



## Review Article

## New drugs in prostate cancer



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## ABSTRACT

The standard primary treatment for advanced prostate cancer has been hormonal therapy since the 1940s. However, prostate cancer inevitably progresses to castration-resistant prostate cancer (CRPC) after a median duration of 18 months of androgen deprivation therapy. In patients with CRPC, docetaxel has been regarded as the standard treatment. However, survival advantages of docetaxel over other treatments are slim, and the need for new agents persists. In recent years, novel agents, including abiraterone, enzalutamide, cabazitaxel, radium-223, and sipuleucel-T, have been approved for the treatment of CRPC, and more such agents based on diverse mechanisms are under investigation or evaluation. In this article, the authors reviewed the current literature on recent advances in medical treatment of prostate cancer, especially CRPC. In addition, the authors elaborated on novel drugs for prostate cancer currently undergoing investigation and their mechanisms.

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## 1. Introduction

Prostate cancer is the fourth most frequent cancer in general and the second most common cancer in men. About 1.1 million cases of prostate cancer were diagnosed worldwide in 2012, accounting for 15% of all cancers in men.<sup>1</sup> The incidence of prostate cancer varies by > 25-fold. The incidence is high in Australia, New Zealand, North America, and Europe (age standardized rate: 85–112), but it remains low in Eastern and South Central Asia (age standardized rate: 4.5–10.5). In addition, prostate cancer is the fifth leading cause of death from cancer in men, with an estimated 307,000 deaths representing 6.6% of total male cancer mortality. There is a relatively smaller variation in mortality than in the incidence worldwide. Mortality rates are generally high in people of African descent (Caribbean, Sub-Saharan Africa: 19–24 deaths/100,000 persons), intermediate in the Americas and Oceania, and very low in South Central Asia (2.9 deaths/100,000 persons). However, the proportion of metastatic prostate cancer is higher in Asian countries than in Western countries.

The initial treatment of choice for metastatic prostate cancer is medical or surgical castration. However, metastatic prostate cancer generally acquires resistance to androgen deprivation therapy (ADT) after a median duration of 18 months. The presumed mechanisms of resistance to ADT include persistence of intratumoral androgen despite castration levels of serum testosterone, increased androgen receptor (AR) protein expression, mutated forms of active AR protein (AR splice variants or AR point mutation), increased activity of AR coregulatory proteins (Src family of proteins), and overactive signaling of other proliferative pathways [mammalian target of rapamycin (mTOR) and retinoblastoma protein pathway].<sup>2–12</sup>

Currently, metastatic castration-resistant prostate cancer (CRPC) is usually treated with chemotherapy (docetaxel, mitoxantrone, and cabazitaxel) or secondary hormonal therapeutic agents such as abiraterone or enzalutamide. Immunotherapy with sipuleucel-T has been employed in treating asymptomatic or minimally metastatic CRPC without visceral metastasis. Bone metastasis is managed with zoledronic acid, denosumab, or radium-223. Radium-223 is used for symptomatic bone metastasis without visceral metastasis. However, the effects of these treatments are less than satisfactory, and the need for novel agents in treating metastatic CRPC is still present.

A considerable number of novel agents against metastatic CRPC based on diverse mechanisms are currently under investigation worldwide. In this article, the authors summarized ongoing clinical

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trials for novel drugs in prostate cancer. In addition, the authors reviewed the current literature and elaborated on novel drugs currently undergoing investigation according to their mechanisms of action, including androgen pathway targeted therapy, cytotoxic chemotherapy, target agents and vaccines, immunotherapy, and gene-based therapy.

## 2. Ongoing clinical trials for drugs on prostate cancer

Owing to the high incidence of prostate cancer, various novel drugs are currently being investigated. The authors listed those currently undergoing Phase II or III clinical trials for prostate cancer, especially metastatic CRPC, in Table 1. As of now, > 30 agents are under clinical evaluation, with some of these in Phase III clinical trials.

