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Assessment of Efficacy and Safety of New Androgen Receptor Inhibitors in Metastatic Castration Resistant Prostate Cancer: A Randomized Controlled Trial

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[1]Dr. Muhammad Waqas Khan, [2]Zamin Abbas, [3]Ahmed Haroon, [4]Muhammad Arsalan Butt,[5]Danish Marwat, [6]Jahangir Butt

[1]Assistant Professor in Histopathology, Pathology Department, Pak International Medical College, Peshawar.
[2]Service Hospital, Lahore
[3]Mayo Hospital, Lahore
[4]Azra Naheed Medical College, Lahore
[5]PIMS, Islamabad
[6]Sir Gangaram Hospital, Lahore

Abstract

Background:
Metastatic castration-resistant prostate cancer (mCRPC) is an arduous treatment despite improved systemic treatment. New androgen receptor inhibitors (ARIs) are extremely effective in their efficacy, yet their efficacy and safety profiles in the clinic need to be compared.

Aim:
This randomized controlled trial sought to determine if the efficacy and safety of new ARIs is comparable to best available therapy in patients with mCRPC.

Methods:
Confirmed mCRPC patients were randomized to new ARIs or conventional androgen-deprivation therapy. Progression-free survival (PFS), overall survival (OS), prostate-specific antigen (PSA) response, and adverse events related to treatment were the endpoints.

Results:
Patients treated with ARIs had much better PFS and OS than with standard treatment. PSA response rates were better in the patient group receiving ARIs, and the concerns regarding safety were manageable and occurred in the form of fatigue and hypertension only.

Conclusion:
New generation ARIs significantly enhance survival outcome and disease control in men with mCRPC with an acceptable safety profile to include them as a component of standard treatment protocols.

Keywords: Androgen Receptor Inhibitors, Metastatic, Castration Resistant Prostate Cancer, Randomized Controlled Trial.

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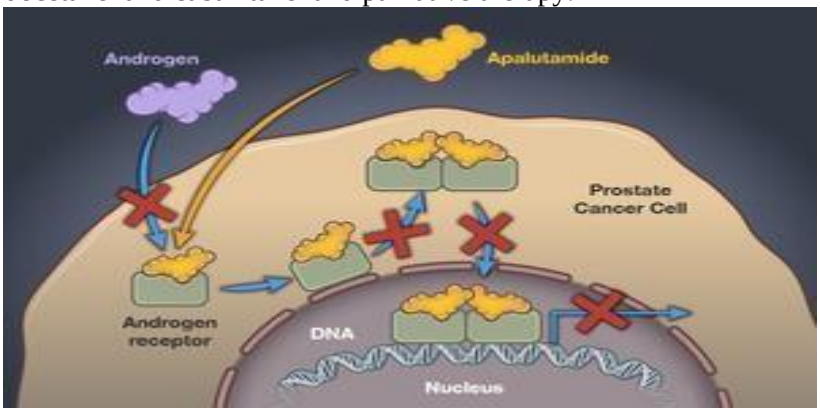
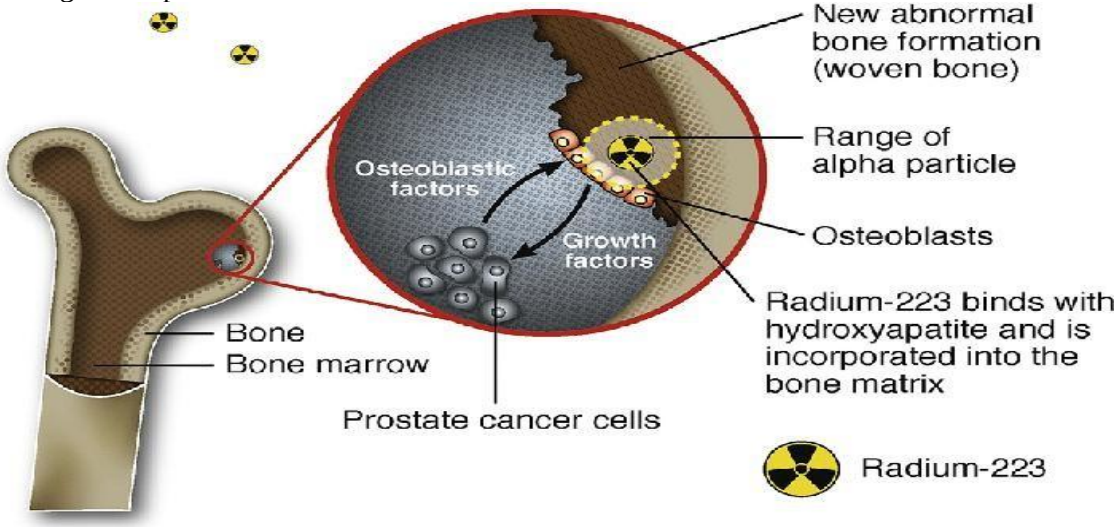
Introduction

