamide (P=0.014). For apalutamide, the median duration to reach PSA90 was 3.1 months, while for enzalutamide, it was 5.2 months. Apalutamide was associated with greater probability of obtaining deep PSA responses and these responses occurred earlier than with enzalutamide (10). Apalutamide and abiraterone acetate were compared in a real-world trial conducted in 2025 by Lowentritt *et al* (33) in ARSI-naïve patients with mCSPC. Utilizing linked clinical and claims data from U.S. community urology practices, the study included 1,879 patients on apalutamide and 2,073 on abiraterone. At 24 months, the apalutamide group exhibited a 26% decreased risk of mortality (HR: 0.74; 95% CI: 0.59-0.93; P=0.010), a benefit that persisted with extended follow-up (HR: 0.72; 95% CI: 0.59-0.88; P<0.001). The percentage of patients for the various PSA levels, for apalutamide vs. abiraterone acetate respectively, were 15.3% vs. 14.4% (≤0.2 ng/ml), 15.2% vs. 14.3% (>0.2 to ≤2 ng/ml) and 9.9% vs. 9.3% (>2 to <5 ng/ml) in the adjusted weighted population. These results suggest that in real-world situations apalutamide may provide greater survival benefits than abiraterone (33). The comparative PSA response between apalutamide and darolutamide when used alongside ADT in real-world settings has not yet been investigated.

Real-world studies comparing apalutamide with enzalutamide or abiraterone used weighting or propensity-score methods to balance observable characteristics and consistently reported a higher likelihood and shorter median time to PSA90 with apalutamide overall (34). However, these analyses did not provide harmonized, drug-to-drug PSA90 data stratified by standard high-vs. low-volume definitions, therefore it remains uncertain whether the magnitude of apalutamide's advantage compared with enzalutamide or abiraterone is identical across all metastatic-burden subgroups. Within apalutamide-treated populations, post-hoc TITAN analyses and real-world multicenter series show that deep and ultralow PSA responses occur in both high- and low-volume mCSPC, suggesting that apalutamide is active across the spectrum of metastatic burden even though formal volume-stratified comparative data vs. other ARSIs are still limited (10,21,35).

PSA response and clinical outcomes across apalutamide, enzalutamide and abiraterone are compared in Fig. 2. A greater PSA90 response was associated with Apalutamide. Median time to PSA90 was shortest with apalutamide as compared with enzalutamide and abiraterone.

Recent research on lipid and carbon metabolism has also clarified how metabolic reprogramming contributes to hormone therapy resistance and disease progression in PC. Gao *et al* (36) demonstrated that acetate utilization via acyl-CoA synthetase short-chain family member 2 promotes neuroendocrine differentiation and castration-resistant growth, and that targeting this pathway can resensitize models to androgen-directed therapy. In parallel, Wenes *et al* (37) showed that mitochondrial pyruvate carrier activity shapes $CD8^+$ T-cell memory differentiation and antitumor function, highlighting how systemic metabolic cues influence immune control of tumors. These mechanistic insights suggest that PSA dynamics observed with ARSIs such as apalutamide reflect not only androgen-receptor blockade but also broader alterations in tumor and immune cell metabolism, supporting future evaluation of rational combinations of AR-directed and metabolism-targeted therapies in mCSPC. A comparative summary of PSA90 response rates and median time to PSA90 for apalutamide, enzalutamide and abiraterone across available real-world studies is provided in Fig. 2.

In Table II, it is shown that apalutamide achieved faster PSA90 (median 3 months) at 12 months. This was higher than enzalutamide and abiraterone. PSA <0.2 ng/ml at 12 months was also highest with apalutamide, correlating with lower 24-month CRPC rates and better survival outcomes (22,23).

