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## REVIEW ARTICLE

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# Recent Advances in the Treatment for Metastatic Castration-Refractory Prostate Cancer

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### ABSTRACT

*In Hong Kong, prostate cancer is the third most common cancer in men, with increasing incidence over the past two decades. Advanced prostate cancer is typically sensitive to androgen-deprivation therapy, but invariably develops into castration-resistant disease. Until recently, patients with castration-resistant prostate cancer who progressed after docetaxel therapy had limited treatment options. Recent advances in this field have resulted in better understanding of the mechanisms of cancer progression and led to the development of new therapeutic strategies for this disease. Agents that have recently become available and demonstrated survival benefits include inhibitors of the androgen receptor pathway, microtubule inhibitors, and bone-targeted therapy. Further promising investigational agents are under clinical evaluation and expected to provide more options to improve patient prognosis. For optimal treatment, the timing, sequencing, and potential combinations of strategies should be considered and individualised for patients. This article summarises recent improvements in the treatment landscape for metastatic castration-resistant prostate cancer and discusses the role of new therapeutics for improving the outlook of patients with this lethal and aggressive disease.*

**Key Words:** *Docetaxel; Drug resistance, neoplasm; Prostatic neoplasms; Testosterone*

## 中文摘要

### 醫治睪丸摘除治療失效前列腺癌的最新發展

鄭維基

前列腺癌在香港男性最常見癌症中排第三位，而且發病率在過去二十年不斷上升。晚期前列腺癌一般對雄激素阻斷治療有反應，但總會發展成為睪丸摘除治療失效的疾病。直至最近為止，患有睪丸摘除治療失效前列腺癌（CRPC）在多西他賽（docetaxel）治療後惡化的患者，可選擇的治療十分有限。近期的發展讓我們對癌症惡化的機制加深了解，因而發展出治療這種疾病的新治療方法。在最近可供使用而且有證據證明具存活益處的藥物包括雄激素受體途徑抑制劑、微管抑制劑及骨靶向治療。其他前景樂觀的研究性藥物正在臨床評估中，預計會帶來更多治療選擇以改善病人的預後。為達到最理想的治療，應考慮並為病人個人化治療的時機、次序和療法的可能組合。本文總結了轉移性CRPC治療的近期進展，並討論新療法對改善患此可致命及具侵略性疾病的病人，其治療成效的作用。

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## INTRODUCTION

Prostate cancer is the third most common cancer in men in Hong Kong, with the incidence increasing markedly over the past two decades. From 1996 to 2010, the age-standardised incidence of prostate cancer in Hong Kong more than doubled, from 11 to 28 per 100,000 population. The mortality rate has remained at around 5 to 5.5 per 100,000 population, making it the fifth most common cause of death in males in Hong Kong.<sup>1</sup>

Although the majority of patients are diagnosed in the early stage, patients with disseminated recurrence or metastatic disease remain challenging to treat. Tumourigenesis and progression of prostate cancer are primarily regulated by androgen binding and signalling through the androgen receptor (AR). For patients with metastatic prostate cancer, androgen deprivation therapy (ADT) is the standard first-line treatment. Androgen deprivation can be accomplished by either bilateral orchiectomy or administering luteinising hormone-releasing hormone agonists, both of which result in a good response rate of 80% to 90%. However, virtually all patients progress to castration-resistant or castration-refractory prostate cancer (CRPC), which is defined by progressive disease with a castration level of testosterone despite ADT. The development of CRPC may be attributed to two main mechanisms: 'adaptation' of cancer cells to the androgen-depleted environment through genetic or epigenetic changes, or 'clonal selection', the outgrowth of AR-negative clones under selection pressure of low androgen conditions.<sup>2</sup> In many patients, it is likely that both mechanisms co-exist, contributing to cancer progression in a low testosterone environment.<sup>3</sup>

For patients who develop CRPC with minimal metastases and a slow prostate-specific antigen (PSA) doubling time, second-line hormonal therapy may be considered. The common options include non-steroidal anti-androgens such as bicalutamide, flutamide, and nilutamide, anti-androgen withdrawal, oestrogen, and ketoconazole. These treatments have been shown to prolong progression-free survival (PFS), but not overall survival (OS).<sup>4</sup>