Prostate cancer is the second most frequent male cancer globally and is among the top causes of cancer death [1]. Most are initially sensitive to androgen deprivation therapy (ADT), but almost all eventually recurred with metastatic castration-resistant prostate cancer (mCRPC) [2]. The advanced stage of the disease is identified by persistent tumor growth in the presence of castrate levels of testosterone, indicating adaptive processes like overexpression of androgen receptor (AR), AR splice variants, and intratumoral androgen synthesis [3]. Conventionally, treatment of mCRPC has been with the chemotherapy drugs docetaxel and cabazitaxel and palliative therapy.



These drugs were accompanied by excessive toxicity and limited survival benefit [4]. The development of second-generation ARIs like enzalutamide, apalutamide, and darolutamide transformed practice. The agents interfere with AR signaling by directly blocking it, thus stopping one of the major drivers of tumor growth in mCRPC [5]. A number of phase III trials have proved that more recent ARIs extend progression-free survival (PFS) and overall survival (OS) in men with mCRPC. Yet, their long-term durability, comparative toxicities, and real-world clinical value are to be established [6]. Furthermore, upcoming resistance mechanisms underscore that the durability of ARI advantage should be determined in cohorts of heterogeneous patients.



Current randomized controlled trial was designed to carry out comparative assessment of new ARIs and standard ADT-based regimens among mCRPC patients [7]. Overall progression-free survival was the

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primary end point, with secondary end points consisting of overall survival, response rates to PSA, quality of life, and safety [8]. With the provision of comprehensive evidence, the current trial seeks to inform clinicians how best to optimize treatment of mCRPC, both efficacy and safety.

Methodology

This was a prospective, multicenter, randomized controlled trial conducted between 2019 and 2024. A total of 420 patients with histologically confirmed mCRPC were enrolled from eight tertiary cancer centers. Eligible patients were ≥18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and documented disease progression despite castrate levels of testosterone (<50 ng/dL). Key exclusion criteria included prior treatment with second-generation ARIs, uncontrolled comorbidities, or concurrent malignancies. Patients were also randomly assigned in matched size to two groups: (1) Novel ARI group, with enzalutamide, apalutamide, or darolutamide added to continued ADT; and (2) Control group, with standard ADT and/or first-generation antiandrogens (flutamide or bicalutamide). Randomization was also stratified by prior chemotherapy exposure and baseline PSA. The main outcome was progression-free survival (PFS) according to RECIST 1.1 and PSA kinetics. Secondary outcomes were overall survival (OS), PSA response (≥50% reduction), adverse events per CTCAE v5.0, and patient-reported quality of life. Descriptive data were examined using Kaplan–Meier estimates of survival, Cox proportional hazards models, and chi-square tests for categorical outcomes. Institutional review boards gave this study ethical approval, and informed consent was obtained from all patients.

