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## INTRODUCTION

# *Current management of advanced and castration resistant prostate cancer*

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**Introduction:** *Newer approaches to the management of advanced prostate cancer have rapidly evolved. While basic androgen deprivation remains as the first line in newly diagnosed hormone naïve metastatic prostate cancer, the agents used and strategies followed have undergone significant changes. Numerous new agents such as sipuleucel-T, abiraterone, enzalutamide, cabazitaxel and radium 223 have all been approved since 2010 to treat metastatic castration resistant prostate cancer (CRPC). New imaging techniques to detect advanced disease such as F-18 PET, 11 C-choline PET and other modalities are becoming available. The concepts of ‘bone health’ and the management of side effects related to androgen deprivation therapy are also gaining attention as men are being treated with longer courses of androgen deprivation. Understanding the theory behind these new agents and management approaches while focusing on the practical clinical considerations are essential to improve outcomes in advanced prostate cancer.*

**Materials and methods:** *A review of the current state of the art in the management of advanced and castration resistant prostate cancer presented in this Canadian Journal of Urology International supplement was*

*performed. Key findings are summarized and presented along with critical updates based on recent publications and meeting presentations.*

**Results:** *Key concepts identified in the management of advanced prostate cancer included the new understanding of prostate cancer based on translational discoveries, applications of various hormonally based strategies in advanced disease including traditional and recently approved agents. The use of new imaging modalities to identify metastatic disease, immunotherapy approaches and discussions of sequencing and which new agents are likely to be available in the future in the management of CRPC were identified. Bone targeted strategies are also addressed in the setting of androgen deprivation and metastatic disease.*

**Conclusions:** *The management of men with advanced prostate cancer has become more multidisciplinary as treatment options have expanded. As the use of these agents and new strategies expand, urologists, medical oncologists and radiation oncologists must all become familiar with this rapidly changing field in order to maximize the outcome of patients with advanced and castration resistant prostate cancer.*

**Key Words:** metastatic prostate cancer, castration resistant prostate cancer, docetaxel, sipuleucel-T, abiraterone, enzalutamide, cabazitaxel, radium 223, bone targeted agents, LHRH agonists and antagonists, prostate cancer imaging

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## Introduction

The development of new approaches in the management of advanced metastatic prostate cancer has accelerated rapidly over the last few years. Basic androgen deprivation therapy (ADT) has been refined and numerous new agents have been approved since 2010 to treat metastatic castration resistant prostate

cancer (mCRPC). Understanding the theory behind these new agents and approaches while focusing on the practical clinical applications are essential to improve outcomes. As the management of these patients with advanced disease becomes more multidisciplinary and the use of these agents expands, urologists, medical oncologists and radiation oncologists must become more familiar with these new treatment strategies. This 2014 CME supplement of *The Canadian Journal of Urology International* will review advanced prostate cancer with a focus on the newer therapeutic agents used for advanced and castration resistant disease.

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## Translational research discoveries redefine advanced prostate cancer

Drs. Tilki and Evans have reviewed the latest scientific discoveries that have resulted in critical changes in our understanding of the development and clinical management of advanced prostate cancer.<sup>1</sup> While seemingly minor to the casual observer, the change in terminology from “hormone refractory prostate cancer” to the use of the term “castration resistant prostate cancer” (CRPC) represents an important paradigm shift in how we manage prostate cancer that is progressing in the setting of castrate levels of testosterone. CRPC is defined by disease progression despite androgen deprivation therapy and may present as either a continuous rise in serum PSA levels, the progression of pre-existing disease, and/or the appearance of new metastases. This is deeply rooted in the recent translational discoveries in the field of basic prostate cancer research with these observations having a direct impact on men with advanced disease. Some of the more critical observations concerning biology of androgens and the androgen receptor axis in the development of CRPC have led to the development of many new therapeutic targets and agents. Several new medications such as the androgen biosynthesis inhibitor abiraterone and the androgen receptor pathway blocker enzalutamide have already found their place as Food and Drug Administration (FDA) approved medications in the United States and several other countries around the world.<sup>2</sup>