Until recently, chemotherapy was the standard of care for patients with metastatic CRPC (mCRPC) no longer responsive to hormonal therapy. Mitoxantrone was the first chemotherapeutic agent approved by the US Food and Drug Administration (FDA) for use in combination with prednisone in mCRPC as it is associated with

better quality of life and lower PSA level than with prednisone alone.<sup>5</sup> In 2004, the standard of care of CRPC changed from mitoxantrone/prednisone to docetaxel/prednisone based on results from two phase III studies.<sup>6,7</sup> The landmark TAX327 trial showed that docetaxel (75 mg/m<sup>2</sup>) given every 3 weeks with prednisone to patients with mCRPC resulted in superior survival compared with mitoxantrone and prednisone (median survival, 18.9 vs. 16.5 months).<sup>6</sup> Improvements in terms of serum PSA reduction, pain, and quality of life were also observed. Systemic chemotherapy may be most appropriate for fit patients with symptomatic mCRPC or asymptomatic patients with high serum PSA levels or rapid PSA doubling time.<sup>4</sup> However, tolerability may be poor in many elderly patients with concurrent medical conditions. Since 2010, advances in molecular and translational research have resulted in an improved understanding of the mechanism of CRPC progression, leading to the development of new, rational approaches for the treatment of mCRPC. This article summarises the clinical evidence supporting several new treatment options for mCRPC and discusses the role of new therapeutics in improving the outlook of patients with this lethal and aggressive disease.

## NEW TREATMENT OPTIONS FOR METASTATIC CASTRATION-REFRACTORY PROSTATE CANCER

With an expanding knowledge of the mechanisms of resistance in mCRPC, many new agents targeting different pathways implicated in prostate cancer progression and resistance have been under development and some have been recently approved for use in clinical practice. These include agents targeting the AR signalling pathway such as androgen biosynthesis inhibitors and AR antagonists, microtubule inhibitors, stress-response inhibitors, and agents that modulate the tumour microenvironment such as bone-targeted therapy, angiogenesis inhibitors, and immunotherapy.

### Abiraterone: Role of Androgen Synthesis Inhibitors

Despite the development of castration resistance, recent research suggests that most CRPC cells continue to express ARs and mediate active AR signalling.<sup>3</sup> Thus, therapies targeting AR signalling remain important in CRPC and several new AR-targeted agents are now part of the treatment armamentarium for patients with mCRPC.

Abiraterone is an oral selective irreversible inhibitor

of CYP17 involved in androgen and oestrogen biosynthesis. Abiraterone exerts its effects by inhibiting 17 $\alpha$ -hydroxylase and C17,20-lyase enzymatic activities essential in the biosynthesis of testosterone in the testes, adrenals, and prostate tumour cells. As 17 $\alpha$ -hydroxylase inhibition also leads to increased mineralocorticoid production, abiraterone must be co-administered with prednisone to counteract the side-effects associated with mineralocorticoid excess.

Abiraterone, in combination with prednisone, has gained regulatory approval worldwide for the treatment of mCRPC after chemotherapy, based on results from the phase III COU-AA-301 trial. This pivotal trial randomised, in 2:1 ratio, 1195 patients previously treated with docetaxel to receive abiraterone plus prednisone or placebo plus prednisone.<sup>8</sup> After a follow-up of 12.8 months, treatment with abiraterone and prednisone resulted in a 35% improvement in median OS compared with placebo and prednisone (14.8 vs. 10.9 months; hazard ratio [HR] = 0.65;  $p < 0.001$ ). Significant improvements in PSA progression, PSA response rate, and PFS were also observed in favour of the abiraterone arm. Results from an updated analysis (follow-up period, 20.2 months) confirmed the benefit of abiraterone and showed a 4.6-month improvement in median OS compared with the control arm (15.8 vs. 11.2 months; HR = 0.74;  $p < 0.0001$ ).<sup>9</sup> The most common adverse events associated with abiraterone were fluid retention (30.5%) and hypokalaemia (17.1%). Grades 3/4 adverse events were few but liver function test abnormalities of grades 3/4 severity were detected in 10.4% of abiraterone-treated patients compared with 8.1% in the control arm, highlighting the importance of liver function monitoring throughout treatment. Since the COU-AA-301 study results, abiraterone has been approved in more than 80 countries worldwide and is now a standard treatment option, in combination with prednisone, for patients with relapsed or progressive mCRPC after docetaxel treatment.