## 3. Androgen pathway targeted therapy

One well-known mechanism responsible for acquisition of castration resistance is activation of AR by alternative androgens. CRPC may bypass testosterone-mediated modulation using the 5 $\alpha$ -androstane-3 $\beta$ -dione pathway, which is regarded as a predominant pathway. Moreover, the 17,20-lyase activity of cytochrome P450 17 (CYP17), in addition to 3 $\beta$ -hydroxysteroid dehydrogenase and 5 $\alpha$ -reductase activity, may form alternative pathways from a cholesterol precursor. CYP17 is regarded as a potent therapeutic target in treating metastatic CRPC. In addition, AR amplification is demonstrated in ~30% of CRPC, and increased expression of AR mRNA has been suggested as a mechanism associated with decreased

hormone sensitivity in addition to enhanced intracellular conversion of androgens to dihydrotestosterone. Although second-generation AR antagonists have been approved for clinical usage, the need for more potent AR antagonists remains. In this section, the authors will briefly summarize several investigational drugs, including CYP17 inhibitors and AR inhibitors.

### 3.1. CYP17 inhibitors

TAK-700 (orteronel; Takeda Pharmaceutical Company, Osaka, Japan) is a CYP17 inhibitor with greater affinity for 17,20-lyase over 17-hydroxylase. In a recent Phase III trial involving patients with post- and pre-docetaxel CRPC, TAK-700 was shown to offer an advantage in terms of radiographic progression-free survival (PFS) without safety concerns, but it did not meet the primary end point of improved overall survival.<sup>13</sup> Takeda Pharmaceutical Company (Osaka, Japan) recently decided to terminate the development of orteronel. However, a Phase III trial (NCT01809691) comparing ADT + TAK-700 versus ADT + bicalutamide by Southwest Oncology Group is currently recruiting metastatic prostate cancer patients.

VT-464 (viamet) is a novel oral CYP17 inhibitor with greater affinity for 17,20-lyase over 17-hydroxylase, which does not require concomitant steroid administration. In preclinical studies, VT-464 showed superior selective suppression of androgen synthesis and AR antagonism compared with abiraterone.<sup>14</sup> VT-464 is currently under Phase I and II clinical trials (NCT02012920).

Galeterone (VN/124-1, TOK-001; Tokai, Boston, Massachusetts, United States) is an oral, semisynthetic, steroidal agent that

