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## Review article

Androgen receptor targeted therapies in metastatic castration-resistant prostate cancer – The urologists' perspective<sup>☆</sup>Jo-Lynn Tan<sup>a, b, \*</sup>, Niranjan Sathianathan<sup>a, c</sup>, Nicolas Geurts<sup>a</sup>, Rajesh Nair<sup>a</sup>, Declan G. Murphy<sup>a, d</sup>, Alastair D. Lamb<sup>a, e</sup><sup>a</sup> Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia<sup>b</sup> School of Medicine, University of Western Australia, Crawley, Australia<sup>c</sup> Department of Urology, University of Minnesota, Minneapolis, MN, USA<sup>d</sup> Australian Prostate Cancer Research Centre, Epworth Healthcare, Richmond, Australia<sup>e</sup> Nuffield Department of Surgery, Old Road Campus, University of Oxford, UK

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## ABSTRACT

Androgen deprivation therapy (ADT), which involves the maximal suppression of circulating testosterone, underpins the treatment approach to metastatic hormone sensitive prostate cancer. Although initial responses are generally favourable, approximately half of cases progress to metastatic castrate resistant prostate cancer (mCRPC), rendering traditional hormonal therapies ineffective. mCRPC is defined by disease progression despite established ADT. New research has improved our understanding of the molecular mechanisms behind metastatic castration-resistant prostate cancer (mCRPC). This has led to a renewed interest in the androgen receptor as a target for therapy, paving the way for the introduction of novel androgen therapies such as abiraterone acetate and enzalutamide. Recent trials on these treatments have demonstrated their benefit to improving overall survival in the setting of mCRPC. The resultant effect is a new, constantly changing, and complex treatment paradigm for treating clinicians, who are now required to know the mechanism of actions of new medications, side effect profiles, modes of administration, and preferred sequencing of various treatment options. Furthermore, treatments involving new androgen biosynthesis are currently being developed and tested. Therefore, in the context of a highly heterogeneous disease with a continuously changing treatment landscape, management of mCRPC can be particularly challenging.

The purpose of this review is to provide an overview of the literature on new androgen receptor targeted therapies, and discuss the changing treatment landscape specific to metastatic CRPC.

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## 1. Introduction

Prostate cancer is currently the most frequently diagnosed cancer in men, and the third leading cause of male cancer death, in developed countries.<sup>1</sup> There is an observable increasing trend in the incidence of prostate cancer worldwide, in the context of increasing use of prostate specific antigen (PSA) testing.<sup>2</sup> However, mortality rates for prostate cancer have fallen in developed countries, and this has been attributed to improved treatment and earlier detection.<sup>3</sup>

Prostate cancer that is detected early is usually treated with local therapy, mainly surgery or radiotherapy. Despite this, up to thirty percent of men in Taiwan have metastatic prostate cancer at the time of diagnosis,<sup>4</sup> and approximately half of metastatic prostate cancers progress to castration resistant disease within two years of follow-up.<sup>5</sup> Metastatic castrate resistant prostate cancer (mCRPC) is broadly defined as disease progression despite established androgen depletion therapy; signs and symptoms of progression include sequential PSA rises, progression of pre-existing disease, and/or the appearance of new metastases evident on imaging (CT, MRI or radionuclide bone scintigraphy).<sup>6</sup>

Androgen deprivation therapy (ADT) underpins the treatment approach to metastatic hormone sensitive prostate cancer.<sup>7</sup> This involves suppressing circulating testosterone to an undetectable level leading to a reduction in cancer cell proliferation and/or cell

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death. Standard approaches to ADT can be divided into surgical – bilateral orchidectomy – and medical using a luteinising hormone-releasing hormone (LHRH) analogues alone or in combination with an androgen receptor (AR) antagonist. Although initial responses to ADT are favourable, disease progression to mCRPC, defined by its resistance to traditional hormonal therapies, is common.<sup>5,8,9</sup>

ADT for mCRPC has been an area of focus in recent years in the light of new research that has improved our understanding of the molecular mechanisms behind mCRPC and the androgen receptor as a target. A number of Phase III trials demonstrating improvement in overall survival and progression-free survival has led to the introduction of novel androgen therapies such as abiraterone acetate and enzalutamide.<sup>10,11</sup> This has resulted in a more complicated paradigm for clinicians, with the ‘jobbing’ oncologist or urologist now required to know the mechanism of actions of new medications, side effect profiles, modes of administration, and preferred sequencing of various treatment options. Indeed, the heterogeneity of mCRPC and consequent permutations of clinical scenarios make management particularly challenging.

The purpose of this review is to provide an overview of the literature on new androgen receptor targeted therapies, and discuss the changing treatment landscape specific to mCRPC.

