

# EXPERT OPINION

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## Emerging drugs for prostate cancer

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**Introduction:** Androgen deprivation therapy is the mainstay treatment for patients with prostate cancer who are not candidates for definitive treatment, are diagnosed with advanced disease on initial presentation or progress after primary treatment. Patients who stop responding to androgen deprivation therapy develop castration resistant prostate cancer (CRPC). Emerging drugs undergoing clinical evaluation and drugs that have recently received FDA approval for the treatment of CRPC are reviewed.

**Areas covered:** As the natural history and signaling pathways of prostate cancer are better understood, new treatments and targeted therapies will be developed. The FDA recently approved 5 medications that increase survival in patients with CRPC. Additional medications and drug classes are being explored that may eventually lead to new treatment options. Articles were identified using a PubMed database search.

**Expert opinion:** Recent FDA medication approvals and the development of emerging treatments are promising for the future of patients with prostate cancer. The addition of new medications challenges physicians to identify the optimal sequence and/or combination in which newer and older medications should be administered. Physicians treating patients with prostate cancer have a growing responsibility to keep pace with these new medications so that they may counsel and treat patients appropriately.

**Keywords:** abiraterone, androgen deprivation therapy, androgen receptor, antiandrogens, cabazitaxel, castration resistance, denosumab, docetaxel, emerging drugs, enzalutamide, prostate cancer, PSA-TRICOM, radium-223, sipuleucel-T, zoledronic acid

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### 1. Background

In the USA, 238,000 new cases of prostate cancer will be diagnosed in 2013 and more than 29,000 deaths will occur predominantly due to metastatic disease [1]. Intent to cure is the primary approach for non-locally advanced prostate cancer. Patients and their multi-disciplinary physicians discuss the risks and benefits of each treatment modality (surgery, radiation or active surveillance) to determine how best to proceed. Androgen deprivation therapy (ADT) is the first-line therapy for patients with metastatic disease or recurrence after primary treatment. ADT targets the androgen axis and is the mainstay treatment for disease progression since Huggins identified in 1941 that prostate cancer is hormone-driven [2]. ADT reduces 90–95% of circulating testosterone and results in a median progression-free survival (PFS) of 12 – 33 months when measured from the time of clinically symptomatic disease [3]. Docetaxel chemotherapy, approved in 2004, is the mainstay therapy for castration-resistant prostate cancer (CRPC) [4,5]. Since 2010, the FDA has approved five new agents from distinct drug classes for the treatment of CRPC (Table 1 and Figure 1) [6-11]. With the advent of new drugs, physicians are challenged with keeping pace with these new medications so that they may counsel and treat patients appropriately.

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**Table 1. Emerging drugs and selected associated trials.**

Drug	Mechanism	Phase of study	Primary endpoint	Description of study	Outcome	Clinical Trial Identifier
Abiraterone	Inhibits 17- $\alpha$ hydroxylase and 17-20 lyase	III/FDA approved	OS	Randomized, double-blind, abiraterone plus prednisone versus placebo plus prednisone in patients with mCRPC and prior docetaxel	Improved OS with abiraterone	NCT00638690
Abiraterone	Inhibits 17- $\alpha$ hydroxylase and 17-20 lyase	III/FDA approved	rPFS, OS	Randomized, double-blind, abiraterone plus prednisone versus placebo plus prednisone in patients with chemotherapy-naïve mCRPC	Improved rPFS and trended toward improved OS with abiraterone	NCT00887198
Orteronel (TAK-700)	Inhibits 17-20 lyase	III	OS	Randomized, double-blind, orteronel plus prednisone versus placebo plus prednisone in patients with mCRPC and prior docetaxel	No improvement in OS with orteronel	NCT01193257
Orteronel (TAK-700)	Inhibits 17-20 lyase	III	OS	Randomized, double-blind, orteronel plus prednisone versus placebo plus prednisone in patients with chemotherapy-naïve mCRPC	Active, not recruiting	NCT01193244
Galeterone (TOK-001)	Inhibits 17-20 lyase	II	Safety, PSA response	Single arm, open-label, galeterone in patients with chemotherapy-naïve mCRPC	Recruiting	NCT01709734
Enzalutamide (MDV3100)	Binds androgen receptor	III/FDA approved	OS	Randomized, double-blind, enzalutamide versus placebo in patients with mCRPC with prior docetaxel	Increased OS with enzalutamide	NCT00974311
Enzalutamide (MDV3100)	Binds androgen receptor	III	OS	Randomized, double-blind, enzalutamide versus placebo in patients with chemotherapy-naïve mCRPC	Active, not recruiting	NCT01212991
ARN-509	Binds androgen receptor	II	QOL	Randomized, open-label, ARN-509 with or without LHRH agonist versus LHRH agonist alone in patients with hormone sensitive patients with BCR	Recruiting	NCT01790126
Cabazitaxel	Stabilizes microtubules	III/FDA approved	OS	Randomized, open-label, cabazitaxel plus prednisone versus mitoxantrone plus	Increased OS with cabazitaxel	NCT00417079

CTC: Circulating tumor cell; CTLA: Cytotoxic T-Lymphocyte Antigen; FDA: Food and Drug Administration; HDAC: Histone deacetylase; HGF: Hepatocyte growth factor; HSP-27: Heat shock protein-27; LHRH: Luteinizing hormone-releasing hormone; mCRPC: Metastatic castration-resistant prostate cancer; OS: Overall survival; PSA: Prostate-specific antigen; PFS: Progression-free survival; Rps: Radiographic PFS; TRICOM: Triad of costimulatory molecules; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor; VEGFR: VEGF receptor.

Table 1. Emerging drugs and selected associated trials (continued).

Drug	Mechanism	Phase of study	Primary endpoint	Description of study	Outcome	Clinical Trial Identifier
Ixabepilone	Stabilizes microtubules	II	Safety, PSA response	prednisone in patients with mCRPC and prior docetaxel Single-arm, open-label, ixabepilone in patients with mCRPC and no prior chemo, prior taxane or two prior chemotherapy regimens	Acceptable toxicity, but acceptable PSA response only in patients with prior taxane treatment	NCT00087139
Eribulin mesylate	Stabilizes microtubules	II	Safety, PSA response	Single-arm, open-label, eribulin mesylate in patients with mCRPC with or without prior taxane chemotherapy	Acceptable toxicity and moderate antitumor activity	NCT00278993
Denosumab	Monoclonal antibody against RANK-L	III/FDA approved	Bone-metastasis-free survival	Randomized, double-blind, denosumab versus placebo in patients with non-metastatic CRPC	Increased bone-metastasis-free survival with denosumab	NCT00321620
Radium-223	Emits alpha particle in areas of increased bone turnover	III/FDA approved	OS	Randomized, double-blind, radium-223 versus placebo in patients with mCRPC and bone metastases	Increased OS with radium-223	NCT00699751
Dasatinib	Inhibits Src tyrosine kinase	III	OS	Randomized, double-blind, docetaxel plus dasatinib versus docetaxel plus placebo in patients with mCRPC	Greater toxicity and no improvement in OS with dasatinib	NCT00744497
Becacizumab	Monoclonal antibody to VEGF	III	OS	Randomized, double-blind, docetaxel plus prednisone with or without bevacizumab in patients with mCRPC	Greater toxicity and no improvement in OS with bevacizumab	NCT00110214
Aflibercept	Recombinant fusion protein to VEGF	III	OS	Randomized, double-blind, docetaxel plus prednisone with or without aflibercept in patients with mCRPC	Greater toxicity and no improvement in OS with aflibercept	NCT00519285
Cabozantinib	TKI targeting VEGFR and MET	III	OS	Randomized, double-blind, cabozantinib versus placebo in patients with mCRPC and prior docetaxel and abiraterone or enzalutamide	Recruiting	NCT01605227
Rilotumumab	Monoclonal antibody against HGF	II	OS	Randomized, double-blind, mitoxantrone and prednisone with and without rilotumumab	Manageable toxicities and no improvement in OS with rilotumumab	NCT00770848

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**Table 1. Emerging drugs and selected associated trials (continued).**