**Table 1** Ongoing clinical trials for novel agents in prostate cancer.

Drug	Registry number	Completion	Enroll	Phase	Status	Patient group
TAK-700 (orteronel)	NCT01707966	Jul 2020	1,486	III	Recruiting	ADT + TAK-700 vs. ADT + bicalutamide
VT-464	NCT02012920	Aug 2016	141	I, II	Recruiting	Treatment-naïve vs. previous abiraterone & Enz
JNJ-56021927 (apamutamide)	NCT01171898	Oct 2026	1,500	III	Recruiting	JNJ-56021927 vs. bicalutamide
BAY1841788 (ODM-201)	NCT02200614	Jun 2020	1,500	III	Recruiting	BAY1841788 vs. placebo
MLN8237 (alisertib)	NCT01799278	Feb 2017	60	II	Not recruiting	Neuroendocrine prostate cancer
PROSTVAC	NCT02649855	Jan 2020	38	II	Recruiting	Simultaneous vs. sequential docetaxel + prosvac
Ipilimumab	NCT01688492	Sep 2016	57	I, II	Not recruiting	Ipilimumab + abiraterone
EPI-506	NCT02606123	Dec 2017	166	I, II	Recruiting	EPI-506
DCVAC	NCT02111577	Jun 2018	1,170	III	Recruiting	DCVAC + chemotherapy vs. placebo + chemotherapy
AZD5363	NCT02525068	Jun 2018	136	II	Recruiting	AZD5363 + Enz
Alisertib	NCT01848067	May 2018	43	I, II	Recruiting	Alisertib + abiraterone
OGX-011 (custirsén sodium)	NCT01578655	Dec 2016	630	III	Not recruiting	Custirsén + cabazitaxel vs. cabazitaxel
177Lu-J591	NCT00859781	Dec 2018	140	II	Recruiting	177Lu-J591 + Keto vs. 111In-J591+Keto
Olaparib	NCT01682772	Dec 2016	89	II	Recruiting	Olaparib
AMG386	NCT01553188	Feb 2017	23	II	Not recruiting	Abiraterone + AMG386 vs. abiraterone
Galeterone	NCT01709734	Aug 2017	144	II	Recruiting	Galeterone
KPT-330 (selinexor)	NCT02215161	Jun 2018	54	II	Recruiting	KPT-330
MK-3475 (pembrolizumab)	NCT02312557	Jan 2017	28	II	Recruiting	Pembrolizumab + enzalutamide
GX301	NCT02293707	Nov 2018	120	II	Recruiting	GX301
Everolimus	NCT00976755	Dec 2017	37	II	Not recruiting	Everolimus
TKI258 (dovitinib)	NCT01741116	Jun 2016	44	II	Recruiting	TKI258
Onapristone	NCT02049190	Dec 2017	75	I, II	Recruiting	Onapristone
ODM-204	NCT02344017	May 2017	75	I, II	Recruiting	ODM-204
Carfilzomib	NCT02047253	Apr 2018	28	II	Recruiting	Carfilzomib
Reolysin	NCT01619813	Dec 2016	85	II	Not recruiting	Docetaxel + reolysin vs. docetaxel
CYT107	NCT01881867	Jan 2017	80	II	Recruiting	CYT107 vs. no therapy
Indoximod	NCT01560923	Apr 2017	50	II	Recruiting	Indoximod vs. placebo
SHR3680	NCT02691975	Jun 2020	140	I, II	Recruiting	SHR3680
LY3023414	NCT02407054	May 2018	144	II	Recruiting	LY3023414 + Enz vs. placebo + Enz
LEE011 (ribociclib)	NCT02494921	Dec 2018	47	I, II	Recruiting	Docetaxel + ribociclib
BKM120	NCT01385293	Dec 2016	66	II	Not recruiting	BKM120
LY2157299	NCT02452008	Jul 2019	60	II	Recruiting	LY2157299 + Enz vs. Enz

ADT, androgen deprivation therapy; Enz, enzalutamide.

suppresses prostate cancer cells through a combination of CYP17 inhibition and AR modulation. Galeterone is the most potent CYP17 inhibitor to date that also has activity against 17-lyase. The ARMOR2 clinical trial (NCT 01709734), an open label, two-part Phase II trial, evaluated the safety and efficacy of optimized galeterone treatment in CRPC patients. Metastatic and non-metastatic treatment-naïve CRPC patients were enrolled and treated with daily oral doses of 1,700 mg, 2,550 mg, or 3,400 mg. Abiraterone-refractory patients were allowed in this study. Preliminary data showed that galeterone was well tolerated at doses up to 3,400 mg daily. Prostate specific antigen (PSA) responses were observed in treatment-naïve metastatic CRPC patients treated at 2,550 mg daily, with 90% and 81% of patients achieving a PSA decline of > 30% and 50%, respectively. Biochemical activity and stable disease have been observed in abiraterone-refractory patients, supporting the possibility of a different response profile for galeterone compared with other second-generation antihormonals.<sup>15</sup>

ASP9521 (Astellas, Tokyo, Japan) is the first orally available 17 $\beta$ -hydroxysteroid dehydrogenase inhibitor. It is presumed not to interfere with glucocorticoid synthesis by bypassing the need for prednisone. In a first-in-human Phase I and II study, ASP9521 evoked no biochemical or radiological response in 13 post-chemotherapy patients.<sup>16</sup>

### 3.2. AR inhibitors

JNJ-56021927 (ARN-509, apalutamide; Aragon, San Diego, California) is a novel second-generation oral AR antagonist that binds to AR with high affinity and blocks nuclear translocation of AR, binding of AR to androgen response elements, and recruitment of coactivators by AR. In a Phase II study with JNJ-56021927, PSA response (> 50% decline in PSA from baseline after 3 months) was observed in 91% of nonmetastatic treatment-naïve cases, 88% of metastatic treatment-naïve cases, and 24% of metastatic post-abiraterone cases. The Phase III studies SPARTAN (NCT01946204) and ATLAS (NCT01171898) are evaluating JNJ-56021927 in patients with nonmetastatic CRPC and high-risk prostate cancer, respectively. Future trials in combination with abiraterone are planned (NCT01792687).