## 2. AR as a therapeutic target for CRPC

The AR is a transcription factor that plays a key role in normal prostate cell growth. There is increasing evidence that androgen receptor activity persists in almost all patients who develop castration-resistant disease, and is thus a valid drug target for all stages of prostate cancer.<sup>5,12</sup> After treatment by medical or surgical castration, prostate cancers adapt to the androgen-deprived environment to maximise androgen receptor function through mechanisms facilitated by the genetic instability of cancer cells.<sup>5,13</sup> These mutations in the androgen receptor gene give “new” receptor functionality by allowing the androgen receptor to be activated by ligands other than testosterone or dihydrotestosterone, such as hydrocortisone and progesterone.<sup>14,15</sup>

## 3. Literature search

We searched each of PubMed, MEDLINE and EMBASE from January 2000 to January 2017 using combinations of the following key words: “prostate cancer”, “androgen deprivation therapy”, “castrate resistant”, “androgen independent”, “anti-androgen”, “androgen receptor”, “androgen receptor targeted therapy”, “androgen receptor blocker”, “androgen receptor signalling”, “androgen receptor signaling inhibitor”, “androgen synthesis inhibitor”, “abiraterone”, and “enzalutamide”. Peer-reviewed articles from retrospective reviews, high quality systematic reviews and meta-analyses were included. Only full-text, English language and peer-reviewed publications were included.

## 4. Treatment options for metastatic castration-resistant disease

Treatment for mCRPC aims to ‘control’ rather than ‘cure’ the disease. Prior to the introduction of novel androgen receptor targeted therapies, chemotherapy was the mainstay of treatment for mCRPC. Chemotherapy acts to interrupt cell division (mitosis), which results in decreased cancer cell proliferation. Those most commonly used in prostate cancer (taxanes) do this by inhibiting microtubule disassembly, an important step in chromosomal replication during the M phase of the cell-cycle. Docetaxel was shown in Phase III trials in 2004 to improve overall survival and became the standard second-line therapy (after androgen

blockade) in conjunction with prednisone.<sup>8,16</sup> Newer chemotherapeutic agents such as cabazitaxel have since been introduced and have been shown to improve overall survival in patients previously treated with docetaxel.<sup>17,18</sup> Other treatment options for mCRPC include immunotherapies such as Sipuleucel-T for asymptomatic or minimally symptomatic mCRPC,<sup>19,20</sup> and radionuclide therapies (e.g. Radium-223, strontium, samarium).<sup>21</sup> The uptake of these last two options has been limited by cost.

Androgen receptor antagonists and androgen synthesis inhibitors are the mainstay of androgen receptor targeted therapies. The first generation AR antagonist was flutamide followed by second-generation bicalutamide and nilutamide. Bicalutamide, a derivative of flutamide, remains the most commonly used AR antagonist, but more recent attention has focussed on third-generation AR antagonist enzalutamide. First and second-generation AR antagonists, though developed to inhibit AR function, were later found to provide incomplete inhibition due to partial or weak AR co-activator and agonist actions.<sup>22</sup> Bicalutamide is usually administered at 50 mg daily, with studies having shown similar responses with this lower dose when compared to higher doses of 200 mg daily and 150 mg daily.<sup>23–25</sup> Mixed efficacy has been shown for nilutamide as a second-line agent for patients who failed treatment with bicalutamide or flutamide.<sup>26,27</sup> Anti-androgen withdrawal syndrome, the sudden clinical improvement and decline in PSA on withdrawal of hormone treatment in hormone resistant prostate cancer, has been shown to occur in a subset of patients (15–30%) and can last up to six months; withdrawal responses have been reported in bicalutamide, nilutamide and flutamide.<sup>28,29</sup>

Historically, anti-androgen therapies focussed on the use of LHRH agonists, with or without the addition of an AR antagonist such as bicalutamide. LHRH analogues work on the principle of negative feedback. There is an initial flare in serum testosterone in response to the increase in LHRH levels, prior to negative regulation leading to suppression of GnRH release from the hypothalamus and consequent reduction in LHRH and testosterone levels. AR antagonists are usually offered prior to starting LHRH treatment to mitigate the initial testosterone spike and continued for approximately two weeks after commencement of LHRH therapy to cover the flare period.<sup>30</sup>

Abiraterone and enzalutamide, the most recently licenced hormone agents, are discussed in greater detail below. Both have been approved as oral agents for mCRPC having been shown to improve overall survival in men with disease progression after docetaxel. Table 1 provides a summary of the mechanism of actions, side effect profiles, and modes of administration.