Recently, the US FDA and European Commission approvals of abiraterone have expanded to include its use, in combination with prednisone or prednisolone, in mCRPC patients who have not received prior chemotherapy. The expanded approval was based on the phase III COU-AA-302 study among 1088 chemotherapy-naïve, asymptomatic, or mildly symptomatic mCRPC patients who were randomised to receive abiraterone plus prednisone or placebo plus prednisone. Results showed that abiraterone plus

prednisone resulted in a significant improvement in radiographic PFS compared with placebo (median, 16.5 vs. 8.3 months; HR = 0.53;  $p < 0.001$ ).<sup>10</sup> Furthermore, updated data from the third interim analysis demonstrated a significantly longer OS favouring the abiraterone arm (median, 35.3 vs. 30.1 months; HR = 0.79;  $p = 0.0151$ ).<sup>11</sup> Although the pre-specified OS efficacy boundary ( $p = 0.0035$ ) was not reached, most likely due to subsequent therapies given to most patients in the placebo arm, there was a clear trend for OS benefit favouring abiraterone plus prednisone treatment. Significantly prolonged time to chemotherapy and opiate use, improved patient quality of life, and good tolerability were also observed in the abiraterone arm.<sup>11</sup> In addition to its use following docetaxel treatment, abiraterone now represents a promising alternative after failure of ADT in mCRPC patients who are poor candidates for chemotherapy.

### **Enzalutamide: a Next-generation Androgen Receptor Antagonist**

Enzalutamide, formerly known as MDV3100, is an oral non-steroidal AR antagonist with a 5- to 8-fold greater binding affinity for AR than bicalutamide.<sup>12</sup> In addition to acting as a competitive inhibitor for AR ligand binding, enzalutamide targets multiple steps in the AR signalling pathway: it prevents AR translocation into the nucleus and induces a conformational change that blocks AR binding to androgen-response elements of the DNA, preventing activation of target genes responsible for prostate cancer growth. Furthermore, enzalutamide is a pure antagonist and does not have agonistic activity in a castration-resistant setting. In a phase I/II study in 140 men with progressive CRPC, enzalutamide monotherapy was associated with a serum PSA decline of 50% or greater in 62% of chemotherapy-naïve patients, and in 51% of patients who had previously received chemotherapy.<sup>13</sup>

The efficacy and safety of enzalutamide were further evaluated in the phase III AFFIRM trial, which randomised 1199 patients with CRPC who failed docetaxel treatment to receive enzalutamide 160 mg daily, or placebo. At the time of the pre-specified interim analysis after 520 deaths, the median OS (primary endpoint) was 18.4 months in the enzalutamide arm compared with 13.6 months in the placebo arm (HR for death in the enzalutamide group = 0.63;  $p < 0.001$ ).<sup>14</sup> On the basis of these results, the study was stopped and patients on placebo were allowed to cross-over and receive enzalutamide. Significant improvements

were also observed in the enzalutamide arm compared with placebo in all secondary endpoints, including PSA response rate, time to PSA progression, radiographic PFS, time to first skeletal event, and quality-of-life response. The rates of adverse events were similar in the two groups, with a lower incidence of grades 3/4 adverse events observed in the enzalutamide group.

Based on the positive AFFIRM data, the US FDA approved enzalutamide for the treatment of patients with mCRPC who previously received docetaxel. Ongoing studies will further evaluate the role of enzalutamide in early stage prostate cancer, including patients with ADT-naïve prostate cancer, those with mCRPC controlled by ADT, and those with progressive disease without prior chemotherapy treatment.

### **Radium-223: Role of Bone-targeted Therapy**

As bone metastases are common in CRPC and responsible for considerable morbidity through complications, specific therapies targeting bone metastases can play an important role in mCRPC treatment. Radium-223 chloride, a targeted alpha-emitter, is the first bone-targeted therapy to demonstrate a survival benefit in mCRPC patients. It binds selectively to bone metastases that have increased bone turnover, and emits high-energy alpha particles of short range (<100  $\mu\text{m}$ ), inducing irreversible double-stranded DNA breaks.<sup>15</sup> The short penetration of the alpha particle minimises treatment toxicity to the bone marrow and nearby unaffected organs.

Radium-223 has been approved by the US FDA since May 2013 for use in CRPC patients with bone metastases and no visceral metastases, based on findings from the phase III ALSYMPCA trial. A total of 922 patients with progressive CRPC and bone metastases were randomised, in 2:1 ratio, to receive radium-223 plus best standard of care or placebo plus best standard of care. Results at the pre-specified interim analysis from 809 patients showed that radium-223 significantly improved OS compared with placebo (median, 14.0 vs. 11.2 months; HR = 0.70;  $p = 0.002$ ).<sup>16</sup> There were marked improvements in terms of prolonged time to first skeletal event compared with placebo (median, 15.6 vs. 9.8 months; HR = 0.66;  $p < 0.001$ ), as well as time to alkaline phosphatase and PSA increases. The safety and tolerability of radium-223 were highly favourable, with a lower incidence of all grades of adverse events (including grades 3/4) observed in the radium-223 group compared with the placebo group.

