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EDITORIAL

# Advances in the treatment of metastatic prostate cancer in China

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Prostate cancer (PC) is among the most common cancer diagnoses in men worldwide and the fifth leading cause of cancer-related deaths. Approximately 1.5 million new cases of PC were reported worldwide in 2022 with nearly 400,000 associated deaths[1]. Notably, the incidence of PC in China has increased substantially compared to the global average[2]. Moreover, the proportion of patients with PC diagnosed with distant metastases is greater in China (30%) compared to developed countries, such as the US (4%)[2].

The prognosis for patients with metastatic prostate cancer (mPC) remains poor with a 5-year survival rate of 34%[3], highlighting the need for effective and well-tolerated therapy options. Research involving treatment options for mPC in China has lagged behind global efforts because many international studies have not included synchronous enrollment of Chinese patients or Chinese-specific cohorts. A systematic review of Chinese practice reported that clinical trials investigating 19 drugs in Chinese mainland for the treatment of PC between 2010 and 2020 mostly focused on endocrine therapy (67.7%)[4]. In contrast, 132 drugs were studied globally within the same time period with a greater focus on chemotherapeutic agents (44.7%), followed by immunotherapy (31.8%), endocrine therapy (18.9%), and radiotherapy (4.6%)[4]. Importantly, Chinese populations have been enrolled in global clinical trials in recent years and innovative drugs have been developed for the treatment of mPC in China.

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Therefore, the current editorial is an update on the current status and future development of treatment options available for mPC in China, which will facilitate optimal clinical decision-making by urologists and ultimately promote patient survival.

## Androgen signaling axis: the primary treatment target

Endocrine-based therapies remain the primary treatment option for Chinese patients with mPC[4]. Patients with metastatic hormone-sensitive prostate cancer (mHSPC) respond well to hormone therapy, which is typically based on androgen deprivation therapy (ADT). However, standard ADT failure can lead to castration-resistant prostate cancer (CRPC), a more aggressive form of the disease. Treatments targeting the androgen signaling axis in China, including abiraterone and enzalutamide, have been approved for mCRPC and are now widely used in clinical practice. Darolutamide, an androgen receptor (AR) inhibitor, plus docetaxel and ADT is approved in China for the treatment of non-metastatic CRPC and was approved for mHSPC in 2023. Notably, rezvilutamide (SHR3680), an AR antagonist, plus ADT was reported to radiographic progression-free survival (rPFS) and overall survival (OS) compared to bicalutamide plus ADT and had a manageable safety profile in patients with mHSPC (NCT03520478)[5]. Rezvilutamide was approved in China in 2022 for the treatment of patients with mHSPC and a high tumor burden.

However, there are several mechanisms through which reactivation of the AR signaling pathway can occur, resulting in resistance to novel hormonal agents (NHAs) and disease progression, as detailed in **Figure 1**. Because drug resistance and the treatment of patients after receipt of NHA is a growing

clinical concern, development of novel AR pathway therapeutics is particularly important worldwide.

PROteolysis TArgeting Chimera (PROTAC) AR degraders target AR for degradation *via* the ubiquitin-protease system. PROTAC AR degraders have recently advanced into phase 1 and 2 trials, and have shown potential for overcoming common resistance mechanisms. Specifically, bavdegalutamide (ARV-110), the first PROTAC to be developed, has demonstrated early efficacy in patients with mCRPC[6]. These results have encouraged further global investigation of bavdegalutamide for the treatment of mCRPC. However, there are no China-specific data available. **Table 1** details current PROTAC AR degraders for which clinical trials are ongoing.

