Emerging therapies in castration resistant prostate cancer

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Introduction: *Prostate cancer continues to be the second leading cause of cancer related mortality in men within the United States. Despite a consistent decline in prostate cancer mortality over the past two decades, the prognosis for men with metastatic prostate cancer remains poor with no curative therapies. In this article, we review the recently approved and emerging therapeutics for patients with castrate resistant prostate cancer.*

Materials and methods: *An advanced search was conducted on the clinicaltrials.gov database, using search terms "metastatic prostate cancer", and limiting results to phase II-IV clinical trials. Clinically relevant emerging therapeutics were selected and a Medline search for supporting documents was performed. An emphasis was placed on newly approved and promising new therapeutics.*

Results: *A total of four Food and Drug Administration approved medications and eight investigational agents were chosen for review. The background and role of these therapeutics in the treatment of prostate cancer treatment is discussed.*

Conclusions: *The past few years have yielded a near exponential increase in treatments for metastatic prostate cancer, many of which have a unique mechanism of action. The estimated median survival for patients with metastatic prostate cancer remains dynamic as we begin to integrate these therapeutics into clinical practice and determine the optimal sequence and timing of treatment.*

Key Words: CRPC, emerging therapies, castration resistant prostate cancer

Introduction

In 2014 alone, it is estimated that there will be 233000 new cases of prostate cancer in the United States. With an estimated 29480 deaths, prostate cancer is the second-leading cause of cancer-related death in men.[1] Although many patients present with organ confined disease, there continues to be a subset of patients that progress or present with metastatic prostate cancer. Until 2009, there were only four drugs approved for the treatment of castration resistant prostate cancer, with only one, docetaxel, that showed improvement in overall survival. The median survival of patients with advanced metastatic prostate cancer, who have failed androgen deprivation therapy, was typically 16 to 20 months in 2009.[2,3] Since 2009, work building on decades of research, dissecting molecular pathways involved in prostate cancer, has resulted in five novel Food and Drug Administration (FDA) approved therapeutic agents, each of which has shown an improvement in overall survival. Although the survival improvements in these recently approved medications are modest, nearly all of them have a distinct mechanism of action, Table 1. The potential for combining therapies or optimally sequencing therapies may offer further improvements in the survival of patients with metastatic prostate cancer.[4] As newer drugs progress through the development pipeline, Table 2, there is real hope for decreasing the mortality from metastatic prostate cancer.

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TABLE 1. **Therapeutic agents and mechanism of action**

FDA approved agents	**Mechanism of action**	**Sponsor**	**Delivery**	**Prednisone supplement**	**Approval date**
Sipuleucel-T	personalized antigen presenting cell-based immunotherapy	Dendreon	IV	no	4/29/2010
Abiraterone	CYP17 inhibitor	Cougar Biotechnology	oral	yes	4/28/2011
Enzalutamide	AR antagonist	Medivation	oral	no	8/31/2012
Radium 223 (Alpharadin)	alpha-particle emitting radiopharmaceutical	Algeta ASA	IV	no	5/15/2013
Investigational agents	**Mechanism of action**	**Sponsor**	**Delivery**	**Prednisone supplement**	
ARN-509	AR antagonist	Aragon Pharmaceuticals	oral	no	
TAK-700	CYP17A1 inhibitor	Millennium Pharmaceuticals	oral	yes	
TOK-001	CYP17 inhibitor, AR antagonist	Tokai Pharmaceuticals	oral	no	
OGX-111	second-generation ASO with a high affinity for CLU RNA	OncoGenex Technologies	IV	yes	
OGX-427	second-generation ASO with a high affinity for Hsp27 expression	Hoosier Oncology Group	IV	yes	
Prostvac	prostate cancer vaccine	Bavarian Nordic	SQ	no	
Ipilimumab	monoclonal antibody blocking CTLA-4	Bristol Myers Squibb	IV	no	
Cabozantinib	tyrosine kinase inhibitor	Exelixis	oral	no	

Androgen axis

In 1941, Huggins and Hodges performed a series of experiments that showed a relationship between metastatic prostate cancer growth and testosterone levels.[5] Since this pioneering study, androgen deprivation therapy (ADT) has been the cornerstone of metastatic prostate cancer therapy. The emergence of gonadrotropin releasing hormone (GnRH) analogues has enabled effective chemical castration of patients with metastatic prostate cancer.[6] In addition, antiandrogens such as bicalutamide offer direct competitive antagonism of the androgen receptor.[7] Metastatic prostate cancer is typically responsive to castration: a vast majority of patients respond to ADT with declines with their tumor burden, as evidenced by decreased serum prostate-specific antigen (PSA) levels.[8] Importantly, ADT is effective in relieving symptoms from metastatic prostate cancer but does not improve overall survival.[9-11] Despite an initial response of prostate cancer to ADT, ADT inevitably fails and disease recurs. Prostate cancer refractory to ADT is termed castration resistant prostate cancer (CRPC).[12] In 2004, a landmark study established that CRPC is still driven by the androgen receptor,[13] and