Based on efficacy data at the interim analysis, the trial was terminated early and patients on placebo were recommended to cross-over to receive radium-223. In real-world practice, radium-223 is expected to provide an effective and well-tolerated treatment alternative, particularly for patients with bone metastases who are too frail for chemotherapy.

### **Orteronel: Potential as a Steroid-free Therapy**

Orteronel, also known as TAK-700, is a potent oral inhibitor of the CYP17 that specifically inhibits C17,20-lyase activity involved in androgen biosynthesis. Unlike other CYP17 inhibitors that target both C17,20-lyase and 17 $\alpha$ -hydroxylase activities, its selectivity for C17,20-lyase can potentially minimise the side-effects associated with mineralocorticoid excess secondary to 17 $\alpha$ -hydroxylase inhibition, and may reduce the need for steroid co-administration. Preliminary data from a phase I/II study of 97 patients treated with orteronel in three doses (300 mg twice daily, 400 and 600 mg twice daily plus prednisone, and 600 mg daily) showed that all treatment arms were well-tolerated and had similar efficacy in terms of PSA response rate.<sup>17</sup> A total of 51 patients had evaluable disease by Response Evaluation Criteria in Solid Tumors (RECIST); among them 10 had a partial response, 22 had stable disease, and 15 had progressive disease. Orteronel in combination with prednisone is currently being compared with placebo plus prednisone in two multicentre phase III trials of mCRPC patients who are naive to chemotherapy (ClinicalTrials.gov, NCT01193244) and those who have progressed on docetaxel (ClinicalTrials.gov, NCT01193257). However, both studies evaluate the use of orteronel with prednisone, which will make the potential advantage of its use as a steroid-free regimen difficult to detect. A phase I/II study is also ongoing to evaluate the efficacy and safety of orteronel in combination with prednisone and docetaxel (ClinicalTrials.gov, NCT01084655).

### **Cabazitaxel: Role of Chemotherapy as Second-line Treatment Option**

Cabazitaxel, a microtubule inhibitor, is a potent taxane recently approved by the US FDA for use in the second-line setting after progression on docetaxel. The phase III TROPIC registration trial clearly demonstrated an OS benefit of cabazitaxel given with prednisone over mitoxantrone plus prednisone in mCRPC patients who had progressed during or after docetaxel treatment (median, 15.1 vs. 12.7 months; HR = 0.72;  $p <$

0.0001).<sup>18</sup> Secondary endpoints also showed significant improvements in time to tumour progression and time to PSA progression favouring cabazitaxel treatment. However, concerns were raised about the increase in grade  $\geq 3$  neutropenia (82% in the cabazitaxel group vs. 58% in the mitoxantrone group) and grade  $\geq 3$  diarrhoea (6% in the cabazitaxel group vs. <1% in the mitoxantrone group). Since this study, co-administration of granulocyte-macrophage colony-stimulating factor has been suggested to reduce the risks of neutropenic complications associated with cabazitaxel use. Two clinical trials are also ongoing to compare the safety and efficacy of cabazitaxel at a lower dose (20 mg/m<sup>2</sup>) compared with the approved dose (25 mg/m<sup>2</sup>) in chemotherapy-naïve mCRPC and progressive disease on docetaxel treatment (ClinicalTrials.gov, NCT01308567 and NCT01308580).

With the increasing availability of new, rationally designed agents that are effective and have less toxicity, the role of cabazitaxel in the second-line setting has been questioned. Cabazitaxel may still play an important role in second-line mCRPC treatment, particularly in

patients with neuroendocrine differentiation, those with short response to ADT and progressive disease within 3 months of docetaxel regimen, and those who fail to respond to abiraterone or enzalutamide.

## OTHER EMERGING THERAPIES IN DEVELOPMENT

There are a variety of promising agents in clinical trials with the potential to prolong survival of patients with mCRPC. These include new agents targeting the AR signalling pathway, such as the CYP17 inhibitor and AR antagonist TOK-001, small-molecule AR antagonist ARN-509, agents targeting other tumorigenesis pathways such as the Src kinase inhibitor dasatinib, vascular endothelial growth factor and c-Met inhibitor cabozantinib, angiogenesis inhibitor tasquinimod, an antisense oligonucleotide to clusterin custirsén, and immunomodulating anti-cytotoxic T-lymphocyte antigen-4 antibody ipilimumab. Given that multiple pathways are implicated in the development of mCRPC, there is a potential for therapies to work synergistically to improve patient prognosis that is more effective than single agent treatment.