MK-5684 (ODM-208) is an oral, non-steroidal inhibitor of the first and rate-limiting enzyme involved upstream in the steroid biosynthesis pathway [cytochrome P450 11A1 (CYP111)], as illustrated in **Figure 1**. Globally, MK-5684 is currently under investigation in a phase 1/2 trial (NCT03436485) for patients with mCRPC pretreated with abiraterone/enzalutamide and taxanes. The initial results from the ongoing CYPIDES trial have shown that MK-5684 treatment effectively inhibits steroid production and is associated with anti-tumor activity in patients with mCRPC[8]. In addition, two global, phase 3 trials (NCT06136624 and NCT06136650) will compare the efficacy of MK-5684 with abiraterone or enzalutamide in patients with mCRPC previously treated with next-generation hormonal

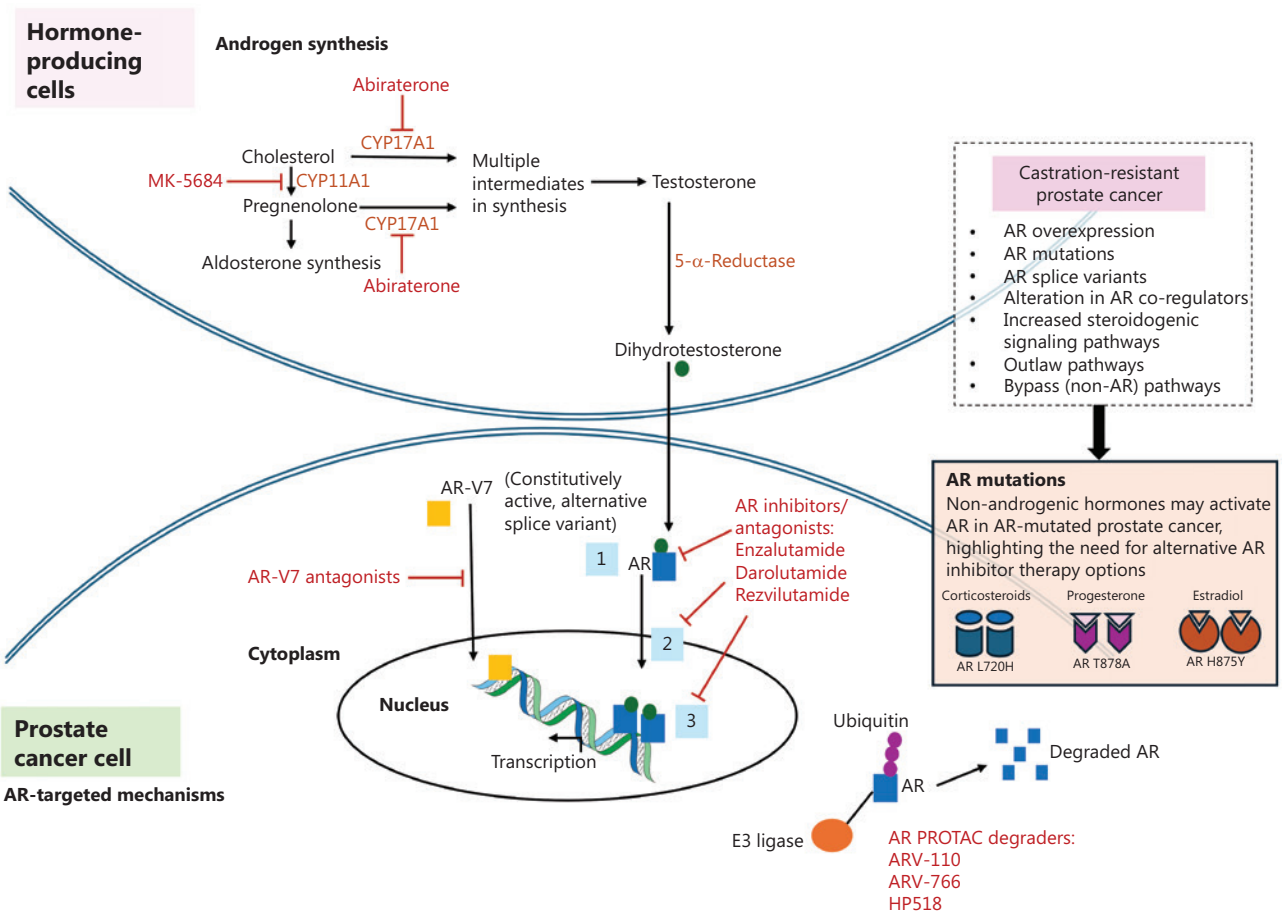



**Figure 1** Novel AR axis-directed therapy for the treatment of metastatic prostate cancer. Mechanism underlying androgen synthesis pathway inhibition (e.g., abiraterone and MK-5684) and AR-targeted mechanisms inhibit AR function by blocking (1) agonist binding, (2) nuclear translocation, and/or (3) DNA binding, and thus transcription of AR (e.g., enzalutamide, darolutamide, and rezvilutamide). Alternative therapeutic options include AR PROTAC degraders *via* a ubiquitin/E3 ligase system or AR-V7 antagonists. Castration resistance can develop through several AR-dependent and -independent processes, including AR mutations that enable non-androgenic hormonal activation. AR, androgen receptor.

**Table 1** Clinical trials designed to investigate PROTAC AR degraders for the treatment of advanced prostate cancer

| Drug name | Clinical trial identifier | Location | Disease setting | Phase | Status | Efficacy results[a] |
|---|---|---|---|---|---|---|
| Bavdegalutamide (ARV-110) | NCT03888612 | US | mCRPC | Phase 1/2 | Primary stage completed; study ongoing | • 46% $PSA_{50}$ rate and RECIST responses occurred in patients with tumors harboring *AR* T878X or H875Y mutations.<br>• A ≥ 50% decrease in PSA occurred in patients without *AR* T878X/H875Y mutations[6]. |
| ARV-766 | NCT05067140 | US | mPC | Phase 1/2 | Ongoing | 50% $PSA_{50}$ rate in patients with *AR* LBD mutations[7]. |
| HP518 | NCT06155084 | China | mCRPC | Phase 1 | Ongoing | – |
| | NCT05252364 | Australia | mCRPC | Phase 1 | Complete | – |
| AC176 | NCT05673109 | China | mCRPC | Phase 1 | Terminated | – |
| | NCT05241613 | US | mCRPC | Phase 1 | Terminated | – |

[a]Listed for phase ≥2 trials for which data are available. AR, androgen receptor; LBD, ligand-binding domain; mCRPC, metastatic castration-resistant prostate cancer; PROTAC, PROteolysis TArgeting Chimera; RECIST, response evaluation criteria in solid tumors; PSA, prostate-specific antigen.

agent (NHA) and taxane-based chemotherapy or NHA. Importantly, both trials are recruiting patients from China.