TABLE 2. **Clinical trials evaluating new therapeutics in patients with metastatic prostate cancer**

	Phase I	Phase II	Phase III	FDA approval	
Androgen receptor					
MDV3100			NCT00974311 (AFFIRM)	8/31/12	Completed, has results
ARN-509		NCT01171898			Active, not recruiting
Androgen production					
Abiraterone			NCT00638690 (COU-301)	4/28/11	Completed, has results
TAK-700			NCT01193257 (ELM-PC 5 (C21005))		Completed, has results
TOK-001		NCT01709734 (ARMOR2)			Active, recruiting
Targeted therapy					
OGX-111			NCT01578655 (AFFINITY)		Active, recruiting
OGX-111			NCT01188187 (SYNERGY)		Active, not recruiting
OGX-111			NCT01083615		Active, not recruiting
OGX-427		NCT01681433 (Pacific)			Active, recruiting
Immunologic					
Sipuleucel-T			NCT00065442 (IMPACT)	4/29/10	Completed, has results
Prostvac			NCT01322490 (BNIT-PRV-301)		Active, recruiting
Ipilimumab			NCT01057810		Active, not recruiting
Ipilimumab			NCT00861614		Active, not recruiting
Radiopharmaceuticals					
Radium 223			NCT00699751	5/15/13	Completed, has results
Tyrosine kinase inhibitors					
Cabozantinib			NCT01605227 (COMET-1)		Active, recruiting
Cabozantinib			NCT01522443 (COMET-2)		Active, recruiting

established the rationale for more effective therapeutic agents targeting the androgen receptor. In addition, despite castrate levels of circulating serum androgens, the local tumor milieu was noted to be replete with androgen.[14,15] These studies led to the development of therapeutic agents targeting both systemic and intratumoral synthesis of androgens. Since the androgen receptor signaling is active in CRPC, several new agents recently FDA approved or in development target the androgen receptor activation by one of three mechanisms:

1. Direct androgen receptor antagonists: Enzalutamide (FDA approved) and ARN-509 (in clinical trials)
2. Androgen biosynthesis inhibitors: Abiraterone (FDA approved), TAK-700 (in clinical trials)
3. Androgen receptors coactivators: OGX-111 and OGX-427 (in clinical trials)

Direct androgen receptor antagonists

Enzalutamide

Enzalutamide is an oral androgen-receptor–signaling inhibitor that inhibits nuclear translocation of the androgen receptor hormone complex, DNA binding, and coactivator recruitment, and induces cell apoptosis. Enzalutamide has a higher affinity for the androgen receptor than bicalutamide.[16] Phase II clinical studies showed antitumor effects at all doses, but maximum tolerated dose was set to 240 mg per day, with a higher frequency of seizures and grade 3 fatigue noted at the 320 mg per day dose.[17] In the AFFIRM phase III clinical trial (NCT00974311), enzalutamide showed an improvement in overall survival by 4.8 months over placebo (18.4 months versus 13.6 months, $p < 0.001$) in patients with metastatic prostate cancer previously

treated with docetaxel [NCT00974311].[18] Enzalutamide does not require concomitant steroid administration. At the dosage of 160 mg per day seizures were encountered in 0.9% of patients receiving enzalutamide.[19] Based on the data from the AFFIRM trial, enzalutamide received FDA approval for administration in the post-docetaxel setting. A second phase III study (PREVAIL) was developed to investigate the utility of enzalutamide in a docetaxel naïve setting [NCT01212991]. The study showed a 29% reduction in risk of death (HR = 0.706, $p < 0.0001$) and an 81% reduction in the risk of radiographic progression (HR = 0.186, $p < 0.0001$) when enzalutamide was compared to placebo. Enzalutamide also delayed time to chemotherapy by 17 months (HR = 0.35, $p < 0.0001$) when compared to placebo.[20] Currently, enzalutamide is awaiting FDA approval for the pre-docetaxel setting.