Drug	Mechanism	Phase of study	Primary endpoint	Description of study	Outcome	Clinical Trial Identifier
Tivantinib	Inhibits MET and microtubule polymerization	II	PFS	in patients with mCRPC and prior taxane chemotherapy	Recruiting	NCT01519414
Temsirolimus	mTOR inhibitor	II	CTC count	Randomized, double-blind, tivantinib versus placebo in patients with mCRPC	Transient CTC improvements, lacked sufficient clinical activity	NCT00887640
Oblimersen	Inhibits Bcl-2	II	Safety, PSA response	Single-arm, open-label, temsirolimus in patients with mCRPC	Greater toxicity and no improvement in OS with oblimersen	NCT00085228
Gossypol	Inhibits Bcl-2	II	OS	Randomized, open-label, docetaxel with and without oblimersen in patients with CRPC	Tolerable toxicities and no improvement in OS with gossypol	NCT00286793
OGX-427	Inhibits HSP-27	II	PFS	Randomized, open-label, prednisone with and without OGX-427 in patients with chemotherapy-naïve mCRPC	Increased PFS with OGX-427	NCT01120470
Custirsen	Inhibits clusterin	III	OS	Randomized, open-label, docetaxel plus prednisone with and without custirsen in patients with chemotherapy-naïve mCRPC	Active, not recruiting	NCT01188187
Sipuleucel-T	Activates T cells	III/FDA approved	OS	Randomized, double-blind, sipuleucel-T versus placebo in patients with mCRPC	Increased OS with sipuleucel-T	NCT00065442
PSA-TRICOM	Activates T cells	III	PFS	Randomized, double-blind, PSA-TRICOM versus placebo in patients with chemotherapy-naïve mCRPC	Increased OS with PSA-TRICOM but PFS not achieved	NCT00108732
Ipilimumab	Monoclonal antibody against CTLA-4	III	OS	Randomized, double-blind, ipilimumab versus placebo in patients with mCRPC treated with radiation	No improvement in OS with ipilimumab	NCT00861614
Tasquinimod	Inhibits S100A9	II	PFS	Randomized, double-blind, tasquinimod versus placebo in patients with chemotherapy-naïve mCRPC	Improved PFS with tasquinimod	NCT01234311

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Table 1. Emerging drugs and selected associated trials (continued).

Drug	Mechanism	Phase of study	Primary endpoint	Description of study	Outcome	Clinical Trial Identifier
Azacytidine	DNA methyltransferase	I/II	Safety, PSA response	Single-arm, open-label, docetaxel retreatment with zacytidine in patients with mCRPC and prior docetaxel	Recruiting	NCT00503984
Vorinostat	HDAC inhibitor	II	Disease progression	Single-arm, open-label, vorinostat in patients with mCRPC and prior chemotherapy	No improvement in disease progression with vorinostat	NCT00330161
Panobinostat	HDAC inhibitor	II	Disease progression	Single-arm, open-label, panobinostat in patients with mCRPC and prior chemotherapy	No improvement in disease progression with panobinostat	NCT00667862

CTC: Circulating tumor cell; CTLA: Cytotoxic T-Lymphocyte Antigen; FDA: Food and Drug Administration; HDAC: Histone deacetylase; HGF: Hepatocyte growth factor; HSP-27: Heat shock protein-27; LHRH: Luteinizing-hormone-releasing hormone; mCRPC: Metastatic castration-resistant prostate cancer; OS: Overall survival; PSA: Prostate-specific antigen; PFS: Progression-free survival; Rpts: Radiographic PFS; TRICOM: Triad of costimulatory molecules; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor; VEGFR: VEGF receptor.

## 2. Medical need

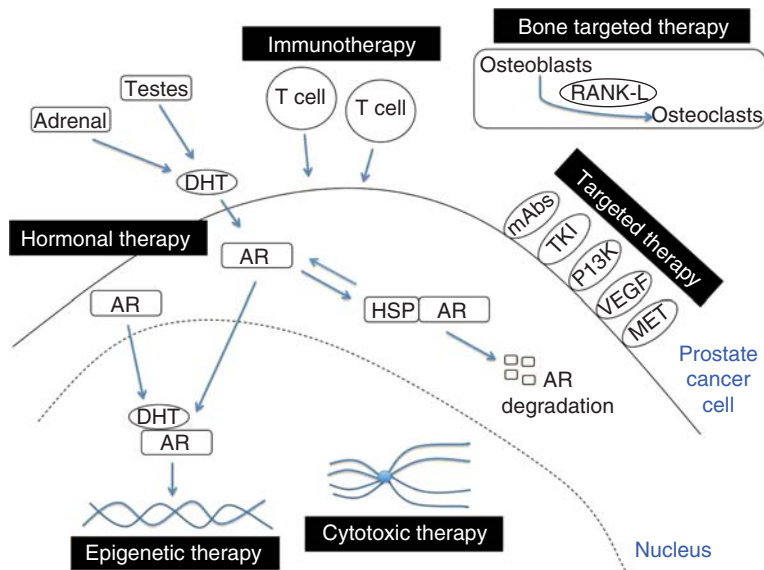
Prostate cancer will continue to be the second most common cause of cancer death in the United States until a cure is discovered. To date, each new therapy increases survival or delays disease progression on the order of months. Current drug regimens need to be evaluated and optimized to obtain the maximum benefit from available treatments. In addition, every effort to develop new medications to increase duration and quality of life will benefit patients.

## 3. Existing treatment

For patients with metastatic prostate cancer and bone metastases, ADT (medical castration) is initiated with a first generation non-steroidal antiandrogen (flutamide, bicalutamide). These agents are taken orally daily and bind competitively to the androgen receptor (AR) inhibiting the binding of testosterone and its more potent form, dihydrotestosterone (DHT). Following a week of administration of the non-steroidal antiandrogen, a luteinizing-hormone-releasing hormone (LHRH) agonist is initiated. Non-steroidal antiandrogens achieve effective androgen blockade, preventing symptomatic 'flare,' which can occur after LHRH agonist initiation. If no bone metastases or other disease are identified, patients can be directly started on LHRH agonists, which are administered subcutaneously in a slow-release depot form every 6 months. Surgical castration remains an option for patients who do not want to receive ADT or are unable to follow up for repeat treatments. Degarelix and other gonadotropin-releasing hormones (GnRH) antagonists may be alternatives to LHRH agonists and non-steroidal antiandrogens. GnRH antagonists block receptors in the pituitary, decreasing LH, follicle-stimulating hormone and testosterone. They do not cause flare, but do require monthly subcutaneous administration.

A vast majority of patients with prostate cancer will initially respond to ADT; however, ADT therapy is not curative. After a variable period of responsiveness to ADT of 2 – 15 years, many patients will progress as their prostate cancers become castration-resistant. At the onset of disease progression, a non-steroidal antiandrogen may be added (maximum androgen blockade). Prostate cancer often adapts to the antiandrogen and converts the antiandrogen to an agonist. Withdrawal of the antiandrogen in these circumstances may cause a temporary decline in disease burden. Patients can also be treated with ketoconazole (androgen synthesis inhibitor), diethylstilbestrol (estrogen therapy) or steroidal antiandrogens; however, these secondary ADT treatments do not increase survival when given prior to chemotherapy.

Intermittent ADT is being evaluated as a possible method to decrease castrate resistance, decrease drug side effects and increase survival. A randomized trial comparing intermittent and continuous ADT in 1535 patients with metastatic



**Figure 1. Current therapies for prostate cancer regulation.**

AR: Androgen receptor; DHT: Dihydrotestosterone; MET: Met proto-oncogene; TKI: Tyrosine kinase inhibitor.

CRPC did not establish non-inferiority of intermittent therapy in comparison with continuous therapy with respect to survival (5.1 years in intermittent group vs. 5.8 years in continuous group; hazard ratio (HR) 1.10; 90%CI: 0.99 –1.23) at a median follow-up of 9.8 years [12]. Patients treated with intermittent therapy reported better erections and mental health at 3 months, but not thereafter. Further evaluation is required to better assess the utility of intermittent ADT for patients with prostate cancer.

Since FDA approval in 2004, docetaxel has been the mainstay of treatment for patients with CRPC. Clinical trials TAX327 and SWOG9916 identified that docetaxel in combination with prednisone or estramustine increased survival by 2 – 3 months compared to mitoxantrone and prednisone [4,5]. However, CRPC patients develop resistance to docetaxel or are unable to tolerate the side effects. Therefore, recently FDA approved sipuleucel-T (2010), cabazitaxel (2010), abiraterone acetate (2011, 2012), enzalutamide (2012) and radium-223 dichloride (2013) have immediate impact on the management of patients with CRPC.