BAY1841788 (ODM-201; Bayer, Leverkusen, Germany) is another second-generation ligand-domain binding AR antagonist, which binds to AR with greater affinity than enzalutamide and does not accumulate in the central nervous system. In a Phase I and II trial, known as ARADES, the median time to PSA progression was 72.3 weeks for chemo-naïve patients and 20.3 weeks for postchemo patients.<sup>17</sup> A Phase III clinical trial (ARAMIS) is underway.

AZD3514 (AstraZeneca, London, United Kingdom) is an oral drug that inhibits AR signaling by inhibiting ligand-driven nuclear translocation of AR and downregulating AR level. In the Phase I trial, AZD3514, PSA decline of  $\geq$  50% was observed in 13% of CRPC patients at a daily dose of 250 mg, and objective soft tissue response was seen in 17%.<sup>18</sup> However, further development of this agent has been terminated.

EPI-001 (ESSA, Vancouver, Canada) covalently binds to the N-terminal domain of AR, which is essential for the receptor's transcriptional activity.<sup>19</sup> It inhibits transcriptional activity of AR and its splice variants, and reduces the growth of CRPC in xenografts. EPI-001 may thus have efficacy in treatment of CRPC progressing after enzalutamide therapy in which AR variants play a role in tumor progression. EPI-506 is also an N-terminal domain inhibitor and is a prodrug of EPI-002.<sup>20</sup> Recently, a Phase I and II trial has been started.

## 4. Cytotoxic chemotherapy and target agents

Docetaxel was approved for metastatic CRPC in 2004 and has been regarded as the standard treatment in patients with CRPC. However, the need for novel cytotoxic chemotherapeutic agents has repeatedly been voiced because of inevitable progression of disease despite docetaxel treatment. Target agents are broadly used against various malignancies. In prostate cancer, the role of target agents was thought to be limited because no well-defined drugable target had been identified in prostate cancer. However, because of the safety and efficacy of target agents, increasing efforts are being put into the development of target agents suitable for prostate cancer. In this section, the authors will introduce investigational cytotoxic chemotherapeutic drugs and target agents.

### 4.1. Cytotoxic chemotherapy

Carboplatin (Sagent, Schaumburg, Illinois, United States), a platinum-based drug, has previously been reported to induce PSA reduction of  $\geq$  50% in patients with prostate cancer that progressed after docetaxel chemotherapy.<sup>21</sup> Everolimus, an mTOR inhibitor, in addition to platinum-based chemotherapy, demonstrated increased antitumor effects and surmounting of resistance to chemotherapy.<sup>22</sup> In this regard, a Phase II study was conducted to evaluate the efficacy of combination therapy using carboplatin and everolimus in metastatic prostate cancer patients. In this study, the combination of carboplatin and everolimus showed no pharmacokinetic interaction, and the median overall survival was 12.5 months in metastatic CRPC patients who progressed under docetaxel-based chemotherapy.<sup>23</sup>

### 4.2. Target agents

Tasquinimod (Ipsen, Paris, France), a potential anticancer drug, is an oral quinolone-3-carboxamide derivative. On Phase II evaluation, the median PFS after tasquinimod treatment was significantly longer than that for placebo (7.6 months vs. 3.3 months,  $P = 0.004$ ).<sup>24</sup> In terms of radiographic response, partial response and stable disease were observed in 7% and 52% of patients after tasquinimod treatment, respectively. On subgroup analyses, CRPC patients with bone metastases showed superior PFS after tasquinimod treatment compared with those with visceral or lymph node-only metastasis. Based on these data, a Phase III trial on metastatic CRPC and bone metastases was conducted, enrolling over 1,200 patients (NCT01234311). However, Active Biotech (Lund, Sweden) reported that tasquinimod failed to prolong survival (hazard ratio: 1.09; 95% confidence interval: 0.94–1.28) although the results are not available as of now. Currently, combination trials with sipuleucel-T (NCT02159950) and cabazitaxel (NCT01513733) are underway.

