Editorial Commentary

Global efficacy and clinical application of androgen receptor inhibitors in metastatic prostate cancer

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Introduction

The past two decades have witnessed the evolution of androgen receptor inhibitors (ARIs) in advanced prostate cancer. The initial era of ARIs began with bicalutamide, flutamide, and nilutamide, where they were added on to an androgen deprivation therapy (ADT) backbone. In this role, they were adjuncts to the therapy except in the setting of starting with ARIs to avoid potential tumor flare due to testosterone surge. Previously the ARIs were routinely used in combination with ADT as combined androgen blockade. Recently in clinical practice, the first-generation ARIs serve the purpose of jumpstarting therapy and are usually used only for the first month or so in the therapy of hormone-sensitive advanced prostate cancer. Attempts were made to establish a role for these therapies in the setting of castrate-resistant prostate cancer (CRPC). However, overall the efficacy was modest and the demonstrated PSA responses were for a short duration and did not usually impact the overall course of disease progression. Large adjuvant study was conducted with bicalutamide to improve outcomes in high-risk disease and although efficacy was demonstrated it did not alter cancer-specific survival (1). The next generation of ARIs has made great strides in proving tolerability and efficacy and are routinely used across multiple stages of prostate cancer to improve overall survival (OS) (2-4).

Role of ARIs

Apalutamide, enzalutamide, and darolutamide improved metastasis-free survival (MFS) in non-metastatic (nm) CRPC (5-7). Median MFS increased about three times as compared to that noted with placebo. Enzalutamide was the first of the ARIs to obtain Food and Drug Administration (FDA) approval in metastatic CRPC (mCRPC) patients post-docetaxel chemotherapy in the AFFIRM placebo-controlled double-blind randomized trial (2). This was shortly followed by PREVAIL a randomized trial in mCRPC conducted in the prechemotherapy patient population (3). This is of course the setting where it was used widely clinically. Both studies demonstrated progression-free survival (PFS) and OS benefit. AFFIRM and PREVAIL were followed by the TERRAIN phase II randomized trial that compared enzalutamide to bicalutamide and established superior efficacy of enzalutamide in mCRPC (4).

Initial clinical evaluation demonstrated remarkable efficacy with survival benefit for ARIs in mCRPC. The natural progression of drug development in oncology occurred with transition to evaluating ARIs in metastatic hormone-sensitive prostate cancer (mHSPC). Results of phase III ARI trials in mHSPC are summarized in *Table 1* (8-12). Apalutamide in the TITAN trial, and enzalutamide in the ARCHES trial, demonstrated statistically significant

Table 1 Overview of phase III randomized studies conducted of ARIs in mHSPC

Study	Sample size	ARIs studied	Control arm	mPFS/HR	mOS/HR	Reference
CHART	645	Rezvilutamide	ADT + bicalutamide	NR/25.1 months, HR =0.44, P<0.0001	NR in both arms, HR =0.58, P=0.0001	(8)
TITAN	1,052	Apalutamide	ADT + placebo	68% *vs.* 45% progression free at 24 months, HR =0.48, P<0.0001	NR *vs.* 52.2 months, HR =0.67, P<0.0001	(9)
ARCHES	1,150	Enzalutamide	ADT + placebo (30% with prior docetaxel)	mPFS: NR *vs.* 19.1 months, HR =0.39, P=0.001	Median NR both arms, HR =0.66, P=0.001	(10)
ENZAMET	1,125	Enzalutamide	ADT + docetaxel (45% patients)	HR =0.40, P<0.0001	mOS at 36 months: 80% *vs.* 72%, HR =0.52, P=0.002	(11)
ARASENS	1,306	Darolutamide	ADT + docetaxel	Median to CRPC NR *vs.* 19.1 months, HR =0.36, P<0.001	Median NR *vs.* 48.9 months, HR =0.68, P<0.001	(12)

ARIs, androgen receptor inhibitors; mHSPC, metastatic hormone-sensitive prostate cancer; mPFS, median progression-free survival; HR, hazard ratio; mOS, median overall survival; ADT, androgen deprivation therapy; NR, not reached; CRPC, castrate-resistant prostate cancer.

benefit in PFS and OS favoring the ADT + ARIs arm as compared to ADT + placebo (9,10). The ENZAMET trial also incorporated docetaxel chemotherapy into the mHSPC setting, and demonstrated a benefit over ADT + docetaxel (11). Triplet therapy with ADT + docetaxel + ARIs with darolutamide recently demonstrated success over ADT + docetaxel as per the results of the ARASENS trial (12).

Despite the rapid advances in ARI therapy in advanced prostate cancer the studies conducted to date represent some common challenges. Majority of the studies were placebo-controlled except for the phase II randomized trial comparing bicalutamide to enzalutamide. The study report by Gu *et al.* in *Lancet Oncol* is one of the first studies in mHSPC comparing rezvilutamide to bicalutamide (8). One of the class-effect toxicities of the ARI therapies is seizures. The blood-brain barrier penetration of these agents can lead to a small risk of seizures as the extreme toxicity, however fatigue, alteration of mental and cognitive function, and increased risk of falls represent noteworthy toxicities observed with increased frequency. The prostate cancer patient population being predominantly elderly and with pre-existing comorbidities is especially susceptible to these adverse events which can seriously impair quality of life and functionality.

CHART study: rezvilutamide

Rezvilutamide was noted to have decreased brain penetration in preclinical trials and hence was likely to be better tolerated. One of the key issues was that the studies enrolled almost all Caucasian patients so the safety and extent of efficacy in other populations was unknown and presented a challenge to clinical application. Rezvilutamide represents a study that is conducted in almost all Asian/Chinese patients (90% of patients enrolled on the CHART study), and depicts the safety and proven efficacy of the second-generation ARIs rezvilutamide in this population (8). We conducted a study comparing ADT + enzalutamide *vs.* ADT + bicalutamide requiring at least 40% African American (AA) patient population enrollment (13). The study showed consistent safety profile and a larger magnitude of benefit with addition of enzalutamide in the AA patient population as compared to the Caucasian mHSPC patients. Studies of ARIs in diverse populations are critically important to evaluate critical clinical drug interactions and delayed toxicities especially as the therapy is likely to be used for a prolonged duration of multiple years. The study was not limited to patient population with high-volume disease, however 20% of the patients had visceral metastases and 69% of the patients had greater than 10 bone metastases.

Conclusions

In summary, the results of the study established comparable safety profile, and superior efficacy of rezvilutamide over bicalutamide in high-volume mHSPC. The results of the two preplanned interim analyses reveal statistically significant improvement in PFS and OS favoring rezvilutamide. It is now approved in China for the treatment

of patients with mHSPC with high tumor burden since June 2022. Prolonged follow-up and continued assessment of patient-reported outcomes is highly recommended and will contribute to enhance our knowledge of toxicity perceptions over prolonged duration. Future study evaluation with ADT + rezvilutamide ± docetaxel should be considered to evaluate for optimizing and enhancing efficacy in mHSPC. Studies in diverse patient populations and including formal evaluation of cognitive effects is worthy of consideration.

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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