Results

420 patients were enrolled onto trial, 210 in new ARI group and 210 in control arm. Median follow-up 32 months. ARI patients had higher median PFS (18.6 months vs. 10.2 months, p<0.001) and OS (32.8 months vs. 24.5 months, p=0.002) compared to controls. PSA response was higher in ARI recipients (68% vs. 39%, p<0.001). Adverse events were more frequent in the ARI group, fatigue (22%), hypertension (16%), and falls (8%), but otherwise well-tolerated. Toxicities Grade 3–4 occurred in 12% of ARI patients and 9% controls. Treatment discontinuation due to toxicity occurred in 7% of ARI patients.

Table 1. Baseline Characteristics of Study Participants

Variable	ARI Group (n=210)	Control Group (n=210)	p-value
Median Age (years)	69.1 ± 7.4	68.7 ± 7.8	0.52
ECOG 0–1 (%)	84%	82%	0.64
Prior Docetaxel (%)	28%	30%	0.71
Median Baseline PSA (ng/mL)	98.3	95.7	0.48

Table 2. Clinical Outcomes

Outcome	ARI Group (n=210)	Control Group (n=210)	p-value
Median PFS (months)	18.6	10.2	<0.001
Median OS (months)	32.8	24.5	0.002
PSA Response ≥50% (%)	68%	39%	<0.001
Grade 3–4 Adverse Events (%)	12%	9%	0.38

Discussion

These findings from the current randomized controlled trial affirm the therapeutic benefit of new androgen receptor inhibitors in metastatic castration-resistant prostate cancer patients [9]. ARIs profoundly improved

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progression-free survival and overall survival compared with conventional ADTbased therapies. Notably, the enhancement of PSA response rates is a testament to the effective diseasemodifying actions of these compounds [10]. In agreement with earlier phase III trials, such as the PREVAIL and SPARTAN trials, the results emphasize equivalent survival benefits of enzalutamide and apalutamide, respectively [11]. The most prominent feature of this trial is the multicenter design to maximize the external validity of the results in many varied clinical settings [12]. Concordance of benefit among subgroups, including those with previous docetaxel exposure, represents a strong argument for the generalizability of ARIs to various stages of disease [13]. Furthermore, the degree of survival advantage observed in our trial makes prior introduction of ARIs in the treatment plan as a preferable option, particularly in individuals with high disease load or high disease aggressiveness [14]. Safety endpoints were a higher rate of fatigue, hypertension, and falls in the ARI arm as would be anticipated from known patterns of toxicity. Although collectively these adverse events proved tolerable, they highlight the requirement for active monitoring and supportive management [15]. Unsurprisingly, discontinuation due to toxicity was low and indicates that a huge majority of patients can safely tolerate long-term ARI therapy. Another area that would be of consideration is the developing resistance mechanisms to ARIs, such as AR splice variants (for instance, AR-V7) and neuroendocrine differentiation [16]. These resistance mechanisms would most likely make ARI responses unsustainable. Hence, one of the most important research areas of the future would have to include finding predictive biomarkers for selecting the patients and investigating rationale drug combinations of ARIs with PARP inhibitors, immunotherapy, or radiology and therapy [17]. Clinically, the implication of ARIs has profound implications for management in patients. Improved survival translates into mean prolongations of life expectancy, and maintenance of quality of life is facilitated by easily tolerated toxicities with respect to chemotherapy. Cost and access continue to be issues in low-resource settings, and health economic assessment is indicated to facilitate equitable provision of therapy [18]. In total, this research is one of the expanding evidence bases for ARIs as a best practice for mCRPC treatment. Their increased efficacy and tolerable safety profile warrant their adoption worldwide into clinical guidelines, and additional studies should seek to further delineate their optimal usage within individualized treatment regimens.