Arginine deiminase (ADI), which degrades arginine, reduces plasma arginine levels and damages tumor cells that lack argininosuccinate synthetase. However, because ADI is highly immunogenic, it is conjugated with polyethylene glycol, resulting in the therapeutic agent pegylated ADI (ADI-PEG 20; Polaris, San Diego, California, United States), which also has a longer half-life. Autophagy and cell death were observed in prostate cancer cells after treating them with ADI-PEG 20 in *in vitro* studies.<sup>25</sup> A recent Phase I study revealed tolerable toxicity when used in combination with docetaxel, and a Phase II study was conducted accordingly.<sup>26</sup>

Alisertib (Takeda Pharmaceutical Company, Osaka, Japan), previously known as MLN8237, is an Aurora A kinase inhibitor, which demonstrated antitumor activity in various solid

neoplasms.<sup>27</sup> Aurora A kinase is reported to be expressed in 40% of neuroendocrine prostate cancers, although it is expressed in only 5% of prostate cancer.<sup>28</sup> In addition, after Aurora kinase inhibitor therapy, complete suppression of neuroendocrine marker expression was observed. Currently, a Phase II study is underway (NCT01848067).

OGX-011 (custirsen sodium; Oncogenex, Bothell, Washington, United States) is an antisense inhibitor for clusterin, which was reported to restore docetaxel sensitivity in docetaxel-resistant prostate cancer cells.<sup>29</sup> A Phase II study involving metastatic CRPC patients demonstrated a PFS of 7.3 months after treatment with OGX-011 and docetaxel, and a PFS of 6.1 months without OGX-011 treatment.<sup>30</sup> The overall survival was 23.8 months in the OGX-011 arm and 16.9 months in the placebo arms. A Phase III clinical trial comparing cabazitaxel/prednisolone in combination with OGX-011 was conducted (NCT01578655).

KPT-330 (Karyopharm, Newton, Massachusetts, United States), also known as selinexor, is a selective exportin-1 inhibitor with antitumor effect demonstrated in prostate cancer models.<sup>31</sup> Exportin-1-1 is reported to be overexpressed in prostate cancer and associated with adverse pathologic findings. A Phase II clinical trial has started and is recruiting metastatic CRPC patients.

AZD5363 (Otsuka, Tokyo, Japan) is a novel Akt inhibitor reported to induce autophagy, although apoptosis is not induced.<sup>32</sup> Phase II trials were recently conducted in combination with enzalutamide (NCT02525068) and docetaxel chemotherapy (NCT02121639).

Cabozantinib (Exelixis, South San Francisco, California, United States) is an oral multikinase inhibitor for MET and vascular endothelial growth factor receptor 2. In a Phase II study, a median PFS of 23.9 weeks was demonstrated in CRPC patients treated with cabozantinib against a PFS of 5.9 weeks in those treated with placebo ( $P < 0.001$ ).<sup>33</sup> However, the mechanism leading to these responses have yet to be fully understood, and a Phase III clinical trial, performed in 2014, failed to demonstrate a clear survival benefit.

AMG386 (trebananib; Amgen, Thousand Oaks, California, United States) is a novel drug that disrupts proliferation of endothelial cells in tumors. A Phase I and II trial is underway to evaluate the efficacy of the combination of abiraterone and AMG386 in metastatic CRPC (NCT01553188).

Everolimus (Novartis, Basel, Switzerland) is a well-known mTOR inhibitor. In a Phase II study, the combination therapy of bicalutamide and everolimus was shown to be effective in CRPC patients who were not previously treated using bicalutamide.<sup>34</sup> Among 24 patients enrolled in the study, 18 (75%) showed a PSA response. A Phase II study evaluating everolimus monotherapy is underway (NCT00976755).

TKI258 (dovitinib; Novartis, Basel, Switzerland), a fibroblast growth factor receptor tyrosine kinase inhibitor, has been shown to inhibit bone metastasis of prostate cancer.<sup>35</sup> A Phase II trial is on the way (NCT01741116).