#### 4. Market review

The market share of sipuleucel-T, cabazitaxel, abiraterone, enzalutamide and radium-223 will be heavily influenced by drug indications, governing body recommendations, side effect profiles, ease of administration, patient preferences and cost to the patient. For example, only abiraterone and sipuleucel-T currently are FDA-approved for use in both pre- and post-docetaxel CRPC patients. The American Urologic Association (AUA) guidelines recommend the use of

abiraterone as a treatment option across all stages of metastatic CRPC, while sipuleucel-T is recommended for only the asymptomatic or mildly symptomatic patient with chemotherapy-naïve, metastatic CRPC [13]. Medical oncologists and urologists are both comfortable treating patients with ADT due to its ease of administration and low side effect profile. In comparison, sipuleucel-T, which involves a complicated administration process, and radium-223, which has risk for myelosuppression and thrombocytopenia, are more likely to be administered by medical oncologists than urologists. Ease of administration, drug side-effect profile and cost will directly influence market share and the types of physicians administering the medication.

#### 5. Current research goals

New drug discoveries are attributed to an improved understanding of the molecular drivers of and signaling pathways in CRPC. The current strategy for treating hormone-sensitive prostate cancer remains targeting the AR signaling pathway. Further research into prostate cancer genetics may identify critical molecular drivers and targets in subsets of advanced disease that may be responsive to distinct therapies targeting those drivers. Additionally, research needs to focus on mechanisms to better target the AR, especially in cases of AR hypersensitivity, by more effectively blocking circulating androgens, intratumoral androgen production of androgens and AR amplification [14].

Liposomal drug encapsulation is a novel mechanism of drug delivery developed to increase tumor uptake and decrease systemic toxicity [15]. Liposomes take advantage of

the increased vascular permeability of tumors to increase intratumoral drug delivery and retention. Liposome encapsulation may also increase circulation time and stabilize drugs decreasing drug breakdown. Liposome surface molecules can be modified to inhibit opsonisation by macrophages and can also potentially be modified to target specific tumor cells. Zoledronic acid is one such drug that may benefit from encapsulation. In addition to its principle action to decrease bone resorption, zoledronic acid has been shown to have anti-tumor activity in pre-clinical studies, but not in large clinical trials [16]. Pre-clinical models evaluating liposome encapsulated zoledronic acid show the potential to increase extratumoral effects and counteract the short plasma half-life and rapid accumulation in bone of the non-encapsulated drug.

Although the benefits of prostate cancer screening are highly controversial, improved screening and detection guidelines may help to identify whether cancer-specific survival is being improved. With the recent development of high-throughput sequencing and molecular classification of prostate cancer, new biomarkers may arise replacing prostate-specific antigen (PSA) as our best method for screening and following prostate cancer [17]. Future biomarkers may be used to identify the specific molecular pathway abnormalities of a patient and predict which drugs will have the best response. Prostate MRI may improve cancer detection and MRI-guided ultrasound prostate biopsies may improve prostate cancer sampling. Detecting and treating cancer earlier and more effectively may prevent the development of disease recurrence and metastatic disease.

## 6. Scientific rationale

Outside of chemotherapy, the androgen pathway is the traditional target for prostate cancer drug development. An increased understanding of prostate biology and signaling pathways will translate into new targeted therapies, increased survival and decreased treatment and disease secondary effects. Scientists are working to improve previous drug classes such as androgen synthesis inhibitors and AR agonists and explore new modalities such as targeting the immune system, growth factors, apoptosis, bone environment and genetic modulators.

## 7. Competitive environment

### 7.1 Androgen synthesis CYP17 inhibitors

Ketoconazole is a CYP17 inhibitor that targets androgen synthesis from the adrenal gland and tumor by inhibiting 17- $\alpha$  hydroxylase and 17,20-lyase enzymes. It also weakly inhibits CYP11 enzymes, which are involved in glucocorticoid and mineralocorticoid synthesis. Ketoconazole is used as a second-line treatment for prostate cancer due to its significant side effects and inability to improve survival [18]. More selective medications targeting the androgen synthesis pathway

have been developed resulting in potentially increased tumor response and decreased side effects.

Abiraterone is one such CYP17 inhibitor that blocks 17- $\alpha$  hydroxylase and 17,20-lyase resulting in increased mineralocorticoid, decreased glucocorticoid and decreased androgen production. Compared to ketoconazole, abiraterone is 10 – 30 times more potent in *in vitro* assays and is more tolerable because it is a less potent inhibitor of CYP11 [19,20]. Daily, low doses of glucocorticoids are required to suppress the compensatory ACTH that can occur while taking abiraterone.

Abiraterone received FDA approval in 2010 for patients with metastatic CRPC previously treated with docetaxel due to the interim results from the COU-AA-301 Phase III study [6,7]. The final analysis was published in 2012 and included 1195 patients randomized to abiraterone plus prednisone or placebo plus prednisone. At final analysis (median follow-up of 20.2 months), the abiraterone group had longer median overall survival (OS) compared to the placebo group (15.8 vs. 11.2 months; HR 0.74; 95%CI: 0.64–0.86;  $p < 0.001$ ). Median time to PSA progression (8.5 vs. 6.6 months; HR 0.63; 95%CI: 0.52–0.78;  $p < 0.001$ ), median radiographic PFS (rPFS) (5.6 vs. 3.6 months; HR 0.66 95%CI: 0.58–0.76;  $p < 0.0001$ ) and proportion of patients with PSA response (29.5 vs. 5.5%;  $p < 0.0001$ ) all favored the abiraterone group compared to the placebo group. Abiraterone toxicity was low with the most common adverse events being fatigue, anemia, back pain, bone pain and fluid retention or edema.

Abiraterone also received FDA approval in 2013 for patients with chemotherapy-naïve, metastatic CRPC due to the interim results from the Phase III COU-AA-302 study. 1080 patients with chemotherapy-naïve and asymptomatic or mildly symptomatic CRPC were randomized to the same abiraterone and placebo arms [9]. At interim analysis (median follow-up of 22.2 months), the abiraterone arm increased median rPFS compared to the placebo arm (16.5 vs. 8.3 months; HR 0.53; 95% CI: 0.45 – 0.62;  $p < 0.001$ ). The abiraterone arm improved OS compared to the placebo arm (median not reached vs. 27.2 months; HR 0.75; 95% CI: 0.61 – 0.93;  $p = 0.01$ ); however, this did not reach the pre-planned significance level of  $p < 0.001$ . Median time to decline in ECOG performance status (12.3 vs. 10.9 months;  $p = 0.005$ ), median time to initiation of chemotherapy (25.2 vs. 16.8 months;  $p < 0.0001$ ), median time to opiate use for cancer-related pain (not reached vs. 23.7 months;  $p < 0.0001$ ) and median time to PSA progression (11.1 vs. 5.6 months;  $p < 0.0001$ ) all favored the abiraterone arm compared to the placebo arm. Abiraterone was associated with mineralocorticoid-related events and liver function test abnormalities. This is the first study to have rPFS as a primary endpoint and obtain FDA approval based on rPFS. rPFS was defined as survival without progression in soft-tissue lesions on CT or MRI imaging based on response evaluation criteria in solid tumors (RECIST) criteria

or progression on bone scan. PSA was not included in the definition of rPFS.

Currently, abiraterone is being evaluated in multiple clinical trials for treatment in earlier stages of prostate cancer. Abiraterone in combination with a LHRH agonist and radiotherapy is being used to treat localized or locally advanced cancer in a Phase II study (NCT01023061). Patients with local or PSA recurrence after surgery are undergoing treatment with abiraterone alone and in combination with a LHRH antagonist (NCT01751451) or in combination with a LHRH agonist and radiotherapy (NCT01780220). Several FDA-approved agents are being evaluated in combination with abiraterone in patients with metastatic CRPC: dutasteride (NCT01393730), cabazitaxel (NCT01845792) and enzalutamide (NCT01650194). Abiraterone is also being evaluated in combination with novel agents that inhibit PI3K/Akt, tyrosine kinase and heat shock protein (HSP) pathways.