### 4.1. Novel androgen receptor antagonist

#### 4.1.1. Enzalutamide

Enzalutamide (MDV-3100) is an androgen receptor signalling inhibitor (ARSI) that binds the androgen receptor ligand binding domain (LBD) and thereby inhibits nuclear translocation of the androgen receptor, thus inhibiting the association of the androgen receptor with nuclear DNA.<sup>31,32</sup> It was discovered by laboratory driven research in New York and is a fine example of bench to bedside science.<sup>33</sup>

A large phase III trial, the AFFIRM study, compared enzalutamide with placebo in men with mCRPC previously treated with docetaxel.<sup>34,35</sup> In this study, overall survival was significantly greater with enzalutamide compared with placebo (median 18.4 vs 13.6 months, HR 0.63, 95% CI 0.53–0.75;  $p < 0.001$ ). Furthermore, enzalutamide demonstrated significant benefit across all study secondary endpoints of this study. These included a greater than 50% decrease in PSA (54% vs 2%;  $p < 0.001$ ), a greater than 90%

**Table 1**

Summary of mechanism of action, side effects, and contraindications for recently approved anti-androgen oral agents for mCRPC.

Drug	Mode of administration	Mechanism of action	Side effect profile	Contraindications
Abiraterone acetate	Oral	Inhibits androgen synthesis via CYP-17	Hepatotoxicity, hypokalaemia, hypertension, gastrointestinal upset	Severe liver dysfunction, hypokalaemia, heart failure
Enzalutamide	Oral	Inhibits AR and AR translocation	Seizures, encephalopathy, hypertension, fatigue, gastrointestinal upset	Seizures

decrease in PSA (25% vs 1%;  $p < 0.001$ ), time to PSA progression (8.3 vs 3.0 months, HR 0.25;  $p < 0.001$ ), soft tissue response rate (43% vs 18%,  $p < 0.001$ ), radiographic progression-free survival (8.3 vs 2.9 months, HR 0.40;  $p < 0.001$ ), quality of life response rate (43% vs 18%,  $p < 0.001$ ), and time to first skeletal-related event (16.7 vs 13.3 months, HR 0.69;  $p < 0.001$ ). Secondary analyses reinforced findings on improved health-related quality of life,<sup>36</sup> but also added that the benefits in overall survival and delayed disease progression were consistent across ages.<sup>37</sup>

Phase III trials from the PREVAIL study investigated the short and long-term efficacy of enzalutamide in chemotherapy naïve men with mCRPC who were asymptomatic or minimally symptomatic.<sup>10,35,38,39</sup> This was a double-blind randomized study, with the treatment group receiving 160 mg of enzalutamide daily. Analysis showed that enzalutamide reduced the risk of radiographic progression or death by 68% (HR 0.32, 95% CI 0.28–0.37;  $p < 0.0001$ ) and the risk of death by 23% (HR 0.77, 95% CI 0.67–0.88;  $p = 0.0002$ ).<sup>35,38</sup> The initial trial was stopped after a planned interim analysis due to survival benefit for patients receiving enzalutamide compared to placebo (median 32.4 vs 30.2 months, HR 0.71, 95% CI 0.60–0.84). Similarly, enzalutamide showed superior benefit compared to placebo for improvements in quality of life based on the median time to clinically significant deterioration (11.3 vs 5.6 months, HR 0.62, 95% CI 0.54–0.72) and visual pain rating scales for clinically significant bone pain (27% vs 18%;  $p < 0.0001$ ).<sup>39</sup> The enzalutamide group also experienced a significantly longer time to first skeletal-related event compared to placebo (31.1 vs 31.3 months, HR 0.72, 95% CI 0.61–0.84;  $p < 0.0001$ ).<sup>39</sup>

Two double-blind phase II randomised studies compared enzalutamide with bicalutamide.<sup>40–42</sup> The TERRAIN study investigated progression free survival in asymptomatic or minimally symptomatic men with mCRPC, by comparing 160 mg enzalutamide daily with 50 mg bicalutamide daily.<sup>42</sup> This study found a significantly longer progression free survival time with enzalutamide versus bicalutamide (15.7 vs 5.8 months, HR 0.44, 95% CI 0.34–0.57;  $p < 0.0001$ ). Further analysis of quality of life data concluded that enzalutamide treatment was associated with better health-related quality of life compared with bicalutamide, although no difference in time to clinically significant pain progression was found.<sup>40</sup> Reinforcing the findings from the TERRAIN study, the STRIVE trial studied men with non-metastatic and metastatic CRPC, and reported a 76% reduction of risk of disease progression or death in the enzalutamide treatment group, compared with bicalutamide (HR 0.24, 95% CI 0.18–0.32;  $p < 0.001$ ).<sup>41</sup> Additionally, in the enzalutamide group compared to bicalutamide group, progression free survival was significantly longer (19.4 vs 5.7 months, HR 0.24, 95% CI 0.18–0.32;  $p < 0.001$ ), time to PSA progression was significantly longer (HR 0.19, 95% CI 0.14–0.26;  $p < 0.001$ ), proportion of patients with a  $\geq 50\%$  PSA response was greater (81% vs 31%;  $p < 0.001$ ) and in metastatic patient, radiographic progression free survival was longer (HR 0.32, 95% CI 0.21–0.50;  $p < 0.001$ ).<sup>41</sup>

The overall data demonstrates with significance that enzalutamide improves overall survival in men with mCRPC who are both chemotherapy naïve and who have previously been treated with

docetaxel. This not only offers this drug as an important first-line therapy, but also as a second-line option in men who have failed docetaxel treatment.