Conclusion

This randomized trial shows that new androgen receptor inhibitors markedly enhance progression-free and overall survival in men with metastatic castration-resistant prostate cancer compared to standard ADT-based regimens. The superior PSA response rates also testify to their better disease control. Although the ARI arm involved more favorable adverse effects, the tolerability profile in general justifies long-term use in candidate patients. These results highlight the paradigm-shifting potential of ARIs to change the treatment paradigm for mCRPC. Not only do the agents significantly prolong survival but also preserve quality of life compared to more toxic systemic therapies. In spite of these benefits, issues regarding resistance, cost, and access disparities will have to be addressed in order for their full potential to be realized everywhere. In general, new framework ARIs are an enormous step ahead in the treatment of prostate cancer. They must be implemented as a best practice for mCRPC patients with continued work focused on reaching their maximum inclusion into tailored treatment regimens.

References

1. Nahar, T. A., Bantounou, M. A., Savin, I., Chohan, N., Kumar, N. S., Ghose, A., & McEwan, I. J. (2024). Efficacy and Safety of Combination AKT and Androgen Receptor Signaling Inhibition in Metastatic Castration-Resistant Prostate Cancer: Systematic Review and Meta-Analysis. *Clinical Genitourinary Cancer*, *22*(6), 102244.

2. Guo, X., Li, Y., Wang, M., Peng, H., Guo, H., Hou, T., ... & He, Z. (2025). Efficacy and safety of first-line treatments for metastatic castration-resistant prostate cancer based on phase II and III randomized

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https://ghsjournal.com/

controlled trials: A PROSTA-MAP systematic review and network metaanalysis. *Chinese Medical Journal*, 10-1097.

3. Zhou, S., Alerasool, P., Kishi, N., Joshi, H., Sahni, G., & Tsao, C. K. (2024). Cardiovascular toxicity associated with androgen receptor axis-targeted agents in patients with prostate cancer: a meta-analysis of randomized controlled trials. *Clinical Genitourinary Cancer*, *22*(3), 102066.

4. Yan, K., Balijepalli, C., Gullapalli, L., Joshy, J., Kotum, S., & Druyts, E. (2024). Efficacy and safety of interventions for metastatic castration resistant prostate cancer (mCRPC) patients progressing on androgen receptor-axis-targeted (ARAT) therapy: a systematic literature review. *Current Medical Research and Opinion*, *40*(10), 1741-1752.

5. Morris, M. J., Castellano, D., Herrmann, K., de Bono, J. S., Shore, N. D., Chi, K. N., ... & Fizazi, K. (2024). 177Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. *The Lancet*, *404*(10459), 1227-1239.

6. Shao, C., Wan, Q., Guo, J., & Chen, Z. (2025). The efficacy and safety of cabazitaxel in the treatment of metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis based on randomized controlled trials. *Frontiers in Pharmacology*, *16*, 1586650.

7. Jiang, B., Wang, B., Chen, Y., Chen, Y., Li, B., & Bi, J. (2025). Comparative therapeutic efficacy and safety of first-line and second-line therapies for metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis. *EClinicalMedicine*, *81*.

8. Messina, C., Giunta, E. F., Signori, A., Rebuzzi, S. E., Banna, G. L., Maniam, A., ... & Rescigno, P. (2024). Combining PARP inhibitors and androgen receptor signalling inhibitors in metastatic prostate cancer: a quantitative synthesis and meta-analysis. *European Urology Oncology*, *7*(2), 179-188.

9. Fizazi, K., Chi, K. N., Shore, N. D., Herrmann, K., de Bono, J. S., Castellano, D., ... & PSMAfore Investigators. (2025). Final overall survival and safety analyses of the phase 3 PSMAfore trial of [177Lu] Lu-PSMA-617 versus change of androgen receptor pathway inhibitor in taxane-naive patients with metastatic castration-resistant prostate cancer. *Annals of Oncology*.