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#### Abiraterone Phase III at a glance

MOA: Inhibits 17- $\alpha$  hydroxylase and 17 – 20 lyase  
 Approval Status: FDA approved in 2010 for post-docetaxel CRPC, FDA approved in 2013 for pre-docetaxel CRPC  
 Effect: 4.6 month improvement in OS for post-docetaxel CRPC, 8.3 month improvement in OS for pre-docetaxel CRPC  
 Toxicity Profile: Fatigue, anemia, back pain, bone pain, fluid retention or edema

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Orteronel (TAK-700) is an oral, 17,20-lyase that does not inhibit 17- $\alpha$  hydroxylase and may have an improved safety profile compared to abiraterone [21]. A Phase III study comparing orteronel plus prednisone to placebo plus prednisone in patients with metastatic CRPC was unblinded at interim analysis (NCT01193257) [22]. Orteronel plus prednisone was unlikely to meet the primary endpoint of improved OS over the control arm (HR 0.894;  $p = 0.226$ ). At interim analysis, orteronel did increase rPFS over the control arm (HR 0.755;  $p = 0.00029$ ) without safety concerns. The Phase III trial comparing orteronel plus prednisone to placebo plus prednisone in chemotherapy-naïve patients with metastatic CRPC is ongoing (NCT01193244). Galeterone (TOK-001) is another oral, 17,20-lyase inhibitor that is currently undergoing Phase II evaluation in patients with CRPC (NCT01709734) [23].

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#### Orteronel Phase III at a glance

MOA: Inhibits 17 – 20 lyase  
 Approval Status: Not approved  
 Effect: No improvement in OS, increased rPFS (HR 0.755,  $p = 0.00029$ )  
 Toxicity Profile: Pending

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## 7.2 Androgen receptor antagonists

Bicalutamide and flutamide are first-generation AR antagonists (non-steroidal antiandrogens) that reversibly and weakly bind to the AR, competing with testosterone and DHT. In the inactivated state the AR is bound to HSP-90, which prevents AR degradation and helps to maintain correct protein conformation. When androgens bind to the AR in the active state, the complex translocates into the nucleus allowing DNA binding and transcription of androgen-dependent genes to occur [24]. Patients treated with AR antagonists will ultimately develop CRPC, which is believed to occur in part due to gene amplification of the AR, overexpression of the AR, formation of splice variants or other mutations of the AR, deregulation of growth factors or cytokines, alteration of co-activators, neuroendocrine differentiation of prostate cancer cells and deregulation of apoptosis signaling [25]. First-generation AR antagonists possess agonist potential as exhibited in the ‘withdrawal syndrome,’ which results in a paradoxical rise in PSA after removal of the AR antagonist.

Enzalutamide is a second-generation AR antagonist that does not have agonist effects [10]. It causes a transformational change of the AR different than bicalutamide resulting in impaired nuclear translocation, co-activator peptide recruitment and DNA binding of the AR. Enzalutamide received FDA approval in 2012 due to the interim results from the stage III AFFIRM study. 1199 patients with metastatic CRPC previously treated with docetaxel were randomized in 2:1 fashion to enzalutamide versus placebo. At interim analysis (mean follow-up of 14.4 months), the enzalutamide arm increased median OS compared to the placebo arm (18.4 vs. 13.6 months; HR 0.63; 95%CI: 0.53 – 0.75;  $p < 0.001$ ). PSA reduction by at least 50% (54 vs. 2% patients;  $p < 0.001$ ), soft-tissue response rate (29 vs. 4% patients;  $p < 0.001$ ), quality-of-life response rate (43 vs. 18% patients;  $p < 0.001$ ) and rPFS (8.3 vs. 2.9 months; HR 0.40;  $p < 0.001$ ) all favored the enzalutamide arm over the placebo arm. Enzalutamide was well tolerated with common side effects including fatigue, diarrhea and hot flashes. Seizures occurred in 1% of patients.

The stage III PREVAIL study (NCT01212991) randomized patients with chemotherapy-naïve, metastatic CRPC to the same enzalutamide and placebo arms and will potentially follow abiraterone and receive both neoadjuvant and adjuvant indications. Enzalutamide is being evaluated in Phase II study in combination with bicalutamide in patients with disease progression despite primary ADT (NCT01664923). Enzalutamide is also being combined with PSA-TRICOM, a therapeutic cancer vaccine, in chemotherapy-naïve patients with metastatic CRPC (NCT01875250 and NCT01867333). Not all patients respond to enzalutamide treatment and theories behind resistance mechanisms include the development of splice variants, which lack or have modified ligand-binding domains and inhibition of multiple signaling pathways such



**Enzalutamide Phase III at a glance**

MOA: Binds AR

Approval status: FDA approved in 2012 for post-docetaxel CRPC

Effect: 4.8 month improvement in OS

Toxicity profile: Fatigue, diarrhea, hot flashes, muscle pain

as PI3K [24]. In order to decrease resistance, enzalutamide is being combined with novel agents in patients with metastatic CRPC: tivozanib (NCT01885949) and abiraterone (NCT01650194).

ARN-509 is another second-generation AR antagonist, which binds directly to the AR with high affinity, inhibiting nuclear transport and DNA-binding capacity. Compared to enzalutamide, ARN-509 is more active at lower doses and is less toxic to the central nervous system, potentially reducing the risk for seizures [26]. Phase II studies are evaluating ARN-509 compared to a LHRH agonist in hormone-sensitive patients with biochemical relapse after local therapy (NCT01790126) and in combination with abiraterone in patients with metastatic CRPC (NCT01792687). Phase I evaluation for ODM-201 (NCT01784757) is ongoing and Phase I evaluation for AZD-3514 (NCT01162395) is complete.

**7.3 Microtubule inhibiting agents**

Docetaxel is an anti-tubulin agent that stabilizes microtubules causing cell arrest and inhibiting anti-apoptotic proteins such as Bcl-2 [27]. It was approved in 2004 as the first medication to increase median OS in patients with metastatic CRPC in two randomized trials against mitoxantrone. Prior to docetaxel, mitoxantrone (approved in 1984) was used to reduce pain and improve quality of life, but not improve survival. Mitoxantrone has historically been used in combination with prednisone as a second-line treatment for metastatic CRPC.

SWOG9916 was a Phase III study that randomized 770 patients with metastatic CRPC to receive either docetaxel (60 mg/m<sup>2</sup> every 3 weeks) and estramustine or mitoxantrone (12 mg/m<sup>2</sup> every 3 weeks) and prednisone [4]. Docetaxel and estramustine increased median OS (17.5 vs. 15.6 months; HR 0.80; 95%CI: 0.67 – 0.97; p = 0.02) compared to the mitoxantrone and prednisone arm. A Phase II study is evaluating the effect of estramustine in patients with metastatic CRPC treated with docetaxel and prednisone with and without estramustine (NCT00541281). TAX327 was a Phase III study that randomized 1006 patients with metastatic CRPC to docetaxel (75mg/m<sup>2</sup> every 3 weeks or 30 mg/m<sup>2</sup> every week) plus prednisone or mitoxantrone (12 mg/m<sup>2</sup> every 3 weeks) plus prednisone [5]. Docetaxel every 3 weeks increased median OS compared to the mitoxantrone arm (18.9 vs. 16.5 months; HR 0.76; 95% CI: 0.62 – 0.94; p = 0.009). Weekly docetaxel trended toward improved survival compared to the mitoxantrone arm (17.4 vs. 16.5 month; HR 0.91; 95% CI: 0.75 – 1.11; p = 0.36). Docetaxel was

associated with higher rates of neutropenia, fatigue, alopecia, diarrhea and sensory neuropathy.

A Phase III study (GETUG-AFU) evaluated the use of docetaxel in patients with hormone-sensitive, metastatic prostate cancer [28]. 385 patients were randomized to ADT alone or in combination with docetaxel. At a median follow-up of 50 months, patients treated with ADT and docetaxel did not have improved median OS compared to patients treated with ADT alone (58.9 months vs. 54.2 months; HR 1.01; 95% CI: 0.75 – 1.36). The study group recommended against the use of docetaxel as a first-line treatment for patients with hormone-sensitive, metastatic prostate cancer.

Cabazitaxel was approved in 2010 as the first agent to improve survival in patients with metastatic CRPC who progressed despite docetaxel treatment. Cabazitaxel, another taxane, stabilizes microtubules causing cell arrest. Compared to docetaxel, cabazitaxel has low affinity for p-glycoprotein, an ATP-dependent pump, which actively extrudes docetaxel from taxane-resistant tumor cells.