## 4.2. Androgen synthesis inhibitors

### 4.2.1. Abiraterone acetate plus prednisone

Abiraterone acetate is a potent and irreversible inhibitor of the CYP17, a critical enzyme in androgen biosynthesis (Fig. 1).<sup>43,44</sup> It primarily inhibits the five percent of androgen biosynthesis that takes place in the pars reticularis of the adrenal glands, but also inhibits de novo androgen synthesis in the testis and also, potentially, the tumour itself. Two Phase III trials, COU-AA-301 and COU-AA-302, have demonstrated the efficacy of abiraterone for mCRPC, showing benefits to overall survival, time to PSA progression, radiological progression-free survival and PSA response rate, when compared to placebo.<sup>11,45–48</sup>

The first trial looked at men with mCRPC who had previously received treatment with docetaxel. In this study, men were randomly assigned to having 1000 mg abiraterone plus 5 mg prednisolone 5 mg twice a day, or to a placebo plus prednisolone. The primary end-point in this study was disease progression, defined by deterioration in pain and performance status, and disease progression on scans and PSA rises. At the interim analysis, abiraterone demonstrated clear survival advantage that exceeded study criteria and thus the trial was terminated early. Final study analysis concluded that abiraterone plus prednisolone offered significantly better survival advantage compared to placebo (15.8 vs 11.2 months; HR 0.74, 95% CI 0.64–0.86;  $p < 0.001$ );<sup>47</sup> this was the case even in patients with liver and lung metastases who had poorer prognosis (median 12.9 vs 8.3 months). Furthermore, abiraterone plus prednisolone showed statistically significant improvements to PSA progression (8.5 vs 6.6 months), radiologic progression-free survival (5.6 vs 3.6 months) and PSA response rates (29.5% vs 6.5%).

Secondary analyses further showed an advantage of abiraterone compared to placebo on the impact of clinically significant bone pain secondary to bone metastases and the functional impact on activities of daily living. Compared to the placebo group, the group on abiraterone experienced a statistically significant increase in the time to the first skeletal-related event such as pathologic fracture, spinal cord compression, or palliative radiation therapy and/or bone surgery.<sup>46</sup>

The COU-AA-302 trial studied men with mCRPC who had not previously received chemotherapy.<sup>45,48,49</sup> In this cohort, the abiraterone plus prednisolone group when compared to the placebo group demonstrated superior overall survival (median 34.7 vs 30.3 months; HR 0.81, 95% CI 0.70–0.93;  $p = 0.0033$ ) and radiographic progression-free survival (median 16.5 vs 8.3 months, HR 0.53, 95% CI 0.45–0.62;  $p < 0.001$ ).<sup>45,49</sup>

Few studies have compared abiraterone to enzalutamide, and thus there is little guidance regarding the sequencing of these two treatments.<sup>50,51</sup> There is an absence of large trials investigating the efficacy of abiraterone after enzalutamide and vice versa. However,

it has been proposed that the treatment effect of abiraterone is greater in patients not previously treated with enzalutamide.<sup>52,53</sup>

Current guidelines recommend abiraterone acetate for patients with asymptomatic or minimally symptomatic mCRPC, including those who are docetaxel naïve,<sup>54,55</sup> and in particular those with good performance status.<sup>56</sup> A low dose oral prednisolone is needed when administering abiraterone to attenuate the side effects associated with mineralocorticoid excess. This means that regular surveillance of blood pressure and serum potassium levels are prudent. Additionally, in chemotherapeutic naïve men who develop disease progression on abiraterone, subsequent use of docetaxel can still offer therapeutic benefit.<sup>57</sup> When selecting between enzalutamide and abiraterone as initial agents for mCRPC treatment, it is important to individualise treatment options based on toxicity profiles, and the impact of prednisone use which is mandatory with abiraterone.<sup>58</sup>

In summary, abiraterone administered with prednisolone offers significant improvement to overall survival and slows disease progression in both the setting of failed docetaxel and chemotherapy naïve mCRPC. Additionally, abiraterone is useful in reducing metastatic bone pain and prolonging the onset of skeletal complications. Data comparing abiraterone and enzalutamide is limited, therefore selection between the two needs to be based on each clinical case.

A summary of key trials investigating the use of androgen receptor targeted therapies in mCRPC is outlined in Table 2.

## 5. Emerging therapies – trials currently underway

The treatment landscape for mCRPC with new androgen biosynthesis is constantly changing with more agents currently being developed and tested.

