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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.

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.[1] 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].[2–12]

Currently, metastatic castration-resistant prostate cancer (CRPC) is usually treated with chemotherapy (docetaxel, mitixantrone, 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 5α-androstanedione pathway, which is regarded as a predominant pathway. Moreover, the 17,20-lyase activity of cytochrome P450 17 (CYP17), in addition to 3β-hydroxysteroid dehydrogenase and 5α-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.[13] 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.[14] 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 + prostvac
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 (custirsen sodium)	NCT01578655	Dec 2016	630	III	Not recruiting	Custirsen + 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 (pembrolizamab)	NCT02312557	Jan 2017	28	II	Recruiting	Pembrolizamab + 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.