Future randomized, large-scale clinical trials are warranted to fully explore the potential of these androgen signaling axis drugs for patients with mCRPC. If these global trials successfully demonstrate significant clinical benefits and acceptable safety profiles, China-specific validation data will be required before these new drugs can be approved for use in clinical practice in China. The prior treatment landscape of mCRPC will also need to be specifically studied because there may be differences in the use of prior NHA and chemotherapy between China and Europe/US, which must be considered when designing a study that combines different population groups within the same clinical trial. Furthermore, additional subgroup analyses into Chinese-specific patient characteristics and biomarkers will be required to allow for more precise clinical decision-making.

## Radiopharmaceuticals: a promising future strategy

Radiopharmaceutical therapy (RPT) has emerged as a novel, targeted therapeutic option to overcome castration resistance in PC. Unlike external-beam radiation strategies, RPT facilitates systemic yet targeted delivery of radioactive cytotoxic atoms to tumor-specific sites, resulting in minimal toxic side effects compared to traditional radiotherapy.

Radium 223 dichloride ($^{223}$Ra) is a bone-targeting radionucleotide that emits high-energy alpha particles over a short range (<100 μm). The alpha particles induce double-stranded DNA breaks in adjacent tumor cells without a significant bystander effect in normal tissue[9]. Notably, data from the ALSYMPCA phase 3 trial (NCT00699751) demonstrated that treatment with $^{223}$Ra results in increased OS in patients with mCRPC and symptomatic bone metastases[9]. $^{223}$Ra was approved for treatment of mCRPC in China in August 2020 based on the results of a multi-center, phase 3 trial (NCT01810770)[10]. Because use of $^{223}$Ra is limited by the lack of efficacy for visceral metastases, combinations with other systemic treatments are currently under development. $^{223}$Ra plus enzalutamide has recently been reported to improve rPFS in patients with mCRPC and bone metastases in the ongoing phase 3 PEACE trial (NCT02194842)[11]. The clinical application of $^{223}$Ra in China is limited by several factors, including the high costs of manufacturing and importation, because alpha-emitting drugs cannot be made in China and must be imported. Widespread use of $^{223}$Ra in China is also restricted by a shortage of nuclear medicine specialists and hospitals within which the treatment can be performed, as well as the close multi-disciplinary cooperation that is required. Limited patient acceptance is another limiting factor to the clinical application of $^{223}$Ra in China, resulting from a lack of information surrounding this new approach.