Cabazitaxel was evaluated in the Phase III TROPIC trial, which randomized 775 patients to cabazitaxel (25 mg/m<sup>2</sup> every 3 weeks) and prednisone or to mitoxantrone (12 mg/m<sup>2</sup> every 3 weeks) and prednisone. At final analysis, the cabazitaxel arm had increased OS (15.1 months vs. 12.7 months; HR 0.70; 95% CI: 0.59 – 0.83; p < 0.0001) compared to the mitoxantrone arm. PFS was also greater in the cabazitaxel arm (2.8 vs. 1.4 months; p < 0.0001). Cabazitaxel was associated with neutropenia, febrile neutropenia and diarrhea.

Two Phase II trials are evaluating early switching from docetaxel to cabazitaxel in response to rising PSA (NCT01718353 and NCT01576029). Cabazitaxel is also being evaluated in conjunction with IMRT for locally advanced prostate cancer (NCT01420250) and after surgery for stage 3 cancers (NCT01650285). Phase III study NCT01308567 is currently evaluating cabazitaxel versus docetaxel as an initial treatment for CRPC. Cabazitaxel is also being evaluated in combination with novel agents bavituximab (NCT01335204), abiraterone (NCT01845792 and NCT01511536), carboplatin (NCT01505868), tasquinimod (NCT01513733) and custirsen (NCT01578655).

**Cabazitaxel Phase III at a glance**

MOA: Stabilizes microtubules

Approval status: FDA approved in 2010 for CRPC

Effect: 2.4 month improvement in OS

Toxicity profile: neutropenia, febrile neutropenia, diarrhea, nausea

Ixabepilone is an epothilone, which differs from taxanes in its mechanism for stabilizing microtubules and developing drug resistance [29]. A Phase II study randomized 92 patients

with metastatic CRPC to ixabepilone (25 mg/m<sup>2</sup> every 3 weeks) with or without estramustine [30]. Patients treated with ixabepilone alone compared to ixabepilone and estramustine had PSA decline of at least 50% in 48% of patients versus 69% of patients, respectively. Ixabepilone (20 mg/m<sup>2</sup> weekly) has single agent activity in patients with metastatic CRPC and an improved toxicity profile compared to drug administration every 3 weeks [31].

Eribulin mesylate is a nontaxane halichondrin B analog microtubule inhibitor, which may overcome resistance typically encountered with taxanes. A Phase II study evaluated the safety and efficacy of eribulin mesylate in 108 patients with metastatic CRPC with and without prior exposure to taxanes [32]. PSA decline of at least 50% was identified in 22.4% of patients without taxane exposure and 8.5% of patients with taxane exposure. Patients without taxane exposure developed less neutropenia (40 vs. 22% patients) and peripheral neuropathy (0 vs. 6% patients) compared to patients with prior exposure.

#### 7.4 Bone-targeted therapies

The majority of patients with metastatic prostate cancer will develop bone metastases resulting in significant morbidity. Cancer cells disturb bone turnover by altering the balance between osteoclasts and osteoblasts, which are involved in bone resorption and formation, respectively. Bone turnover can be evaluated with serum alkaline phosphatase (ALP, a marker for osteoblast activity), urinary N-telopeptide (uNTX, a marker for osteoclast activity) and radiographic imaging [33].

Bisphosphonates have high affinity for the bone matrix, inhibit osteoclast activity and induce osteoclast apoptosis. A Phase III study randomized patients with metastatic CRPC to receive zoledronic acid (4 mg intravenously) or placebo every 3 weeks for 15 months. The zoledronic acid arm had fewer patients with at least one skeletal-related event (SRE) (38 vs. 49% patients;  $p = 0.028$ ), lower annual incidence of SRE (0.77 vs. 1.47;  $p = 0.005$ ), longer median time to first SRE (488 days vs. 321 day;  $p = 0.009$ ) and 36% less risk of SRE (RR 0.64; 95%CI: 0.485 – 0.845;  $p = 0.002$ ) compared to the placebo arm [34]. Common side effects included flu-like symptoms and serious side effects included renal dysfunction and hypocalcemia. Initial results from the Zometa European Study (ZEUS) support prior studies in identifying no survival benefit or difference in the incidence of bone metastasis among 1433 high-risk prostate cancer patients randomized to zoledronic acid or placebo [35].

Cancer cells induce osteoblasts to express RANK ligand (RANK-L) and downregulate osteoprotegerin, a RANK ligand inhibitor [36]. RANK-L activates RANK on osteoclasts and induces bone resorption. Denosumab is a monoclonal antibody with high affinity for RANK-L. A Phase III study randomized patients with metastatic CRPC to receive denosumab (120 mg subcutaneously every 4 weeks) or zoledronic acid (4 mg intravenously every 3 weeks) [37]. Patients treated

with denosumab had delayed time to first SRE (20.7 months vs. 17.1 months; HR 0.82; 95%CI: 0.71 – 0.95;  $p = 0.008$ ) compared to the zoledronic acid arm, but no difference in OS or PFS. Denosumab, in contrast to zoledronic acid, does not require renal dosing. Common side effects included flu-like symptoms and serious side effects included hypocalcemia and osteonecrosis of the jaw. A second Phase III study randomized patients to receive denosumab (120 mg subcutaneously) versus placebo every 4 weeks. Denosumab increased bone metastasis-free survival by a median of 4.2 months compared to placebo (29.5 months vs. 25.2 months; HR 0.85; 95%CI: 0.73 – 0.98;  $p = 0.028$ ) and delayed time to first bone metastasis (33.2 months vs. 29.5 months; HR 0.84; 95%CI: 0.71 – 0.98;  $p = 0.032$ ) [38]. OS did not differ between the two groups.

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#### Denosumab Phase III at a glance

MOA: Monoclonal antibody against RANK-L

Approval status: FDA approved in 2010 for patients with bone metastases from prostate cancer, FDA approved in 2011 for patients at high first for fracture including ADT

Effect: 3.6 month delay in first SRE, 4.2 month increase in bone metastasis-free survival

Toxicity profile: Anemia, back pain, decreased appetite, nausea, constipation

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Radiopharmaceuticals are molecules linked to a radiation source that target sites of increased bone turnover. They either mimic calcium (radium-223) or require a carrier molecule to achieve uptake to the bone [39]. Beta-emitters, samarium-153 and strontium-89, are approved for symptomatic bone metastases; however, they are highly myelotoxic and do not improve OS. Radium-223 is an alpha-emitter that was evaluated in the Phase III ALSYMPCA study in patients with symptomatic bone metastases from CRPC who received, were considered unfit for or declined docetaxel [40]. The study randomized 921 patients to radium-223 or placebo every 4 weeks. Patients treated with radium-223 compared to placebo had improved median OS by 3.6 months (14.9 vs. 11.3 months; HR 0.70; 95%CI: 0.58 – 0.83;  $p < 0.001$ ). Median time to first symptomatic skeletal event (15.6 vs. 9.8 months; HR 0.66; 95%CI: 0.52 – 0.83;  $p < 0.001$ ), median time to increase in total ALP (7.4 vs. 3.8 months; HR 0.17; 95%CI: 0.13 – 0.22;  $p < 0.001$ ), median time to increase in PSA (3.6 months vs. 3.4 months; HR 0.64; 95%CI: 0.54 – 0.77;  $p < 0.001$ ), patients with at least 30% reduction in total ALP (47 vs. 3% patients;  $p < 0.001$ ) and patients with normalization of total ALP (34 vs. 1% patients;  $p < 0.001$ ) all favored radium-223 compared to placebo. Radium-223 was associated with low rates of myelosuppression, fewer adverse events and increased quality of life compared to placebo. Radium-223 received FDA approval in 2013 for the treatment of patients with symptomatic bone metastases from CRPC.

A Phase I/II study is being conducted to evaluate the combination use of radium-223 with docetaxel in patients with bone metastases and CRPC (NCT01106352).