5. Implications for future clinical research

Role of PSA reduction as a surrogate endpoint in CT and monitoring PSA in real-world clinical practice. PSA reduction has emerged as a valuable surrogate endpoint in both clinical trials and real-world practice for patients with advanced PC. Multiple studies have shown that early and deep declines in PSA, particularly PSA50 (≥50% decline), PSA90 (≥90% decline), and PSA levels ≤0.2 ng/ml, are strongly correlated with improved clinical outcomes, including OS, rPFS, time to CRPC, and quality of life. The TITAN and

Table II. PSA response and clinical outcomes with apalutamide, enzalutamide and abiraterone.

Parameters / Arms	Maughan *et al* (2024) (23)		
	Apalutamide (n=315)	Enzalutamide (n=1181)	Abiraterone (n=1760)
Proportion of patients (%) with PSA90 response			
At 3 months	49%	38%	37%
At 12 months	66%	61%	57%
Median time (months) to achieve PSA90 response			
	3 months	4.82 months	4.62 months
Proportion of patients (%) with PSA <0.2 ng/ml			
At 12 months	74%	61%	58%
Clinical Outcomes [proportion (%) of patients]			
Progressed to CR at 24 months	23%	37%	33%
OS rate at 24 months	66%	55%	59%
Lowentritt *et al* (2023) (22)			
Arms	Apalutamide (n=589)	Enzalutamide (n=597)	Abiraterone (n=553)
Proportion of patients (%) with PSA90 response			
At 3 months	48%	35.1%	36.7%
At 12 months	72.3%	61.6%	54.7%
Proportion of patients (%) with PSA <0.2 ng/ml			
At 12 months	81%	63%	58%
Clinical outcomes [proportion (%) of patients]			
Progressed to CR at 24 months	33.5%	38.6%	44.5%
OS rate at 24 months	NA	NA	NA

CR, castration resistance; OS, overall survival; PSA, prostate-specific antigen; PSA90, a ≥90% reduction in PSA levels.

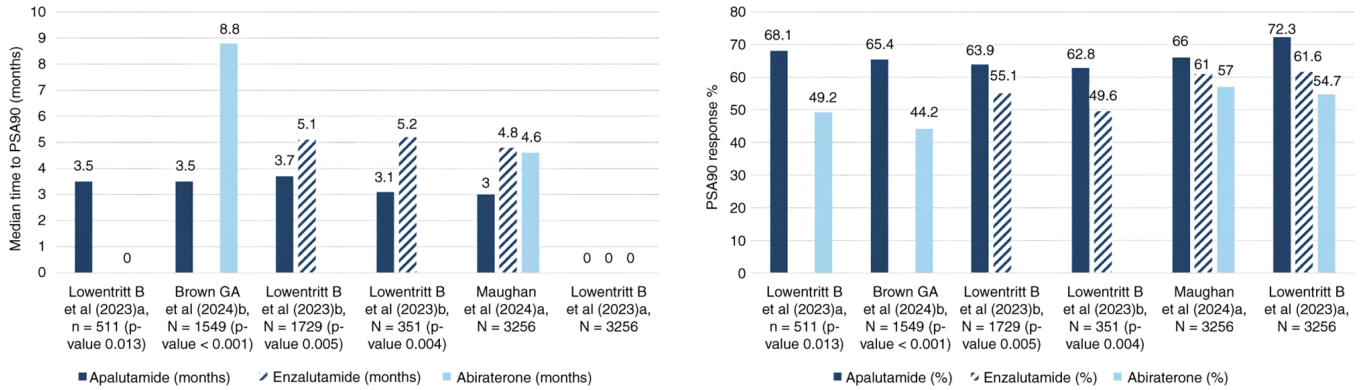

Figure 2. Comparative summary of PSA90 response and median time to PSA90 with apalutamide, enzalutamide and abiraterone in real-world studies. PSA, prostate-specific antigen; AR, androgen receptor; DHT, dihydrotestosterone.