## Androgen deprivation in advanced prostate cancer

Reducing serum testosterone to low levels or so called “castrate” levels has been the mainstay of advanced prostate cancer for decades. The utility of this androgen ablation approach in metastatic disease is clearly established. In addition, the androgen deprivation strategies have been refined and adapted in other clinical settings. These include applications in adjuvant and neoadjuvant settings for radiation therapy and surgery and expanded interest and use of the intermittent hormonal therapy for advanced disease. Critical in the application of androgen deprivation is the importance of periodic measurement of serum testosterone levels to verify effective castration, generally considered to be <50 ng/dL.<sup>3</sup> Lastly, while the standard androgen ablation relies primarily upon luteinizing hormone releasing hormone (LHRH) analogues, Rove and Crawford provide insights on the use of both LHRH agonists and antagonists for androgen ablation while Moul discusses the practical applications of LHRH antagonists in the

spectrum of advanced prostate cancer.<sup>4,5</sup> Dr. Moul also references a recent global pooled trial analysis of the risk of cardiac events within 1 year of initiating androgen deprivation. Cardiac events were noted to be significantly lower among men treated with a GnRH antagonist compared with GnRH agonists, an observation that is likely to continue to fuel the debate over cardiovascular risk and androgen deprivation strategies.<sup>6,7</sup>

Intermittent androgen deprivation therapy (IADT) involves cycles of ADT that are interrupted by injection-free intervals where testosterone levels are permitted to rise above castrate levels. It has proposed that IADT potentially reduces some of the bone and cardiovascular health sequelae of ADT and may improve oncologic outcomes, although this is not without some controversy. Dason and associates review how the approach works and most importantly summarize the major clinical trials that have been performed in this area.<sup>8</sup> The authors also provide useful summaries of the potential long term ADT complications such as the metabolic syndrome and bone health issues.

## Secondary hormonal manipulation in advanced prostate cancer

Many new agents have been approved for advanced CRPC over the last few years. Prior to 2010, docetaxel remained the only agent approved when androgen deprivation failed. Secondary hormonal manipulation in CRPC was commonly performed with the concept first widely promoted by Small and Vogelzang.<sup>9</sup> Drs. Al-Asaad and Winkvist review current management guidelines and discuss what the role of secondary hormonal manipulation is in the current CRPC space.<sup>10</sup> Table 1 summarizes some of the more common and traditional secondary hormonal manipulations used before the introduction of newer agents such as abiraterone that some consider as a form of secondary hormonal manipulation.

**TABLE 1. Traditional secondary hormonal manipulations in the setting of castration resistant prostate cancer<sup>9,10</sup>**

Type of therapy	Response rate (rarely durable)
Steroids	10%-20%
Ketoconazole	30%-60%
Estrogens	40%-60%
Antiandrogens	20%
Antiandrogen withdrawal	20%

## Role of imaging in CRPC

Determining the transition of CRPC to mCRPC is of vital importance for many reasons. First, the early identification of asymptomatic bony metastatic lesions may allow intervention to minimize the burden in terms of morbidity and cost of skeletal related events.<sup>11</sup> Secondly, medications such as sipuleucel-T are only indicated for asymptomatic or minimally symptomatic mCRPC.<sup>12</sup> This progression to mCRPC with detectable radiographic lesions is a seminal event significantly affecting treatment decisions. There is currently little formal guidance concerning the frequency of imaging in patients without symptoms. Recent recommendations by the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group have been published in attempt to address these limitations.<sup>13</sup> In addition to standard imaging technologies, a series of newer imaging modalities such as F-18 PET, 11 C-choline PET are becoming available to identify more accurately the presence of early metastatic prostate cancer before routine bone scan detection. Prostate cancer imaging advances are reviewed by Dr. Leung and associates.<sup>14</sup>