**Table 2** Clinical trials of PARP inhibitors most relevant to the treatment landscape of mCRPC in China

| mCRPC | Olaparib | Niraparib | Talazoparib |
|---|---|---|---|
| Monotherapy | PROfound (NCT02987543)[15]; positive results in patients with alterations in *BRCA1*, *BRCA2*, or *ATM*; China-specific cohort (NCT05457257)*. | | |
| Combination therapy | Olaparib plus abiraterone [PROpel (NCT03732820)]; positive results independent of *HRR* mutational status[16]; China-specific cohort (NCT05171816). | Niraparib plus abiraterone and prednisone [MAGNITUDE (NCT03748641)]*; positive results in patients with *HRR* mutations[17]. | Talazoparib plus enzalutamide [TALAPRO-2 (NCT03395197)]*; positive results in unselected cohorts and patients harboring *HRR* gene alterations[18]. |

*Including Chinese population involvement. ATM, ataxia–telangiectasia-mutated; *BRCA1/2*, breast cancer gene 1/2; DNA, deoxyribonucleic acid; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly ADP-ribose polymeras.

Many small molecules and antibodies targeting prostate-specific membrane antigen (PSMA), a protein that is highly expressed in the majority of bone, visceral, and lymph nodes of PC metastases[12], have been developed, labelled with emitters (e.g., $^{177}$Lu, $^{161}$Tb, $^{131}$I, $^{90}$Y, $^{67}$Cu, $^{47}$Sc), and studied in preclinical and clinical studies in patients with PSMA-expressing disease. By targeting PSMA, these agents have the advantage of not being limited to bone metastases, unlike $^{223}$Ra. $^{177}$Lu-PSMA-617 is a beta-emitting, medium-energy radioisotope that has been approved in Europe/US for pretreated patients with progressive, PSMA-positive mCRPC. While $^{177}$Lu-PSMA-617 has not been approved in China, the RPT manufacture issues that have affected the alpha-emitting $^{223}$Ra do not affect the beta-emitting $^{177}$Lu. Indeed, construction has begun on at least one large $^{177}$Lu-focused radioligand manufacturing plant in Zhejiang[13].

PSMA-targeted therapy remains a major avenue of clinical research and a potential future direction. Several trials are currently evaluating the efficacy of combining $^{177}$Lu-PSMA-617 with different therapeutic strategies for the treatment of mPC, including ADT [PSMAddition (NCT04720157)], NHAs [ENZA-p (NCT04419402)], PARPis [such as olaparib] [LuPARP (NCT03874884)], and immune checkpoint inhibitors [EVOLUTION (NCT05150236); PRINCE (NCT03658447)]. Notably, the international PSMAddition phase 3 trial, which was designed to compare $^{177}$Lu-PSMA-617 plus ADT *versus* ADT in patients with mHSPC, is currently recruiting from hospitals in China. Investigations into alternative PSMA-targeted radionucleotides for the treatment of mPC are ongoing. A clinical trial design for the treatment of patients with mCRPC with $^{177}$Lu-XT033, another PSMA targeted radionucleotide, was approved in China in December 2022 and may provide important new data.

However, one of the current limitations to PSMA-targeted radionucleotide treatment is the gap between patient diagnosis and treatment because the clinical application of next-generation PSMA-positron emission tomography (PSMA-PET) has not replaced conventional imaging, despite demonstrating superior accuracy[14]. Therefore, future research is needed with respect to the appropriate use of PSMA-PET for monitoring patients, prognostication, and informing treatment decisions in Chinese patients.