ARN-509

Like enzalutamide, ARN-509 is an oral competitive androgen receptor antagonist that impairs androgen receptor binding to DNA and androgen receptor target gene modulation, and induces cell apoptosis. ARN-509 has a slightly higher affinity for the androgen receptor than enzalutamide[21] and showed a greater efficacy than enzalutamide in a murine xenograft model of human CRPC.[16] In a phase I clinical study, ARN-509 was safe and well-tolerated across all dose levels, with a minimum effective dose projected to be > 180 mg/day. Unlike enzalutamide, no seizures were noted. Dosage of 240 mg/day was selected for phase II studies, with a primary endpoint of PSA response at 12 weeks, and secondary endpoints evaluating antitumor effects and changes in circulating tumor cells (CTC) [NCT01171898]. The three treatment arms in the phase II study included: 1) non-metastatic CRPC which is chemotherapy and abiraterone naïve; 2) metastatic CRPC which is chemotherapy and abiraterone naïve; 3) metastatic CRPC recurrent after abiraterone treatment. A second phase II clinical trial is underway with an estimated primary completion date in 2015 [NCT01790126] that will evaluate the utility of ARN-509 dosed at 240 mg/day in the setting of hormone sensitive prostate cancer with the primary quality-of-life endpoint measures.

Androgen biosynthesis inhibitors

Abiraterone

Abiraterone-acetate, a prodrug for abiraterone, is a cytochrome P450 c17 (CYP17) inhibitor, blocking androgen synthesis by the adrenal glands, testes, and within the prostate tumor in a ligand-dependent fashion.[22] In the initial phase III clinical trial [Cou-301, NCT00638690], abiraterone in combination with prednisone showed an improvement in overall survival by 3.9 months over placebo-matched controls in a post-docetaxel setting (14.8 months versus 10.9 months, $p < 0.001$) and all secondary endpoints confirmed superiority.[23] Abiraterone required concomitant administration of steroids. These data led to FDA approval for abiraterone for the post-docetaxel setting. A follow up phase III clinical trial [Cou-302: NCT00887198] in the pre-docetaxel setting also showed that abiraterone improved radiographic progression-free survival (16.5 months versus 8.3 months, $p < 0.001$), showed a trend toward improved overall survival (median not reached, versus 27.2 months, hazard ratio, 0.75; 95% CI, 0.61 to 0.93; $p = 0.01$) and significantly delayed initiation of chemotherapy in patients with metastatic CRPC.[24] Currently, abiraterone is FDA approved in the pre-docetaxel setting.

TAK-700

TAK-700 selectively inhibits the 17,20-lyase activity of CYP17A1, and generally does not lead to secondary mineralcorticoid excess that is seen in abiraterone-acetate, and may permit steroid-free dosing. In a phase I/II study [NCT00569153], 96 patients with metastatic CRPC in a chemo-naïve setting received TAK-700 at various dosing intervals with and without prednisone supplementation. The study was limited by a large percentage of patients (50%) due to either adverse events (AEs) or disease progression. In decreasing order of frequency, the most common AEs were fatigue (72%), nausea (44%), and constipation (31%).[25] PSA response rates (≥ 50% decrease) at 12 weeks were significant with 63% (300 mg BID), 52% (400 mg BID + prednisone), 41%(600 mg BID + prednisone), and 62% (600 mg QD) in their respective groups.[26]

In a July 2013 press release, Takeda Pharmaceuticals announced that the ELM-PC 5 phase 3 study [NCT01193257] was unblinded based on the recommendation of the Independent Data Monitoring Committee (IDMC). Overall survival would likely not be significant in the Orteronel plus prednisone when compared to the control arm (HR 0.894, $p = 0.23$). There was, however, a significant improvement in radiographic progression-free survival (rPFS) in the Orteronel plus prednisone arm over the control arm (HR 0.755, $p = 0.0003$).[27] Currently, there are four active phase III clinical trials investigating TAK-700.

TOK-001

TOK-001, formerly known as VN/124-1, inhibits prostate cancer growth by 17A-hydroxylase/17,20-lyase (CYP17) inhibition and down-regulation of

wild type and mutant androgen receptor protein expression.[28-30] Phase I clinical studies [NCT00959959] resulted in > 50% PSA decline in 11/49 patients (22%) and an additional 13/49 (26%) had 30%-50% declines. Thirty-six of 49 (74%) patients completed 12 weeks of the study but early discontinuation was seen in 13 of 49 (26%) patients for toxicity (6/13), progression (5/13), or withdrawal of consent (2/13). The maximal tolerated dose was not reached in this study. TOK-001 is currently being reformulated with potential phase II clinical trials planned in the near future.[31] Additional modifications to exploit the chemical framework of TOK-001to create novel potent/efficacious androgen receptor degrading agents (ARDAs) are underway.[32]