## Immunotherapy in CRPC

While prostate cancer has traditionally been considered a “non-immunogenic tumor” recent discoveries have made prostate cancer a target of immunotherapy.<sup>15</sup> The active cellular immunotherapy, sipuleucel-T, was a first-in-class agent approved for mCRPC in 2010. This was based on the 4.1 months survival in the IMPACT trial demonstrating superiority of this novel approach in mCRPC.<sup>16</sup> The review by Gomella and associates discusses the development of sipuleucel-T and other evolving immunotherapy strategies and addresses the practical applications of administration of the sipuleucel-T.<sup>12</sup>

## Androgen biosynthesis inhibition

As noted by Tilki and Evans, the androgen axis remains active in the setting of CRPC.<sup>1</sup> This observation and others including the discovery that metastatic prostate cancer can generate its own androgens has led to the development of agents that can impact androgen production in all sites in the body, including within the tumor itself. Abiraterone is the first approved androgen biosynthesis inhibitor for mCRPC. Abiraterone acetate, a pregnenolone derivative, is an oral inhibitor of the steroidogenic enzyme CYP17. Abiraterone possesses dual 17- $\alpha$  hydroxylase and C17,20-lyase

blocking activity that results in decreased gonadal and extra-gonadal androgen synthesis.<sup>17</sup> While initially approved for post-docetaxel administration, it is now available in the pre-chemotherapy setting. The development, mechanisms of action and practical treatment considerations of abiraterone are reviewed by Mostaghel and Lin.<sup>18</sup>

## Inhibition of the androgen receptor signaling pathway

In considering the androgen sensitivity of CRPC, inhibition of the androgen receptor signaling pathway is a viable strategy. Enzalutamide, formerly known as MDV3100, was developed and now approved as an orally administered androgen receptor inhibitor indicated for the treatment of patients with mCRPC who have previously received docetaxel. In contrast to the androgen receptor blocker bicalutamide, enzalutamide has no agonist properties. Enzalutamide competitively inhibits androgen receptor binding and androgen receptor nuclear translocation and interaction with DNA.<sup>19</sup> Based on the results of the recently reported PREVAIL trial (enzalutamide in the pre-chemotherapy mCRPC setting) at the American Society of Clinical Oncology (ASCO) 2014 Genitourinary (GU) Cancers Symposium in San Francisco, it is widely anticipated that this agent will be approved in this setting in the future.<sup>20</sup> The PREVAIL trial demonstrated improved overall survival and radiographic progression-free survival in patient with mCRPC who have not received chemotherapy. Drs. Hoffman-Censits and Kelly provide an introduction to the preliminary clinical trials that support the use of enzalutamide and discuss the practical applications of enzalutamide for the clinician.<sup>21</sup>

## Bone targeted therapy with radium 223 dichloride

A hallmark of advanced prostate cancer is the frequent involvement of the bone. These metastatic lesions can cause pain or result in skeletal related events such as spinal cord compression or fractures with the extent of osseous metastasis directly correlated with overall survival. Radiopharmaceuticals have been available for many years to palliate painful bony metastasis. Commonly used agents to treat prostate cancer bony metastasis have included the beta particle emitting agents strontium 89 and samarium 153 with marrow suppression being their main limiting toxicity. While effective at short term palliation, neither of these agents has shown any utility in extending survival.<sup>22</sup> Radium

223 dichloride (formerly known as alpharadin) is a first-in-class alpha particle-emitting radiopharmaceutical approved for the treatment of patients with CRPC with symptomatic bone metastases and no known visceral metastasis. Radium 223, a calcium mimetic, targets bone but as an alpha emitter has a shorter range with less bone marrow toxicity when compared to the existing beta emitting agents.