SPARTAN trials demonstrated that patients achieving early PSA90 or PSA ≤0.2 ng/ml had significantly prolonged OS and rPFS. Patients achieving PSA90 or ultra-low PSA levels early in therapy have improved long-term outcomes. PSA dynamics, such as PSA velocity, defined as any decrease in PSA levels over time and PSA50, can inform decisions regarding treatment intensification, de-escalation, or switching to alternative therapies. While PSA reduction is a useful surrogate, it should be interpreted alongside imaging and clinical context, especially in non-secretory variants or atypical disease biology.

Limitations. Overall, the main limitation is that PSA response with ARSIs, while strongly prognostic, is not a fully validated surrogate for individual survival outcomes and can be discordant with radiographic and clinical progression. PSA decline is an imperfect surrogate endpoint in mCSPC. Although early and deep PSA responses with apalutamide plus ADT are consistently associated with improved clinical outcomes, PSA kinetics do not always fully reflect tumor burden or survival benefit, particularly in non-secretory or neuroendocrine variants where radiographic progression may occur despite low or declining PSA levels. Furthermore, the comparative evidence

favoring apalutamide over enzalutamide or abiraterone is indirect and derived primarily from retrospective real-world cohorts rather than head-to-head RCTs. As these studies were conducted across different healthcare settings and time periods, residual confounding from unmeasured factors such as performance status, metastatic burden, visceral involvement, comorbidities and treatment sequencing may have influenced the observed differences in PSA kinetics and clinical outcomes. Therefore, PSA responses should be interpreted as supportive early indicators of treatment activity rather than definitive surrogates for OS, and current comparative findings should be considered hypothesis-generating rather than conclusive evidence of superiority.

Although PSA response is a valuable prognostic biomarker and an early indicator of treatment activity in mCSPC, PSA changes alone should not be considered sufficient grounds for treatment switching in the absence of radiographic or clinical evidence of progression. Treatment decisions should integrate PSA kinetics with imaging findings, clinical assessment, symptom burden, and overall disease status to ensure an accurate evaluation of therapeutic benefit and disease progression.

In addition, while emerging real-world analyses in mCSPC and nmCRPC have begun to compare apalutamide and darolutamide, these data are observational and heterogeneous; they suggest at least comparable, and in some cases more favorable, survival and PSA outcomes with apalutamide, whereas darolutamide may offer advantages in tolerability and treatment persistence in other disease settings.

Recommendations for future studies. Future studies should consider monitoring PSA dynamics as one of the study end points. It could be useful as a predictive biomarker in mCSPC as a key indicator to identify the transition to mCRPC (disease progression). Investigating the predictive utility of early PSA dynamics, in forecasting long-term survival and PFS is essential and requires longitudinal research. The present review is limited by its reliance on retrospective and real-world studies, which may introduce selection bias and lack standardized outcome measures. Additionally, heterogeneity in study designs, endpoints, and follow-up durations limits direct comparison across treatment regimens.

6. Conclusion

Achieving a rapid and deep PSA response is a key prognostic marker in mCSPC. Evidence from retrospective real-world studies consistently demonstrates that apalutamide plus ADT leads to higher proportion of patients achieving PSA responses and faster PSA decline compared with enzalutamide plus ADT or abiraterone acetate plus ADT. Patients achieving PSA90 (≥90% decline) and PSA ≤0.2 ng/ml within the first 6-12 months demonstrated significantly improved rPFS, OS, and delayed progression to CRPC. Additionally, time to PSA suppression correlates with long-term survival benefits, reinforcing its role as an early surrogate endpoint for treatment efficacy. The data supports early PSA monitoring to optimize treatment strategies in mCSPC, with deep PSA suppression emerging as a critical parameter for improved clinical outcomes. Further studies are warranted to refine biomarker-driven treatment approaches.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SN, CMV, AU, AM and SM wrote, reviewed and edited the manuscript. PS, SD, GP and CK wrote the original draft. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

Dr Pankaj Sonone, Shruti Dharmadhikari, Dr Gaurav Puppalwar, Dr Chintan Khandhedia, Dr Amey Mane and Dr Suyog Mehta are employees of Sun Pharma Laboratories Ltd. SN, CMV and AU declare that they have no competing interests.

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