Targeted therapy against androgen receptor coactivators

OGX-111

Clusterin (CLU) is a stress-induced androgen-receptor regulated cytoprotective chaperone that is upregulated in cell death. Increased concentrations confer treatment resistance in experimental and clinical studies.[33,34] Custirsen, a second-generation antisense oligonucleotide (ASO), has high affinity for CLU RNA, and has been shown to suppress CLU levels.[35,36] Treatment with custirsen increased tumor cell death and improved chemosensitivity to multiple drugs, including docetaxel and mitoxantrone, in preclinical CRPC prostate cancer models. In a phase II clinical study [NCT00258388], men with metastatic CRPC with disease progression after two or more cycles of first line docetaxel-based therapy showed improvements in overall survival, although not statistically significant, when custirsen was combined with docetaxel and prednisone, compared to docetaxel and prednisone alone (23.8 months versus 16.9 months).[37] Currently, there are three randomized phase III clinical trials underway evaluating the utility of OGX-111 in combination with chemotherapy.

OGX-427

Heat Shock Protein 27 (Hsp27) is a chaperone protein that regulates cell signaling and survival pathways involved in cancer progression and is uniformly expressed in metastatic CRPC.[38] Its expression is induced by hormonal withdrawal and/or chemotherapy, and inhibits treatment induced apoptosis through multiple mechanisms.[39,40] In prostate cancer, Hsp27 complexes with androgen receptor and enhances transactivation of androgen receptor-regulated genes.[41] OGX-427 is a 2nd generation antisense oligonucleotide that inhibits Hsp27 expression. Phase I clinical studies showed that the drug was well tolerated [NCT00487786]. In a phase II clinical study investigating the utility of OGX-427 in chemotherapy-naïve patients, patients with minimal symptoms were randomized to receive OGX-427 weekly with prednisone or prednisone only [NCT01120470]. In the OGX-427 plus prednisone arm, 71% of patients were progression-free at 12 weeks, compared to 33% in the prednisone only arm. 41% of patients who received OGX-427 plus prednisone experienced a > 50% decline in PSA, versus 20% of patients who received prednisone alone.[42] A separate phase II clinical trial is investigating the utility of OGX-427 in combination with abiraterone versus abiraterone alone, and is in active recruitment with estimated completion date listed as June 2015 [NCT01681433].

Immunologic therapies

Immunologic therapies offer an alternative approach for patients with CRPC. Indeed, sipuleucel-T was the first of the new generation of FDA-approved agents against metastatic CRPC in April 2010. These immunomodulatory agents offer the potential for long term therapeutic responses against CRPC.

Sipuleucel-T

Sipuleucel-T is a personalized antigen presenting cell-based immunotherapy product that showed a 4.1 month improvement in overall survival (25.8 months versus 21.7 months, hazard ratio for death in the sipuleucel-T group, 0.78; 95% confidence interval [CI], 0.61 to 0.98; p = 0.03) in a phase III clinical trial [NCT00065442].[43] Sipuleucel-T is FDA approved for metastatic prostate cancer across all stages. However patients treated with sipuleucel-T show an absence in significant difference of objective tumor disease progression,[44,45] Despite early approval of sipuleucel-T, it has failed to gain widespread traction and marketshare.[46]

Prostvac-VF

Prostvac-VF is a prostate cancer vaccine approach consisting of a recombinant vaccinia vector as a primary vaccination, followed by multiple recombinant fowlpox booster vaccinations.[47] Phase II studies showed an increase in OS (25.1 months versus 16.6 months, p = 0.0061), but no statistically significant difference in the median progression-free survival (3.8 months versus 3.7 months, p = 0.60). These results mirror those seen with sipuleucel-T and follow a trend of improved overall survival without a change in measurable tumor response.[48] A phase III trial with an estimated primary completion date at the end of 2015 is investigating the use of Prostvac-VF in 1200 men

with chemotherapy-naïve metastatic prostate cancer allocated to one of three treatment arms; (Arm V+G) PROSTVAC-V/F plus adjuvant dose GM-CSF, (Arm V) PROSTVAC-V/F plus GM-CSF placebo, (Arm P) double placebo [NCT01322490].