Galeterone is an agent with a dual mechanism of action, with both anti-androgen synthesis and AR degrading properties. It blocks androgen synthesis via selective and irreversible CYP17A1 inhibition; AR degradation occurs by degrading the T877A AR and possibly the AR-V7.<sup>59</sup> Phase III trials are underway comparing galeterone with enzalutamide in abiraterone or enzalutamide treatment-naïve mCRPC patients. Niclosamide is an anti-helminthic that works via IL-6-Stat3-AR pathway to inhibit AR-V7 activity and enhance enzalutamide and abiraterone efficacy. Early trials are currently underway in cohorts of mCRPC patients who are AR-V7 positive.<sup>60,61</sup> Another agent, EPI-506, is currently undergoing Phase I and II trials in mCRPC patients who have failed both enzalutamide and abiraterone. Its mechanism of action lies in AR-antagonistic activity, and by targeting both full-length AR and AR-V7 thereby blocking receptor transcriptional activity.<sup>62</sup>

## 6. Companion diagnostics

Companion diagnostics refers to the use of genomic and molecular predictive biomarkers to guide therapy and is a novel area of research in the management of mCRPC. The molecular heterogeneity of CRPC increasingly lends support to an individually tailored approach to treatment based on disease biology. An example of the successful use of this approach is the TOPARP trial, which investigated the use of poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors for the treatment of mCRPC. They demonstrated good treatment responses in patients with DNA repair gene defects and who had not responded to previous treatments.<sup>63</sup>

Recent data has demonstrated support for the importance of the AR-V7 biomarker in understanding mechanisms of resistance to abiraterone and enzalutamide.<sup>64</sup> Given the interpatient molecular heterogeneity and potential for changes in disease biological profile

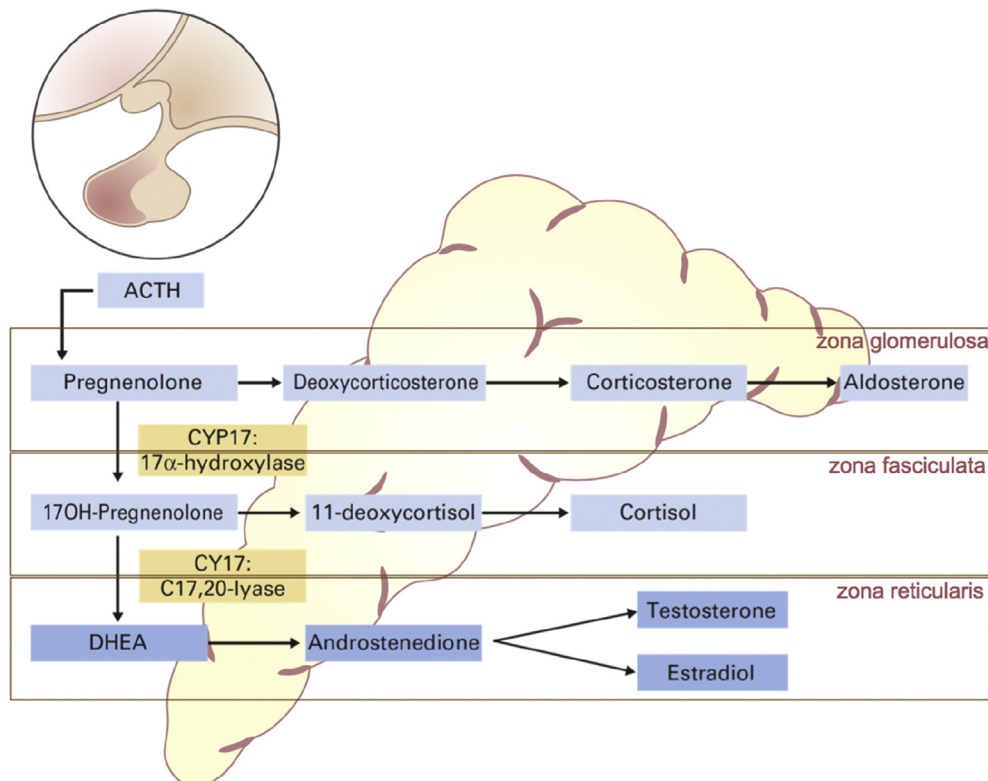


Fig. 1. CYP17 is a critical enzyme in the adrenal biosynthesis pathway in the zona reticularis.

**Table 2**

Summary of trials by design, setting, primary and secondary outcomes.