Radium 223 dichloride has been included in the latest 2014 edition of the National Comprehensive Cancer Network (NCCN) prostate cancer treatment guidelines where it has been given a category 1 recommendation as both a first-line and second-line option for the treatment of patients with symptomatic bone metastases and no known visceral disease.<sup>23</sup> The role of all radiopharmaceuticals including the practical considerations in the use of radium 223 is discussed by Dr. Den and associates.<sup>24</sup>

## Chemotherapy for mCRPC

Historically, no chemotherapeutic agents had been shown to be effective in the management of advanced prostate cancer. The only agent formally approved for metastatic prostate cancer progressing on hormonal ablation before 2004 was mitoxantrone and that indication was only for palliation when used in combination with prednisone. In 2004 docetaxel was formally approved "with prednisone in androgen independent (hormone refractory) metastatic prostate cancer".<sup>25,26</sup> This taxane served as the mainstay for prostate cancer that escaped hormone suppression until the next medication sipuleucel-T was approved in 2010. Docetaxel has remained as an important agent in this patient population and many of the newer drugs approved including abiraterone and enzalutamide were initially approved only after this chemotherapy had failed. Cabazitaxel, a microtubule inhibitor related to docetaxel, has also recently been approved in the post-docetaxel setting. The official label states cabazitaxel is indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.<sup>27</sup> While much excitement has been generated amongst all of the newer agents recently approved for mCRPC, chemotherapy remains a proven option. Dr. Petrylak, an early pioneer in the use of docetaxel in prostate cancer, provides a review on the recent history of chemotherapy for prostate cancer and explains the effective management strategies to maximize outcome and limit toxicity using docetaxel and cabazitaxel chemotherapy for mCRPC.<sup>26</sup>

Of note it is likely that chemotherapy will become even more critical in the management of metastatic prostate cancer even before the demonstration of castration resistance. The National Cancer Institute (NCI) has just announced the preliminary results of the ECOG 3805 trial (CHAARTED: ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer).<sup>28</sup> Men received either ADT alone or ADT with the chemotherapy drug docetaxel every 3 weeks over a period of 18 weeks. A significant improvement in the overall survival was noted favoring the participants who had received docetaxel chemotherapy in addition to the ADT compared to the ADT alone (3 year survival rates of 69.0% versus 52.5% respectively). Further analysis showed that patients with a high extent of metastatic disease accounted for most of the benefit in the overall survival from docetaxel plus ADT (3 year survival rates of 63.4% versus 43.9% for ADT alone). Median follow up to date is 2 years. Full details are expected at the 2014 ASCO meeting in Chicago but this could represent another major paradigm shift and expanded role for cytotoxic chemotherapy in the initial therapy of hormone naïve metastatic prostate cancer.

## Bone health in prostate cancer

Bone health is a major issue in prostate cancer as it can impact quality and duration of life of the patients. The core concepts of "bone health" in prostate cancer as summarized by Dr. Tombal refer to the diagnostic, primary and pharmacological prevention, and treatment of cancer treatment induced bone loss (CTIBL) and metastasis, and their respective complications such as osteoporotic fractures and skeletal related events or SREs.<sup>29</sup> ADT can induce significant changes in bone mineral density and increase the risk of fracture. EAU guidelines recommend treating osteoporotic patients based on DEXA scanning with denosumab or bisphosphonates, but do not provide guidance for patients with osteopenia.<sup>30</sup> NCCN guidelines recommend a variety of agents such as bisphosphonates (zoledronic acid or alendronate), or denosumab 60 mg SQ every 6 months) for men with a high likelihood of fracture on androgen deprivation.<sup>23</sup>

Strategies to prevent bone metastasis are also reviewed here although this still remains a major issue to address. The presence of bony metastatic lesions can further weaken the integrity of the bone. It is estimated that in men with progressive life threatening metastatic prostate cancer over 90% of men will have bone metastasis. EAU and NCCN treatment guidelines recommend that bone metastatic CRPC patients should receive either zoledronic acid or denosumab and both

TABLE 2. Agents with overall survival benefit in metastatic castration resistant prostate cancer