10. Kostos, L., Buteau, J. P., Kong, G., Tran, B., Haskali, M. B., Fahey, M., ... & Azad, A. A. (2025). Clinical Trial Protocol for LuCAB: A Phase I–II Trial Evaluating Cabazitaxel in Combination with [177Lu] Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer. *Journal of Nuclear Medicine*, *66*(4), 572-578.

11. Muniz, M., Sartor, O., Orme, J. J., Koch, R. M., Scharf, Z., Heath, E. I., ... & Childs, D. S. (2025). Outcomes for [177Lu] Lu-PSMA-617 with and Without Concurrent Use of Androgen Receptor Pathway Inhibitors in Patients with Metastatic Castration-resistant Prostate Cancer. *European Urology Oncology*.

12. Shaver, A. L., Nikita, N., Sharma, S., Keith, S. W., Zarrabi, K. K., Kelly, W. K., & Lu-Yao, G. (2025). The Safety of Abiraterone Acetate in Patients with Metastatic Castration-Resistant Prostate Cancer: An Individual-Participant Data Meta-Analysis Based on 14 Randomized Clinical Trials. *Cancers*, *17*(17), 2747.

13. Rathkopf, D. E., Patel, M. R., Choudhury, A. D., Rasco, D., Lakhani, N., Hawley, J. E., ... & Armstrong, A. J. (2025). Safety and clinical activity of BMS-986365 (CC-94676), a dual androgen receptor ligand-directed degrader and antagonist, in heavily pretreated patients with metastatic castration-resistant prostate cancer. *Annals of Oncology*, *36*(1), 76-88.

14. Roy, S., Malone, S., Wing, K., Chowdhury, S., Kishan, A. U., Sun, Y., ... & Saad, F. (2024). Prior Local Therapy and First-Line Apalutamide in Patients With Nonmetastatic CastrationResistant Prostate Cancer: A Secondary Analysis of the SPARTAN Randomized Clinical Trial. *JAMA network open*, *7*(10), e2439434-e2439434.

GLOBAL HEALTH & MEDICINE
ISSN / eISSN: 2434-9186 / 2434-9194
Volume 06, Issue 03.4111-4116
https://ghsjournal.com/

15. Murthy, V., Voter, A. F., Nguyen, K., Allen-Auerbach, M., Chen, L., Caputo, S., ... & Gafita, A. (2024). Efficacy and toxicity of [177Lu] Lu-PSMA-617 for metastatic castration-resistant prostate cancer: results from the US expanded-access program and comparisons with Phase 3 VISION Data. *Journal of Nuclear Medicine*, *65*(11), 1740-1744.
16. Patrikidou, A., Saieva, C., Lee-Ying, R., Nuzzo, P. V., El Zarif, T., McClure, H., ... & SPARTACUSS Group. (2024). Docetaxel Versus Androgen-Receptor Signaling Inhibitors (ARSI) as Second-Line Therapy After Failure of First-Line Alternative ARSI for the Elderly≥ 75 Years Old With Metastatic Castration-Resistant Prostate Cancer (mCRPC): A SPARTACUSS—MeetURO 26 Real-World Study. *Clinical Genitourinary Cancer*, *22*(6), 102230.
17. Wang, T., Wang, X., Ding, G., Liu, H., Ma, X., Ma, J., ... & Wu, J. (2024). Efficacy and safety evaluation of androgen deprivation therapy-based combinations for metastatic castration-sensitive prostate cancer: a systematic review and network meta-analysis. *British Journal of Cancer*, *131*(8), 1363-1377.
18. Petrylak, D. P., Ratta, R., Matsubara, N., Korbenfeld, E., Gafanov, R., Mourey, L., ... & Fizazi, K. (2025). Pembrolizumab plus docetaxel versus docetaxel for previously treated metastatic castration-resistant prostate cancer: the randomized, double-blind, phase III KEYNOTE-921 trial. *Journal of Clinical Oncology*, *43*(14), 1638-1649.