Trial name/authors	Year	Journal	Cohort size	Trial design	Comparator	Setting	Primary outcome findings	Secondary outcome findings	Take home message
Scher et al.	2017	European Urology JAMA Oncol	161	Cross-sectional cohort study	ARSi vs taxane <sup>a</sup>	mCRPC pre-chemotherapy	4.3 months ↑ overall survival (OS) in taxane-based chemotherapy vs ARSi when nuclear specific AR-V7 positive CTCs are present <sup>b</sup>	↓ risk of death in nuclear-specific AR-V7 positive CTCs and receiving taxane treatment	Nuclear-specific (but not nuclear-agnostic) AR-V7 localization can reliably inform treatment selection between ARSi and taxanes using a CTC AR-V7 biomarker.
PREVAIL, Phase III trial	2016	European Urology	1717	Randomised, placebo controlled, double-blind	Enzalutamide vs placebo	Chemotherapy naïve mCRPC, asymptomatic or minimally symptomatic	2.2 months ↑ OS and radiographic progression free survival (PFS)	↑ in health-related quality of life; ↑ in duration before first skeletal-related event	Enzalutamide ↓ the risk of radiographic PFS and death in mCRPC.
TERRAIN, Phase II	2016	Lancet Oncology	375	Randomised, double-blind	Enzalutamide vs bicalutamide	Asymptomatic or minimally symptomatic mCRPC, with disease progression on ADT <sup>c</sup>	9.9 months ↑ in PFS compared to bicalutamide	↑ in health-related quality of life	Enzalutamide ↑ survival and should be offered over bicalutamide in patients with asymptomatic or mildly symptomatic mCRPC.
STRIVE, Phase II	2016	Journal of Clinical Oncology	396	Randomised, double-blind	Enzalutamide vs bicalutamide	Non-metastatic or mCRPC	13.7 months ↑ in PFS compared to bicalutamide	↑ in time to PSA progression, proportion of patients with a ≥50% PSA response, and radiographic PFS	Enzalutamide ↓ risk of prostate cancer progression or death compared with bicalutamide in patients with non-metastatic or metastatic CRPC.
AFFIRM, Phase III trial	2014	Lancet Oncology	1199	Randomized, placebo controlled, double blind	Enzalutamide vs placebo	mCRPC, previously treated with docetaxel	4.8 months ↑ OS; 5.4 months ↑ radiographic PFS	↑ in health-related quality of life	Enzalutamide ↑ the survival of mCRPC in men previously treated with docetaxel.
COU-AA-302, Phase III	2014	European Urology Journal	1088	Randomised double-blind, placebo controlled	Abiraterone plus prednisolone vs placebo plus prednisolone	Chemotherapy naïve mCRPC	4.4 months ↑ OS and 8.2 months ↑ radiographic PFS	↓ pain and functional deterioration	In chemotherapy naïve mCRPC, abiraterone delays disease progression, and offers clinical benefit with a favourable safety profile in treatment durations of ≥24 mo.
COU-AA-301, Phase III	2012	Lancet Oncology	1195	Randomised, double-blind, placebo controlled	Abiraterone plus prednisolone vs placebo plus prednisolone	mCRPC, with disease progression after docetaxel therapy	4.6 months ↑ OS	Slowed disease progression, 2 months ↑ radiographic PFS	Abiraterone acetate ↑ OS in patients with mCRPC who progressed after docetaxel therapy.

<sup>a</sup> ARSi = Androgen receptor signalling inhibitor.<sup>b</sup> CTC = circulating tumour cells.<sup>c</sup> ADT = androgen deprivation therapy.



throughout various treatment phases for mCRPC, the understanding of the molecular profile during each phase of therapy can maximize treatment accuracy and benefit. Further exploration of this and other novel biomarkers are key to paving the way for personalized treatment for mCRPC.

At present, nuclear-specific protein localization using tissue or tumour biopsy at present offers the most clinical utility. However, given that metastases throughout the body can have different levels of AR expression and genomic profiles, performing biopsies of all metastases is not feasible. Non-invasive methods of detecting AR variants can offer important clinical advantages.

A newly proposed method of molecular profiling is through “liquid biopsy”, which is the analysis of circulating tumour cells via serum blood samples. Detection of AR-V7 mRNA in lysed circulating tumour cells is possible; its presence can inform about the resistant nature of the disease to AR synthesis inhibitors i.e. abiraterone and enzalutamide. Scher et al. have shown that approximately 20% of resistances can be identified using this method making it a promising means of non-invasive molecular profiling for mCRPC. However, it has not yet demonstrated an ability to surpass or complement the need for nuclear-specific protein localization.<sup>65,66</sup>

## 7. Future directions

The treatment landscape continues to change. With the most recent recommendations published by the Prostate Cancer Working Group 3, recommendations for drug trials are focussing on targeted therapies based on disease histology and biomarkers and with a shift towards treatment sequencing.<sup>67</sup>

Importantly, we need studies that investigate sequencing of different AR targeted therapies on selected patient groups and overall survival. Current data shows inconclusive clinical benefit in the sequential use of abiraterone and enzalutamide for specific scenarios,<sup>52,53</sup> yet the clinical benefit in patients who have an identified mechanism of resistance may be significant. This highlights the clinical value of AR molecular profiling for accurate identification of the different mechanisms of resistance.

Further research to expand our understanding of molecular mechanisms of mCRPC will not only guide the therapeutic approach, but also offer new insights into genomic and proteomic analysis for molecular profiling thus improving our treatment sequence selection, and ultimately enabling personalized precision medicine.