## 5. Vaccines, immunotherapy, and gene-based therapy

Despite advances in treatment of prostate cancer, curative therapy is not yet available for CRPC. Novel therapeutic options have thus been sought, and vaccines, immunotherapy, and gene-based therapy are considered to be attractive candidates in this respect. Up to now, sipuleucel-T is the only such treatment approved by the Food and Drug Administration. In this section, the authors will briefly introduce investigational vaccines, immunotherapy, and gene-based therapy for CRPC.

### 5.1. Vaccine

GX301 (Genovax, London, United Kingdom) is a dual-adjuvant telomerase vaccine. GX301 is reported to be safe and highly immunogenic in patients with prostate cancer.<sup>36</sup> A Phase II randomized trial is underway (NCT02293707).

Prostvac (Barvarian Nordic, Martinsried, Germany) is a vector-based therapeutic cancer vaccine. A Phase II study reported that prostvac was well tolerated and it improved overall survival compared with control vectors (25.1 months vs. 16.6 months) in patients with minimally symptomatic CRPC.<sup>37</sup> However, another Phase II study, which evaluated the effect of the combination of docetaxel and prostvac, failed to show improvements in overall survival; this lack of positive results may be due to limited accrual of patients.<sup>38</sup> Investigation on the relative efficacy of simultaneous versus sequential docetaxel + prostvac is currently ongoing (NCT02649855).

DCVAC is an autologous dendritic cell-based vaccine. In a Phase I and II trial, combination chemioimmunotherapy with DCVAC and docetaxel resulted in longer than expected survival (19 months vs. 11.8 months) without significant complications.<sup>39</sup> A Phase III study, evaluating the merits of DCVAC when added to standard chemotherapy, is due to commence (NCT02111577).

### 5.2. Immunotherapy

Ipilimumab (yervoy; Bristol-Myers Squibb, New York, United States) is a monoclonal antibody that blocks the activity of CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and was approved by the Food and Drug Administration for the treatment of melanoma in 2011. As preclinical and clinical studies suggested that radiotherapy might activate the immune system in patients with prostate cancer,<sup>40,41</sup> a Phase III trial of ipilimumab in addition to radiotherapy for metastatic CRPC patients was initiated. However, this Phase III study did not show any improvement in overall survival (11.2 months vs. 10.0 months,  $P = 0.053$ ) after radiotherapy followed by ipilimumab, compared with radiotherapy followed by placebo.<sup>42</sup> Currently, combination trials with abiraterone (NCT01688492), ADT (NCT01498978), sipuleucel-T (NCT01804465), and prostvac (NCT02506114) are underway.

177Lu-J591 (ATLAB, Nantes, France), a humanized monoclonal antibody, was primarily developed in a radiolabeled form for PET, binding to the extracellular domain of prostate-specific membrane antigen (PSMA). After binding to PSMA, the 177Lu-J591-PSMA complex undergoes endocytosis and is accumulated in prostate cancer cells. In this regard, 177Lu-J591 is considered to be a potential carrier for cytotoxic drug conjugates to maximize therapeutic effectiveness<sup>43</sup> and a promising agent for radioimmunotherapy. Currently, a Phase 2 clinical trial is in the process of patient recruitment (NCT00859781).

### 5.3. Gene-based therapy

Olaparib (AstraZeneca, London, United Kingdom), recently approved for treating ovarian cancer with BRCA1/2 mutations, is a poly-ADT-ribose polymerase inhibitor. Poly-ADT-ribose polymerase is involved in the DNA repair process, and genomic aberrations observed in CRPC are thought to confer sensitivity to poly-ADT-ribose polymerase inhibitors. In recent studies, olaparib showed a considerable response rate of 33% in post-docetaxel prostate cancer patients with defects in DNA repair genes,<sup>44</sup> and a Phase II trial has commenced (NCT01682772).

## 6. Conclusion

Treatment regimens for prostate cancer have undergone recent changes due to the introduction of new drugs such as docetaxel, enzalutamide, abiraterone acetate, cabazitaxel, radium-223, and sipuleucel-T. More novel agents are undergoing evaluation or awaiting approval to address their shortcomings, and clinicians should be aware of recent developments in order to provide optimal care to patients with prostate cancer, especially CRPC.

## Conflicts of interest

There is no financial disclosure from any authors.

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