Drug	Trial	Comparator	Primary endpoint	FDA approval
<b>Chemotherapy-naïve</b>				
Abiraterone acetate + prednisone	COU-AA-302 <sup>33</sup>	Placebo + prednisone	OS benefit 5.2 months*	Dec 2012
Sipuleucel-T	IMPACT <sup>16</sup>	Placebo	OS benefit 4.1 months	Apr 2010
Radium 223 dichloride	ALSYMPCA <sup>34</sup>	Placebo	OS benefit 3.6 months	May 2013
Enzalutamide (interim analysis)	PREVAIL <sup>20</sup>	Placebo	OS benefit 2.2 months	N/A
<b>Post-chemotherapy</b>				
Abiraterone acetate + prednisone	COU-AA-301 <sup>35</sup>	Placebo + prednisone	OS benefit 4.6 months	Apr 2011
Enzalutamide	AFFIRM <sup>36</sup>	Placebo	OS benefit 4.8 months	Aug 2012
Cabazitaxel + prednisone	TROPIC <sup>37</sup>	Mitoxantrone + prednisone	OS benefit 2.4 months	June 2010
Docetaxel + prednisone	TAX327 <sup>38</sup>	Mitoxantrone + prednisone	OS benefit 2.4 months	May 2004

FDA = Food and Drug Administration; OS = overall survival

\*p = 0.0151. Did not meet the prespecified value for statistical significance (Pre-specified significance by O'Brien-Fleming boundary = 0.0008)

note the superiority of the latter in delaying SRE.<sup>23,29</sup> The role of bone targeted therapy such as radium 223 in the setting of mCRPC is also addressed in this supplement by Den and associates.<sup>24</sup>

### Sequencing mCRPC: an evolving challenge

The availability of numerous agents in the CRPC space is certainly good news. However, the downside of having multiple choices across the spectrum of advanced disease creates uncertainty concerning the optimum way to combine or sequence the medications to derive maximum benefit. Dr. Dreicer thoughtfully considers where some of these newer agents might be best positioned in a "clinically rational and economically viable manner".<sup>31</sup> He notes that certain sequencing issues will be addressed by formal trials such as an ongoing phase III trial randomizing patients with mCRPC to receive either docetaxel or cabazitaxel ([www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT01308567).

### What's next in advanced prostate cancer?

Dozens of clinical trials evaluating new therapeutics in men with metastatic prostate cancer are in progress. Some of these include new first in man agents while others involve the application of existing agents in new settings or in combination with other agents. While many agents under evaluation such as ARN-509, TAK-700 and TOK-001 continue on the theme of interacting within the androgen axis while others interfere with

other pathways of prostate cancer progression such as cabozantinib and OGX-011. Based on the proof of principle that of sipuleucel-T immunotherapy is effective, this area continues to be a targeted area of interest in prostate cancer with several other prostate cancer vaccines and immune check point inhibitors in late stage clinical trials. Thoreson and associates have reviewed the emerging therapies in CRPC and focus on some of the trials that will provide near term results.<sup>32</sup>

### Conclusions

The rapid advances in our therapeutic options for advanced prostate cancer are impressive and at the same time overwhelming and sometimes difficult to place in proper clinical context. Table 2 summarizes some of the recent agents, trials, and outcomes of the latest medications used in the management of mCRPC. One challenge going forward is to demonstrate that some of these newer agents in development are superior to the previously approved agents. Since patients who fail some of these newer agents can be treated with existing drugs if they progress, the effectiveness of the new drug may not be as pronounced.

Prostate cancer guidelines from many organizations such as the AUA, EAU, CUA and NCCN have incorporated most of these new therapeutic agents and approaches to advanced and CRPC.<sup>23,30,39,40</sup> As clinicians begin to understand the rationale for these newer agents and the practical aspects of their clinical application their use will likely expand to benefit more eligible patients.

## Disclosure

Dr. Leonard G. Gomella serves as a consultant to Astellas, Bayer, Dendreon and Janssen. Dr. Daniel P. Petrylak has received consulting fees from Bayer, Bellicum, Dendreon, Sanofi Aventis, Johnson and Johnson, Exelixis, Ferring, Millineum, Medivation and Pfizer. He also has received grant support from Oncogenex, Progenics, Johnson and Johnson, Millineum, Celgene and Dendreon. Dr. Bobby Shayegan has no relevant financial relationships to disclose. □

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