## PARP inhibitors: further investigations required for precision treatment

Poly ADP-ribose polymerase inhibitors (PARPis) are a relatively recent therapeutic strategy in prostate cancer and are another important aspect of the era of targeted treatment for prostate cancer. PARP inhibitors have demonstrated efficacy in prostate cancer with mutations in homologous recombination repair (*HRR*) genes because tumors with *HRR* gene mutations are particularly sensitive to agents that induce DNA damage.

Clinical trials for several PARPis, which have influenced or will influence clinical practice of mCRPC in China are outlined in **Table 2**. At present, olaparib monotherapy remains the only PARPi to be approved in China for patients with BRCA1/2-mutated mCRPC (2021). In the move towards first-line treatment of mCRPC, the efficacy and safety of several PARPis plus different NHAs are being investigated as novel combination therapies for patients with mCRPC due to the synergy between these agents. Olaparib combined with abiraterone [PROpel (NCT03732820)] was shown to successfully prolong rPFS and OS compared to abiraterone and placebo in patients with mCRPC, independent of *HRR* mutational status[16]. It is worth noting that the PROpel study has since completed enrollment for a China-specific cohort. Furthermore, talazoparib

combined with enzalutamide [TALAPRO-2 (NCT03395197)], has shown significant improvements in OS *versus* enzalutamide monotherapy in patients with mCRPC unselected and selected for *HRR* gene alterations[18]. Importantly, the TALAPRO-2 study includes patients from hospitals in China. Combination treatment with niraparib, another PARPi, plus abiraterone acetate and prednisone (AAP) [MAGNITUDE (NCT03748641); global trial recruiting patients from China] increased rPFS in patients with mCRPC (*HRR*-mutation positive) compared to placebo plus AAP[17]. Overall, the array of PARPi plus NHA studies, with some demonstrating OS benefit, is encouraging and will expand treatment options for Chinese patients.

Despite the established efficacy, there are challenges associated with the clinical application of PARPis in China. Given the efficacy observed in biomarker-selected populations, improved, unobstructed access to in-hospital molecular testing facilities across non-core city and community hospitals is required. One potential solution is increased application of circulating tumor DNA (ctDNA) testing following failed tissue examinations because ctDNA analysis in patients with mCRPC has been associated with successful treatment selection, prognostication, and understanding of therapeutic resistance[19]. Considering the potential diversity of alterations in DNA repair genes between Chinese and Caucasian populations[20], it will be important to establish the germline and somatic *HRR* gene mutational landscape of PC in Chinese patients to optimize treatment selection and explore the efficacy of PARPis plus NHAs in patients with different *HRR* gene mutations. Notably, there are no data from a large sample to support the use of PARPis plus NHAs in patients previously treated with an NHA. It is especially important that these data are generated for the future application of PARPis because NHAs, such as abiraterone and enzalutamide, have become the standard-of-care for patients with mHSPC.

## Conclusions

Despite recent therapeutic advances, mPC continues to be a lethal form of cancer, for which there is a significant clinical unmet need for more effective targeted treatments. There is currently a disparity in the treatment landscape for mPC between Europe/US and China. In general, there are fewer therapeutic options available to patients in China and the overall progress of clinical research is slower due to differences in drug approvals and the limited number of Chinese patients included in some global trials. However, in recent years a greater number of Chinese patients are being enrolled in global trials and in some areas Chinese research is at the forefront, which will help bridge the treatment gap. As more precision treatment options and combinations become available, Chinese patients will have access to a greater number of treatment options, including biomarker-selected populations. Furthermore, because of the heterogeneous nature of mPC, it will be important to support China-specific research to identify reliable biomarkers to ascertain which patients will benefit from targeted therapies. Thus, having access to molecular testing will be critical to develop optimal management strategies. Furthermore, research into alternative strategies that hold prognostic value, such as profiling extracellular vesicles secreted by tumors, will support the development of precision medicine for PC. Overall, there needs to be a greater participation of Chinese patients in global research and a focus on the development of new treatment strategies within China.

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## Conflict of interest statement

Zhenhua Liu and Luyao Yang are employed by MSD China. The other authors report no conflicts of interest.

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