Ipilimumab

Ipilimumab is a monoclonal antibody blocking the immune checkpoint molecule cytotoxic T-lymphocyte antigen-4 (CTLA-4). Ipilimumab has shown a survival advantage in melanoma,[49] but the utility in prostate cancer has yet to be established. Several phase I/II clinical studies have evaluated ipilimumab in combination with GVAX, PROSTVAC, docetaxel, and radiotherapy, with promising results.[50-53] Currently, there are two phase III clinical trials investigating the utility of ipilimumab. The first study [NCT00861614] evaluated ipilimumab versus placebo following radiotherapy in post docetaxel metastatic CRPC patients. Preliminary results were released by Bristol-Myers Squibb showing that the primary endpoint of overall survival was not met (HR = 0.85; 95% CI = 0.72-1.00; p = 0.053).[54] The final results were released at the 2014 Genitourinary Cancers Symposium which showed that an improvement in progression free survival (HR = 0.70; 95% CI = 0.61-0.82) and a reduction in the PSA level by 50% or more (13.1% versus 5.3%).[55] The second [NCT01057810] is comparing the efficacy of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naïve castration resistant prostate cancer.

Tyrosine kinase inhibitors

The utility of tyrosine kinase inhibitors (TKI) and vascular endothelial growth factor (VEGF) inhibitors have been shown to improve survival in many different types of cancers.[56-58] The utility of this modality of treatment is currently being investigated in the field of metastatic CRPC.

Cabozantinib

Cabozantinib is an oral tyrosine kinase inhibitor with specific activity against MET and VEGF receptor 2 (VEGFR2). In a phase II randomized discontinuation trial, progression free survival was improved in the cabozantinib arm when compared to placebo (23.9 weeks versus 5.9 weeks, $p < 0.001$). Using response evaluation criteria in solid tumors (RECIST) criteria, 5% of patients showed a partial response, 75% showed stable disease, and 11% showed disease progression to treatment. One hundred forty-nine patients showed evidence of bone metastases at baseline and of these patients, 12% showed complete resolution, 56% showed partial resolution, 28% showed stable disease, and 3% showed progressive disease in response to treatment with cabozantinib.[59] Currently, there are two phase III studies evaluating the utility of cabozantinib in metastatic CRPC. The first trial [COMET-1; NCT01605227] is a randomized double-blind trial of patients with metastatic CRPC who progressed on docetaxel and either abiraterone or MDV3100 independently. The study will compare cabozantinib to prednisone with the primary endpoint being overall survival and secondary endpoints being bone scan response. This study has completed accrual and is currently awaiting planned analyses. The second trial [COMET-2; NCT01522443] is another randomized double-blind trial of patients with metastatic CRPC who progressed on docetaxel and either abiraterone or MDV3100. The study will compare cabozantinib to mitoxantrone plus prednisone with the primary endpoint of pain response. Secondary endpoints include bone scan response and overall survival. The study has an estimated primary completion date in June 2014.

Radiopharmaceuticals

Radiopharmaceuticals such as strontium-89 (89Sr) and samarium-153 (153Sm) ethylene diamine tetramethylene phosphonate (EDTMP), are beta-emitting radioisotopes and have long been used for palliation of bone pain in metastatic prostate cancer.[60] This mode of treatment is governed by the dose-limiting toxicity of myelosuppression. In comparison to a beta-emitting radioisotope, an alpha-emitting radioisotope has a much higher linear energy transfer (LET) and subsequently has a smaller influence on the surrounding bone marrow and an increased anti-tumor effect. These phenomena explain the decreased bone marrow toxicity and improved overall survival recently exhibited in alpha-emitting radioisotopes.[61]

Radium 223

Radium 223 is a novel alpha-particle–emitting radiopharmaceutical targeting bone metastases. In a phase III clinical study of patients with progressive, symptomatic metastatic CRPC with ≥ 2 bone metastasis, radium 223 showed improvement in overall survival when compared to placebo by 3.7 months (14.9 months versus 11.2 months, $p < 0.001$)[NCT00699751]. Additionally, time to first skeletal related event was significantly delayed in the radium 223 treatment arm when compared to placebo (15.6 months versus 9.8 months, $p < 0.001$).[62] Radium 223 represents a unique therapeutic option for metastatic prostate cancer and will likely find a role in the management in CRPC patients with metastatic bone lesions.

Conclusion

Building on decades of research, the past few years have yielded a near exponential increase in treatment modalities for patients with metastatic prostate cancer. Individually, these improvements in overall survival may appear modest, however, nearly all of them have a distinct mechanism of action and the possibility of synergistic effects have yet to be established. Going forward, the promise of a durable impact on the mortality from metastatic prostate cancer will likely stem from further elucidation of molecular pathways involved in prostate cancer, as well as defining the optimal sequence of treatment for patients with metastatic prostate cancer.

Disclosure

Drs. Gregory R. Thoreson, Bishoy A. Gayed and Paul H. Chung have no potential conflict of interest.
Dr. Ganesh Raj has served on Speaker/Advisory boards of Bayer, Janssen, Medivation, Astellas and Merck. 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. □

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