## Conflict of interest declaration

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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## References

- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;**65**:87–108.
- Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. *Eur Urol* 2012;**61**:1079–92.
- Cuzick J, Thorat MA, Andriole G, et al. Prevention and early detection of prostate cancer. *Lancet Oncol* 2014;**15**:e484–92.
- Hung CF, Yang CK, Ou YC. Urologic cancer in Taiwan. *Jpn J Clin Oncol* 2016;**46**:605–9.
- Lamb AD, Massie CE, Neal DE. The transcriptional programme of the androgen receptor (AR) in prostate cancer. *BJU Int* 2014;**113**:358–66.
- Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;**26**:1148–59.
- Botrel TE, Clark O, dos Reis RB, et al. Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. *BMC Urol* 2014;**14**:9.
- Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;**351**:1502–12.
- Buttiglierio C, Tucci M, Bertaglia V, et al. Understanding and overcoming the mechanisms of primary and acquired resistance to abiraterone and enzalutamide in castration resistant prostate cancer. *Cancer Treat Rev* 2015;**41**:884–92.
- Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;**371**:424–33.
- de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;**364**:1995–2005.
- Imamura Y, Sadar MD. Androgen receptor targeted therapies in castration-resistant prostate cancer: bench to clinic. *Int J Urol* 2016;**23**:654–65.
- Katsogiannou M, Ziouziou H, Karaki S, Andrieu C, Henry de Villeneuve M, Rocchi P. The hallmarks of castration-resistant prostate cancers. *Cancer Treat Rev* 2015;**41**:588–97.
- Taplin ME, Bubley GJ, Shuster TD, et al. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N Engl J Med* 1995;**332**:1393–8.
- Zhao XY, Malloy PJ, Krishnan AV, et al. Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. *Nat Med* 2000;**6**:703–6.
- Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;**351**:1513–20.
- de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;**376**:1147–54.
- Sternberg CN, Petrylak DP, Sartor O, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol* 2009;**27**:5431–8.
- Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;**363**:411–22.
- Schellhammer PF, Chodak G, Whitmore JB, Sims R, Frohlich MW, Kantoff PW. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. *Urology* 2013;**81**:1297–302.
- Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;**369**:213–23.
- Chen Y, Clegg NJ, Scher HI. Anti-androgens and androgen-depleting therapies in prostate cancer: new agents for an established target. *Lancet Oncol* 2009;**10**:981–91.
- Scher HI, Liebertz C, Kelly WK, et al. Bicalutamide for advanced prostate cancer: the natural versus treated history of disease. *J Clin Oncol* 1997;**15**:2928–38.
- Joyce R, Fenton MA, Rode P, et al. High dose bicalutamide for androgen independent prostate cancer: effect of prior hormonal therapy. *J Urol* 1998;**159**:149–53.
- Kucuk O, Fisher E, Moinpour CM, et al. Phase II trial of bicalutamide in patients with advanced prostate cancer in whom conventional hormonal therapy failed: a Southwest Oncology Group study (SWOG 9235). *Urology* 2001;**58**:53–8.
- Davis NB, Ryan CW, Stadler WM, Vogelzang NJ. A phase II study of nilutamide in men with prostate cancer after the failure of flutamide or bicalutamide therapy. *BJU Int* 2005;**96**:787–90.
- Kassouf W, Tanguay S, Aprikian AG. Nilutamide as second line hormone therapy for prostate cancer after androgen ablation fails. *J Urol* 2003;**169**:1742–4.
- Small EJ, Baron A, Bok R. Simultaneous antiandrogen withdrawal and treatment with ketoconazole and hydrocortisone in patients with advanced prostate carcinoma. *Cancer* 1997;**80**:1755–9.
- Lorente D, Mateo J, Zafeiriou Z, et al. Switching and withdrawing hormonal agents for castration-resistant prostate cancer. *Nat Rev Urol* 2015;**12**:37–47.
- Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. *J Clin Oncol* 2014;**32**:3436–48.
- Bianchini D, Lorente D, Rodriguez-Vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. *Eur J Cancer* 2014;**50**:78–84.
- Brasso K, Thomsen FB, Schrader AJ, et al. Enzalutamide antitumour activity against metastatic castration-resistant prostate cancer previously treated with docetaxel and abiraterone: a multicentre analysis. *Eur Urol* 2015;**68**:317–24.

33. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation anti-androgen for treatment of advanced prostate cancer. *Science* 2009;**324**:787–90.
34. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;**367**:1187–97.
35. Evans CP, Higano CS, Keane T, et al. The PREVAIL study: primary outcomes by site and extent of baseline disease for enzalutamide-treated men with chemotherapy-naïve metastatic castration-resistant prostate cancer. *Eur Urol* 2016;**70**:675–83.
36. Cella D, Ivanescu C, Holmstrom S, Bui CN, Spalding J, Fizazi K. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized clinical trial. *Ann Oncol* 2015;**26**:179–85.
37. Sternberg CN, de Bono JS, Chi KN, et al. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. *Ann Oncol* 2014;**25**:429–34.
38. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. *Eur Urol* 2017;**71**:151–4.
39. Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol* 2015;**16**:509–21.
40. Heidenreich A, Chowdhury S, Klotz L, et al. Impact of enzalutamide compared with bicalutamide on quality of life in men with metastatic castration-resistant prostate cancer: additional analyses from the TERRAIN randomised clinical trial. *Eur Urol* 2017;**71**:534–42.
41. Penson DF, Armstrong AJ, Conception R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. *J Clin Oncol* 2016;**34**:2098–106.
42. Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *Lancet Oncol* 2016;**17**:153–63.
43. Hoy SM. Abiraterone acetate: a review of its use in patients with metastatic castration-resistant prostate cancer. *Drugs* 2013;**73**:2077–91.
44. Potter GA, Barrie SE, Jarman M, Rowlands MG. Novel steroidal inhibitors of human cytochrome P45017 alpha (17 alpha-hydroxylase-C17,20-lyase): potential agents for the treatment of prostatic cancer. *J Med Chem* 1995;**38**:2463–71.
45. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015;**16**:152–60.
46. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol* 2012;**13**:1210–7.
47. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012;**13**:983–92.
48. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol* 2014;**66**:815–25.
49. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013;**368**:138–48.
50. Zhang W, Wu TY, Chen Q, et al. Indirect comparison between abiraterone acetate and enzalutamide for the treatment of metastatic castration-resistant prostate cancer: a systematic review. *Asian J Androl* 2017;**19**:196–202.
51. Tan PS, Haaland B, Montero AJ, Kyriakopoulos CE, Lopes G. Hormonal therapeutics enzalutamide and abiraterone acetate in the treatment of metastatic castration-resistant prostate cancer (mCRPC) post-docetaxel—an indirect comparison. *Clin Med Insights Oncol* 2014;**8**:29–36.
52. Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann Oncol* 2013;**24**:1807–12.
53. Noonan KL, North S, Bittling RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol* 2013;**24**:1802–7.
54. Lowrance WT, Roth BJ, Kirkby E, Murad MH, Cookson MS. Castration-resistant prostate cancer: AUA guideline amendment 2015. *J Urol* 2016;**195**:1444–52.
55. Cookson MS, Roth BJ, Dahm P, et al. Castration-resistant prostate cancer: AUA Guideline. *J Urol* 2013;**190**:429–38.
56. Azad AA, Eigl BJ, Leibowitz-Amit R, et al. Outcomes with abiraterone acetate in metastatic castration-resistant prostate cancer patients who have poor performance status. *Eur Urol* 2015;**67**:441–7.
57. de Bono JS, Smith MR, Saad F, et al. Subsequent chemotherapy and treatment patterns after abiraterone acetate in patients with metastatic castration-resistant prostate cancer: post hoc analysis of COU-AA-302. *Eur Urol* 2017;**71**:656–64.
58. Zhang T, Zhu J, George DJ, Armstrong AJ. Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistant prostate cancer. *Expert Opin Pharmacother* 2015;**16**:473–85.
59. Yaqub F. Galeterone activity in castration-resistant prostate cancer. *Lancet Oncol* 2015;**16**:e10.
60. Liu C, Armstrong C, Zhu Y, Lou W, Gao AC. Niclosamide enhances abiraterone treatment via inhibition of androgen receptor variants in castration resistant prostate cancer. *Oncotarget* 2016;**7**:32210–20.
61. Liu C, Lou W, Zhu Y, et al. Niclosamide inhibits androgen receptor variants expression and overcomes enzalutamide resistance in castration-resistant prostate cancer. *Clin Cancer Res* 2014;**20**:3198–210.
62. Attard G, Montgomery R, Vaishampayan U, et al. A phase 1/2 open-label study of safety and antitumor activity of EPI-506, a novel AR N-terminal domain inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC) with progression after enzalutamide or abiraterone. *Eur Urol Suppl* 2016;**15**.
63. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015;**373**:1697–708.
64. Antonarakis EL, CX, Wang H, Lubner B, Nakazawa M, Chen Y, Roeser JC, Fedor HL, Lotan TL, Zheng QZ, De Marzo AM, Isaacs JT, Isaacs WB, Nadal R, Paller CJ, Denmeade SR, Carducci MA, Eisenberger MA, Luo J. Androgen receptor splice variant, AR-V7, and resistance to enzalutamide and abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2014;**32**.
65. Scher H, Graf Ryon P, Schreiber Nicole A, et al. Nuclear-specific AR-V7 protein localization is necessary to guide treatment selection in metastatic castration-resistant prostate cancer. *Eur Urol J* 2017;**71**:874–82.
66. Lamb AD, Lawrence MG, Sandhu S. Practical polling for prostate cancer: AR-V7-based treatment selection. *Eur Urol* 2017;**71**:883–5.
67. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol* 2016;**34**:1402–18.