**Table.** American Urological Association treatment guidelines recommendations for six index patients with CRPC.<sup>19</sup>

Index patient	Recommendations
(1) Asymptomatic, non-metastatic CRPC	<ul style="list-style-type: none"> <li>• Should observe with continued androgen deprivation</li> <li>• May offer first-generation anti-androgens or first-generation androgen synthesis inhibitors to patients unwilling to accept observation</li> </ul>
(2) Asymptomatic or minimally symptomatic mCRPC without prior docetaxel	<ul style="list-style-type: none"> <li>• Should not offer systemic chemotherapy or immunotherapy outside of a clinical trial</li> <li>• Should offer abiraterone plus prednisone, docetaxel or sipuleucel-T* to patients with good PS</li> <li>• May offer first-generation anti-androgen, ketoconazole plus steroid or observation to patients who do not want or cannot receive standard therapies</li> </ul>
(3) Symptomatic mCRPC, good PS, no prior chemotherapy	<ul style="list-style-type: none"> <li>• Should offer docetaxel to patients with good PS</li> <li>• May offer abiraterone plus prednisone</li> <li>• May offer ketoconazole plus steroid, mitoxantrone or radionuclide therapy to selected patients who do not want or cannot receive standard therapies</li> <li>• Should not offer estramustine or sipuleucel-T*</li> </ul>
(4) Symptomatic mCRPC, poor PS, no prior docetaxel	<ul style="list-style-type: none"> <li>• May offer abiraterone plus prednisone</li> <li>• May offer ketoconazole plus steroid or radionuclide to patients who are unwilling or unable to receive abiraterone</li> <li>• May offer docetaxel or mitoxantrone to selected patients whose poor PS is directly related to the cancer</li> <li>• Should not offer sipuleucel-T*</li> </ul>
(5) Symptomatic mCRPC, good PS, prior docetaxel	<ul style="list-style-type: none"> <li>• Should offer abiraterone plus prednisone, cabazitaxel or enzalutamide; cabazitaxel or enzalutamide if patient has already received abiraterone</li> <li>• May offer ketoconazole plus steroid if abiraterone, cabazitaxel, or enzalutamide unavailable</li> <li>• May offer docetaxel re-treatment to patients who discontinued because of reversible side-effects but were benefiting from treatment at the time of discontinuation</li> </ul>
(6) Symptomatic mCRPC, poor PS, prior docetaxel	<ul style="list-style-type: none"> <li>• Should offer palliative care; alternatively, may offer to selected patients abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid, or radionuclide therapy</li> <li>• Should not offer systemic chemotherapy or immunotherapy</li> </ul>

Abbreviations: CRPC = castration-refractory prostate cancer; mCRPC = metastatic castration-refractory prostate cancer; PS = performance status.

\* Not available in Hong Kong.

## APPLYING EVIDENCE IN CLINICAL PRACTICE

Facing a significant increase in treatment options for CRPC, clinical decisions on the optimal treatment and sequencing of agents have become increasingly complex. To aid clinical decision-making, the American Urological Association published guidelines on CRPC management in 2013, providing evidence-based treatment recommendations on six index patients representing the most common clinical scenarios in daily practice. These recommendations are summarised in the Table.<sup>19</sup> The guidelines also recognise the propensity of bone metastases in prostate cancer and recommend preventive therapy for fractures and skeletal-related events for all patients, regardless of index status. For patients with bone metastases, physicians may offer denosumab or zoledronic acid for the prevention of skeletal-related events. Radium-223 was approved by the FDA only after the guideline publication and, thus, has not been included in the treatment recommendations.

## CONCLUSION

Medical and surgical castration remain the first-line therapy for patients with metastatic prostate cancer. For patients who develop castration-refractory disease despite first-line hormonal therapy, several agents that have demonstrated improvements in OS are now available. More treatment options will become available in the near future as a variety of novel agents are now undergoing clinical evaluation, many of which have reached phase III clinical trials. Today, treatment can be optimised by sequencing and combining therapeutic agents effectively for individual patients. Further investigations are needed to develop validated biomarkers to predict response, resistance or toxicity to single agents or a combination of agents, to ensure optimal, personalised therapy for each patient. From a disease that was once limited to mostly palliative care, recent therapeutic advances represent small, but definite and optimistic, progress in the management and prognosis of patients with mCRPC.

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