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#### Radium-223 Phase III at a glance

MOA: Alpha particle emitter in areas of increased bone turnover  
Approval status: FDA approved in 2013 for CRPC with bone metastases

Effect: 3.6 month improvement in OS

Toxicity profile: Anemia, bone pain, nausea, fatigue, diarrhea

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Src signaling is involved in many pathways including cell survival, cell proliferation, angiogenesis and bone turnover. Src inhibitors decreased proliferation, invasion and migration of prostate cancer cell lines *in vitro* and reduced prostate cancer growth and metastasis in mouse studies [41]. Dasatinib is an inhibitor of several tyrosine kinases including Src. A Phase I/II study evaluated the combination of dasatinib and docetaxel in 46 patients with metastatic CRPC [42]. PSA decline of at least 50% was identified in 13/46 (28%) patients. Of the patients with measurable disease, 18/30 (60%) patients had a partial response, uNTX was decreased in 33/38 (87%) patients and ALP levels were decreased in 26/34 (61%) patients. Grade 3–4 toxicity was exhibited in 13/46 (28%) patients. A double-blind, placebo-controlled Phase III study randomized 1522 patients to receive docetaxel plus dasatinib or docetaxel plus placebo [43]. No benefit in OS was obtained with the addition of dasatinib (21.5 vs. 21.2 months, HR 0.99; 95%CI: 0.87 – 1.13,  $p = 0.90$ ). Secondary endpoints including objective response rate, reduction in uNTX, PFS or pain reduction were not achieved. Adverse events occurred most frequently in patients receiving dasatinib and included anemia, neutropenia, hypocalcemia and GI bleeding. Dasatinib's poor performance may be attributed to continued AR signaling and being predominantly a bone-targeting drug with poor tumor-availability outside of bone similar to zoledronic acid.

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#### Dasatinib Phase III at a glance

MOA: SRC TKI

Approval status: Not approved

Effect: No improvement in OS

Toxicity profile: Anemia, neutropenia, hypocalcemia and GI bleeding

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### 7.5 VEGF, MET and PI3K/Akt signaling

Met proto-oncogene (MET) and vascular endothelial growth factor (VEGF) signaling pathways may play a role in prostate cancer progression and bone metastasis. MET is overexpressed in the setting of ADT and has the highest expression in bone

metastases, compared to lymph node and soft tissue [44]. VEGF is involved in angiogenesis, expressed in cancer cells and is a predictor of OS in patients with CRPC.

Bevacizumab is a monoclonal antibody to VEGF. Preclinical studies showed promise; however, a Phase III study randomized 1050 patients with chemotherapy-naïve CRPC to docetaxel and bevacizumab or docetaxel and placebo. The bevacizumab arm did not increase survival compared to the placebo arm (22.6 vs. 21.5 months; HR 0.91; 95%CI: 0.78 – 1.05;  $p = 0.181$ ) [45].

Aflibercept is a recombinant human fusion protein that binds VEGF and placental growth factor. The recently published Phase III VENICE study randomized 1224 patients with metastatic CRPC to aflibercept and docetaxel or placebo and docetaxel. At final analysis (median follow up 35 months) the aflibercept arm had a median OS of 22.1 months compared to 21.2 months of the placebo group (HR 0.94; 95% CI: 0.82 – 1.08;  $p = 0.38$ ) [46].

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#### Aflibercept Phase III at a glance

MOA: Recombinant fusion protein to VEGF

Approval status: Not approved

Effect: No improvement in OS

Toxicity profile: Diarrhea, stomatitis and ulceration, hypertension, fatigue, dysphonia

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Tyrosine kinase inhibitors (TKIs) of the VEGFR, sunitinib and sorafenib, have been evaluated in Phase II or III studies. Unfortunately, these drugs did not increase median OS in patients with metastatic CRPC [47]. Cabozantinib (XL-184) is an oral TKI that targets both VEGFR and MET and is FDA approved for medullary thyroid cancer. A Phase II study enrolled 171 patients with CRPC to be treated daily with cabozantinib during a lead-in period of 12 weeks [48]. At the end of the lead-in period, patients with stable disease per RECIST criteria were randomized to cabozantinib or placebo. Due to positive changes on bone scan and decreased pain during the lead-in stage, random assignment was discontinued after 122 patients were enrolled. Forty-nine additional patients were enrolled thereafter for open-label treatment. Of the 116 patients with follow-up bone scan studies, 65 (56%) had partial resolution, 14 (12%) had complete resolution and 33 (28%) had stable disease. At 12 weeks, 5% of evaluable patients had objective partial response based on RECIST criteria, 75% had stable disease and 11% had disease progression. Thirty-one patients were randomized prior to suspension of random assignment. The treatment arm had increased PFS compared to the placebo arm (23.9 vs. 5.9 weeks; HR 0.12;  $p < 0.001$ ) as well as decreased pain and narcotic use. The FDA denied the design of a Special Protocol Assessment aimed at rapid approval of cabozantinib with the primary endpoint of pain reduction in advanced prostate cancer patients. Two Phase III studies are being

conducted in patients with bone-dominant metastatic CRPC who have progressed despite docetaxel and secondary enzalutamide or abiraterone therapy. The COMET-1 trial will evaluate OS and bone scan response of patients randomized to cabozantinib or prednisone (NCT01605227). COMET-2 will evaluate pain response and bone scan response of patients randomized to cabozantinib or mitoxantrone with prednisone (NCT01522443).

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#### Cabozantinib Phase III at a glance

MOA: TKI targeting VEGFR and MET

Approval status: Not approved

Effect: 17-week improvement in PFS, 56% partial resolution and 12% complete resolution on bone scan

Toxicity profile: Fatigue, decreased appetite, diarrhea, nausea, constipation, weight decreased

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Rilotumumab is a monoclonal antibody that blocks the binding of hepatocyte growth factor to MET. A Phase II study randomized 141 patients with post-chemotherapy CRPC to mitoxantrone and prednisone in combination with rilotumumab or placebo [49]. The primary endpoint OS was not achieved. Median PSF was 3.0 months for the rilotumumab arm versus 2.9 months for the placebo arm (HR: 1.02; 80%CI: 0.79 – 1.31). Tivantinib is a TKI, which binds to and disrupts MET signaling. A Phase II study is evaluating PFS by RECIST criteria in chemotherapy-naïve, metastatic CRPC patients treated with tivantinib versus placebo (NCT01519414).

The PI3K/Akt pathway regulates multiple cell processes. More than 50% of metastatic prostate cancers exhibit activation of PI3K/Akt pathways frequently through the loss of PTEN [50]. A Phase II study was conducted to evaluate the efficacy of temsirolimus in men with post-docetaxel, metastatic CRPC [51]. Only eleven of the twenty planned patients were accrued because the trial was stopped prematurely due to lack of efficacy and feasibility. Circulating tumor cells (CTC) were evaluated as a measure of disease response since epithelial-mesenchymal transition is suspected to be involved in the development of CRPC. Median CTC decline was 48% and 3 patients experienced decline in CTCs to < 5. However, 73% of men had a persistently unfavorable number of CTCs ( $\geq 5$ ) and only 1 patient had a  $\geq 30\%$  PSA decline. Median PFS was 1.9 months and median OS was 8.8 months. Toxicities included hypophosphatemia, central nervous system hemorrhage, fatigue, anemia, stomatitis, hypokalemia and weakness. Novel PI3K pathway inhibitors (GDC-0068 and GDC-0980) are being evaluated in Phase I studies in combination with abiraterone in patients with post-docetaxel CRPC (NCT01485861) and (BEZ235 and BKM120) in patients with post-docetaxel and post-abiraterone CRPC (NCT01634061). A Phase I study will evaluate everolimus plus radiation therapy for salvage

treatment of biochemical recurrence after prostatectomy (NCT01548807).

#### 7.6 Agents targeting the apoptosis pathway

Treatments for cancer initiate a cellular stress response that activates the apoptosis pathway resulting in cell death. Dysregulation of the apoptosis pathway occurs in prostate cancer and may contribute to treatment resistance and the initial development of cancer [52]. Bcl-2, HSP-27 and clusterin are among the many proteins involved in apoptosis that are linked to prostate cancer. Bcl-2 is a family of proteins involved in the intrinsic apoptosis pathway, which promotes cell survival and is often overexpressed in CRPC. Oblimersen is an antisense medication that inhibits the translation and expression of Bcl-2 allowing apoptosis to occur [53]. In a Phase II study, 221 patients with chemotherapy-naïve CRPC were randomized to docetaxel and prednisone with and without oblimersen. Compared to the docetaxel alone arm, the combined docetaxel with oblimersen arm had a larger partial response according to RECIST criteria (24 vs. 18% patients) and a more frequent decreased PSA response (37 vs. 46% patients). Primary endpoints, PSA response rate and major toxic event rate, were not achieved.

Gossypol is a BH3 mimetic that binds to Bcl-2 preventing the binding of pro-apoptotic proteins. A Phase II study randomized 281 patients with chemotherapy-naïve CRPC to receive docetaxel combined with gossypol or placebo. Median OS was not different between the treatment and placebo arms (18.1 vs. 17.8 months; HR 1.07; 95%CI: 0.72 – 1.55;  $p = 0.63$ ) [54].

HSP-27 is a cytoprotective chaperone protein involved in stabilizing cells during times of stress [55]. HSP-27 overexpression is linked to poor prognosis and stabilization of the AR in prostate cancer [56,57]. OGX-427 is an anti-sense oligonucleotide developed to inhibit HSP-27 expression. Interim results are available from a Phase II study comparing prednisone with or without OGX-427 in 38 patients with chemotherapy-naïve CRPC [58]. Primary endpoint, PFS at 12 weeks, was greater in patients treated with OGX-427 compared to the prednisone alone (71 vs. 33% patients). PSA decline of at least 50% (41 vs. 20% patients) and objective response rate (38 vs. 0% patients) were also greater in patients treated with OGX-427 compared to prednisone alone. A second Phase II study is evaluating OGX-427 in patients with metastatic CRPC and disease progression on abiraterone (NCT01681433).

Clusterin is another cytoprotective chaperone protein that inhibits multiple pathways of apoptosis and is linked to treatment resistance [55]. Custirsen (OGX-011) is an antisense oligonucleotide complementary to clusterin mRNA, which inhibits clusterin expression. It was first evaluated in a randomized Phase II study comparing custirsen combined with docetaxel to docetaxel alone in 82 patients with metastatic CRPC [59]. The study was not designed to compare

differences between the two arms. The primary endpoint, PSA decline of at least 50% from baseline, occurred in 58% of patients treated with custirsen and docetaxel and 54% of patients treated with docetaxel alone. Custirsen combined with docetaxel improved median PFS (7.3 vs. 6.1 months; HR 0.86; 95%CI: 0.54 – 1.38) and median OS (23.8 vs. 16.9 months; HR 0.61; 95%CI: 0.36 – 1.02) compared to docetaxel alone. A multivariate analysis identified treatment assignment to custirsen as a prognostic factor for improved OS (HR 0.50; 95%CI: 0.29 – 0.87;  $p = 0.01$ ). The Phase III SYNERGY study will evaluate OS and PFS in patients with metastatic CRPC treated with custirsen combined with first-line docetaxel (NCT01188187). Patients with metastatic CRPC will also be treated with custirsen in combination with second-line cabazitaxel to evaluate OS and PFS (NCT01578655) and in combination with second-line cabazitaxel or docetaxel to evaluate pain, palliation and progression (NCT01083615).

### 7.7 Immunotherapy

Effective treatment of prostate cancer via modulation of the immune system was exhibited in trials for sipuleucel-T. Sipuleucel-T received FDA approval in 2010 for the treatment of patients with chemotherapy-naïve and asymptomatic or minimally symptomatic metastatic CRPC. Sipuleucel-T treatment involves leukopheresis of peripheral blood mononuclear cells (PBMC), culture of PBMCs with a prostatic acid phosphatase fusion protein linked to granulocyte macrophage colony stimulating factor (GM-CSF) and infusion of the product back into the patient. This is an involved process requiring separate visits for the initial collection and infusion and a 2-day culturing process at a centralized facility. Rapid adoption of sipuleucel-T has been affected by both the complexity of administration and significant financial treatment cost. The Phase III IMPACT study randomized 512 patients with chemotherapy-naïve and asymptomatic or minimally symptomatic metastatic CRPC to receive sipuleucel-T infusions or untreated PBMCs [8]. At median follow-up of 34.1 months, patients treated with sipuleucel-T had increased median OS (25.8 vs. 21.7 months; HR 0.78; 95%CI: 0.61 – 0.98;  $p = 0.03$ ). However, the two treatment arms did not differ in terms of PSA response or PFS. Adverse events were more frequent with sipuleucel-T and included chills, fever and headache.

Ongoing Phase II clinical trials are evaluating the optimal sequence of ADT and sipuleucel-T in patients with rising PSA and non-metastatic disease after primary treatment (NCT01431391). Repeat sipuleucel-T treatment is being studied in patients with metastatic CRPC with prior treatment in the androgen-dependent setting (NCT01338012). Phase II studies are also being conducted to evaluate sipuleucel-T treatment in patients with metastatic CRPC undergoing external beam radiation to a single metastasis (NCT01807065) and in patients with metastatic

CRPC treated with concurrent or sequential abiraterone (NCT01487863).

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### Sipuleucel-T Phase III at a glance

MOA: Activates T Cells

Approval status: FDA approved in 2010 for CRPC

Effect: 4.1 month increase in OS

Toxicity profile: Chills, fatigue, back pain, pyrexia, nausea

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PSA-TRICOM is a poxviral vaccine, which consists of recombinant viral vectors for PSA and immune enhancing co-stimulatory molecules CD54, CD80 and CD58. The vaccine infects antigen-presenting cells (APCs) and creates surface proteins, which activate T cells to initiate a targeted immune response and T cell-mediated tumor cell destruction against prostate cancer cells [60]. A Phase II study randomized 125 patients with minimally symptomatic metastatic CRPC to PSA-TRICOM and GM-CSF or control vector and saline injection [61]. The study was powered to evaluate PFS, which was not achieved. PSA-TRICOM patients had PFS of 3.8 months compared to 3.7 months for the control arm (HR 0.88; 95%CI: 0.57 – 1.38;  $p = 0.6$ ). At 3 years post treatment, patients treated with PSA-TRICOM had improved OS (30 vs. 17% patients) and longer median OS (25.1 vs. 16.6 months; HR 0.56; 95%CI: 0.37 – 0.85;  $p = 0.0061$ ) compared to controls. A Phase III study is evaluating the use of PSA-TRICOM with and without GM-CSF in patients with asymptomatic or minimally symptomatic metastatic CRPC (NCT01322490). A Phase II study is evaluating the use of PSA-TRICOM in combination with flutamide compared to flutamide alone in patients with non-metastatic CRPC in the setting of rising PSA (NCT00450463) and with or without docetaxel in patients with metastatic CRPC (NCT00045227). PSA-TRICOM is also being evaluated in combination with enzalutamide in patients with non-metastatic castration-sensitive prostate cancer (NCT01875250) and metastatic CRPC (NCT01867333).

Cytotoxic T lymphocyte antigen 4 (CTLA-4) negatively regulates T cell activity and can therefore downregulate anti-tumor responses. Ipilimumab is a monoclonal antibody, which binds to the CTLA-4 receptor and activates T cell anti-tumor activity. A Phase III, double-blind clinical trial randomized 799 patients with post-docetaxel metastatic CRPC to either ipilimumab or placebo following radiation (NCT00861614) [62]. Patients received bone-directed radiation after random assignment to ipilimumab or placebo. Ipilimumab did not increase OS compared to placebo (11.2 vs. 10 months; HR = 0.85; 95%CI: 0.72 – 1.00;  $p = 0.053$ ). Median PFS (HR = 0.70; 95%CI 0.61–0.82) and PSA decline of at least 50% (13.1 vs. 5.3%) favored ipilimumab. A Phase III study will continue to evaluate the role of ipilimumab in treating patients with chemotherapy-naïve metastatic CRPC (NCT01057810). Ipilimumab is also being evaluated

in Phase II studies in combination with abiraterone and prednisone in patients with chemotherapy-naïve, metastatic CRPC (NCT01688492) and with ADT in patients with metastatic CRPC (NCT01498978) and metastatic castration-sensitive disease (NCT01377389).

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#### **Ipilimumab Phase III at a glance**

MOA: Monoclonal antibody against CTLA-4

Approval status: Not approved

Effect: No increase in OS

Toxicity profile: Fatigue, diarrhea, pruritus, rash colitis

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Tasquinimod is an oral medication with antiangiogenic and immunomodulatory properties. It was evaluated in a Phase II study of patients with minimally symptomatic, metastatic CRPC [63]. PFS at 6 months was longer with tasquinimod compared to placebo (7.6 vs. 3.3 months,  $p = 0.0042$ ). PSA did not differ between the two groups and the tasquinimod arm had more frequent Grade 3–4 adverse events. Tasquinimod is being evaluated in a Phase III study of chemotherapy-naïve, metastatic CRPC patients (NCT01234311). Tasquinimod is also being evaluated in combination with cabazitaxel in patients with post-docetaxel, metastatic CRPC (NCT01513733) and as a maintenance therapy in patients with metastatic CRPC who are not progressing after docetaxel treatment (NCT01732549).

#### **7.8 Epigenetics in prostate cancer**

DNA methylation and histone modification are two hallmark epigenetic cancer mechanisms that influence prostate cancer. Epigenetic changes are chemical modifications to DNA that result in heritable changes in gene expression, but do not alter the original DNA sequence. DNA methylation is catalyzed by DNA methyltransferase and results in methylation of 5' CpG-rich promoter regions, which leads to gene silencing. Hypermethylation silences transcription directly by inhibiting the binding of transcription factors and indirectly by attracting methyl-binding domain proteins, which recruit histone deacetylases (HDACs) to condense the chromatin structure, effectively blocking transcriptional enzymes from binding to the promoter region [64].

Azacytidine is a hypomethylating agent currently approved for myelodysplastic syndrome. It was evaluated in an open-label Phase II trial in 36 chemotherapy-naïve patients with progressive metastatic or non-metastatic CRPC on combined androgen blockage with PSA doubling time (PSA-DT) < 3 months [65]. PSA-DT was calculated over a period of 4 weeks at baseline and monthly while at therapy. Azacytidine was administered subcutaneously for 5 days each month for up to 12 cycles in 34 patients (81% metastatic disease). Primary end-point, PSA-DT  $\geq 3$  months, was achieved in 19 patients (55.8%). Overall median PSA-DT was prolonged compared to baseline (2.8 vs. 1.5 months,  $p < 0.01$ ). Fourteen

patients had a post-therapy PSA decline and one patient had a  $\geq 30\%$  decline. Median clinical PSF was 12.4 weeks. Most common grade 3 adverse effects included fatigue and neutropenia. Further evaluation of azacitidine's clinical activity is being conducted in a Phase I/II study evaluating azacitidine with docetaxel and prednisone in patients with chemotherapy metastatic CRPC progressing after docetaxel treatment (NCT00503984).

Vorinostat, romidepsin and panobinostat are HDAC inhibitors identified in Phase II studies to have limited clinical activity and significant side effects [66]. Vorinostat was evaluated in 17 patients with metastatic CRPC and progression on chemotherapy [67]. Medication was administered orally and daily. All patients were taken off therapy due to significant side effects prior to evaluation of the primary end point progression rate at 6 months. Two patients had stable disease and no patient achieved PSA decline  $\geq 50\%$ . 44% of patients experienced grade III adverse effects with the most common being fatigue, nausea, anorexia, vomiting, diarrhea and weight loss. Panobinostat was evaluated in 35 patients with metastatic CRPC and progression on chemotherapy. Panobinostat was administered intravenously on days 1 and 8 for a 3-week cycle. Only 4 patients were alive without progression of disease at 24 weeks and no patient achieved PSA decline  $\geq 50\%$ . Significant toxicity was identified with the most common being fatigue, nausea, thrombocytopenia, decreased appetite and diarrhea. Perhaps HDACs will show stronger clinical efficacy in combination therapy. Current studies include vorinostat with temsirolimus (Phase I, NCT01174199) and panobinostat with bicalutamide in patients with CRPC (Phase I/II, NCT00878436).

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#### **8. Potential development issues**

An unfulfilled and critical need exists for novel drugs that target prostate cancer directly. Only 2 of 5 prostate cancer drugs recently approved by the FDA target the AR (enzalutamide) or decrease the availability of ligands that activate the AR (abiraterone). The AR is expressed almost ubiquitously in the human body, including tissues such as skin, brain, breast and muscle (skeletal, smooth and cardiac). Emerging drugs need to have less cross reactivity with these extra-prostatic sources and more selectivity for prostatic sources. For example, side effects of enzalutamide include fatigue, diarrhea, hot flashes, but most concerning, seizures. ARN-509 is a second-generation AR antagonist in development and is predicted to have more activity at lower doses and less toxicity to the central nervous system than enzalutamide. The development of androgen resistance is a principal reason for disease progression. As the androgen resistance mechanism is better understood, emerging drugs will be able to sustain progression-free and cancer-specific survivals.

Several drugs targeting PI3K/Akt, HDAC and Src kinase signaling pathways have shown pre-clinical promise, but have failed to translate into improved outcomes in clinical

studies. The early theory is that these drugs do not target principle pathways in human prostate cancer signaling, do not affect the central AR and/or do not directly target prostate cancer cells effectively. Further evaluation may need to be conducted to determine whether combining failed drugs with other current treatments is worthwhile to pursue.

The majority of developing drugs target cell proliferation, cell signaling or the immune system. Debate exists over whether cell proliferation is best treated with cytostatic or cytotoxic chemotherapy. At this time, cytotoxic treatment is not used for prostate cancer, but theoretically may lead to longer progression-free and OSs compared to cytostatic treatments. Combination therapy will become a challenge as drugs continue to be developed and receive FDA approval. An example of early success of combination therapy was identified in the synergistic growth inhibition and apoptosis of prostate cancer cells treated with R115777 farnesyltransferase inhibitor and zoledronic acid in pre-clinical studies [68]. In a similar manner, combination therapy may allow more effective targeting of the AR from multiple facets ultimately improving patient outcomes.

## 9. Conclusion

Prostate cancer drug development is making significant strides. The addition of 5 new FDA approved medications from different drug classes significantly increases the treatment options for patients with CRPC. The extent to which OS will improve with these new medications remains to be determined as the optimal sequence and/or combination of these drugs remains to be identified. In addition, we estimate that another 20 or so drugs may emerge by the year 2020 as viable FDA-approved options for patients with prostate cancer. As new drugs and combinations emerge, physicians have a growing responsibility to keep pace with these new medications so that they may counsel and treat patients appropriately.

## 10. Expert opinion

The recent approval of medications by the FDA (abiraterone, enzalutamide, cabazitaxel, radium-223 and sipuleucel-T) and the development of emerging treatments in the pipeline are promising signs for the future of prostate cancer. Second-generation drugs, such as ARN-509, that are second-generation versions of currently FDA-approved medications (enzalutamide) are promising. Furthermore, the results from the Phase III COMET-1/2 (cabozantinib) and SYNERGY (custirsen) studies are highly awaited as they are potential drugs closest to being evaluated for FDA approval.

Currently approved medications improved median OS in patients with metastatic CRPC in the order of 2.4 to

4.8 months in Phase III clinical studies. Sequential and/or combination therapy will play strong roles in future prostate cancer treatments; however, it is unknown whether patients will experience diminishing returns or synergism from the sequential or combined use of these medications. The initial evaluation of sequential and/or combination therapy of currently approved drugs will set precedence for how future prostate cancer drugs will be evaluated. Additional questions that need to be addressed include the following: Similar to the continuation of ADT after the development of castration resistance, do these medications need to be continued after disease progression? How will the earlier use of newer generation anti-androgens in castration-sensitive patients affect the biology of the cancer and development of castration resistance?

Personalized medicine may be the future of prostate cancer treatment algorithms. In theory, patients would be screened with PSA or an improved biomarker or even MRI. Patients would then undergo tissue sampling with standard transrectal ultrasound (TRUS) or MRI/US fusion-guided biopsies. Biopsy cores would be evaluated not only for the histologic presence of cancer but also the molecular characteristics of disease aggressiveness, predominant molecular pathways and susceptibility to potential drugs. The ability to study epigenetic markers from prostate biopsy cores has been introduced [69]. Patients would first undergo medical treatment with a drug tailored to their cancer pathway and reserve surgical therapy for medical treatment failures. Appropriate follow-up and definition of medical treatment failure would need to be determined.

Significant research milestones need to be achieved before physicians are able to offer personalized medicine to their patients. In the meantime, physicians have sufficient work at hand dealing with current and emerging drug indications. It is the responsibility of physicians and governing bodies to organize together, to develop appropriate clinical trials that will help answer the concerning questions discussed in this review and to provide consensus based on available data. This will help to relieve confusion among physician and patients and result in the most optimized patient outcomes.

## Declaration of interest

GV Raj has served on Speaker/Advisory boards of Dendreon, Bristol Myers Squibb, Aureon, Janssen, Millenium, Amgen and Astellas. He has several patent applications on potential therapeutics (not discussed in this article) in prostate cancer. He also receives research funding from Janssen and C-diagnostics Corp. All remaining authors have no conflicts of interest.

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