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Collaborative Review – Prostate Cancer

New Therapies for Castration-Resistant Prostate Cancer: Efficacy and Safety

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Abstract

Context: Prostate cancer (PCa) is the most common noncutaneous malignancy and the second leading cause of cancer mortality amongst men in the Western world. Up to 40% of men diagnosed with PCa will eventually develop metastatic disease, and although most respond to initial medical or surgical castration, progression to castration resistance is universal. The average survival for patients with castration-resistant prostate cancer (CRPC) is 2–3 yr.
Objective: To discuss the biologic rationale and evidence supporting current management of patients with CRPC and to review promising novel agents.
Evidence acquisition: Electronic databases (PubMed, ClinicalTrials.gov), relevant journals, and conference proceedings were searched manually for preclinical studies, clinical trials, and biomarker analyses focused on the treatment of CRPC. Keywords included *castrate resistant prostate cancer and: targeted therapy, novel therapy, immunotherapy, androgen therapy, bone therapy, mechanisms, biomarkers,* and *trial endpoints;* no time range was specified. Information pertaining to current studies was discussed with key opinion leaders.
Evidence synthesis: We focus on the efficacy and safety of approved agents, promising therapies that have proceeded to phase 3 evaluation, and those that have enhanced our understanding of the biology of CRPC. Biomarkers are considered in the context of novel targeted agents and immunotherapy.
Conclusions: CRPC has many targets. Four new agents with different mechanisms of action have recently been shown to have positive results in large phase 3 randomized trials, and have already been approved in the United States for CRPC: cabazitaxel, sipuleucel-T, denosumab, and abiraterone acetate. With our improved understanding of tumor biology and the incorporation of new prognostic and molecular biomarkers into clinical trials, we are making progress in the management of patients with CRPC.
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1. Introduction

Prostate cancer (PCa) is the most common noncutaneous malignancy and a leading cause of cancer mortality in men in the Western world, accounting for an estimated 94 000 deaths in Europe in 2008 and 32 050 deaths in the United States in 2010 [1]. Although <5% of patients present with metastatic disease, up to 40% of men eventually develop metastases despite local therapy [2]. Metastases are frequently osseous, can cause substantial pain, and increase risk for fractures and other skeletal related events (SREs). Once metastases have developed, PCa is incurable and all therapy is palliative.

Surgical or medical castration is highly effective in shrinking tumor burden, decreasing prostate-specific antigen (PSA) levels, enhancing quality of life, and improving survival [2]. However, most patients will eventually experience disease progression despite castration, with a median duration of response of 12–24 mo [2]. Although some patients will respond initially to secondary hormonal manipulations, castration-resistant prostate cancer (CRPC) will inevitably develop [2].

Following hormonal manipulations, cytotoxic chemotherapy had been the only therapy shown to improve survival for patients with CRPC [3–5]. In 1996, mitoxantrone was the first chemotherapy to show a palliative benefit for patients with CRPC in combination with steroids compared with steroids alone (29% vs 12%; $p = 0.01$) [6]. Although no survival benefit was seen with mitoxantrone in two phase 3 trials [6,7], it was the first chemotherapy to be approved by the US Food and Drug Administration (FDA) for the treatment of men with CRPC. In the late 1990 s, the microtubule-stabilizing taxane agents showed promise in preclinical and early phase clinical trials. Based on these results, docetaxel was prospectively evaluated in two phase 3 clinical trials. In Southwest Oncology Group (SWOG) 9916, docetaxel administered every 3 wk in combination with estramustine was compared with mitoxantrone plus prednisone; there was a 27% increase in progression-free survival (PFS), a 55% increase in objective response rate (ORR), and 1.9-mo improvement in median overall survival (OS) favoring docetaxel plus estramustine (17.5. mo vs 15.6 mo; $p = 0.02$) [4]. In TAX327, patients with CRPC received two different schedules of docetaxel (weekly or every 3 wk) plus prednisone or mitoxantrone with prednisone [3]. There again was a survival benefit favoring docetaxel every 3 wk compared to mitoxantrone (OS: 19.2 mo vs 16.3 mo; $p = 0.009$), but no significant difference in survival was seen with weekly docetaxel (median survival: 17.8 mo). With long-term follow-up, there was a 21% improvement in OS in favor of docetaxel and prednisone every 3 wk [5]. Pain control and PSA-ORR (45% vs 32%) were also higher with docetaxel. Toxicity was tolerable, and although 32% of patients suffered from grade >3 neutropenia, the incidence of neutropenic fever in either study was <3%. Based on these landmark trials, docetaxel administered every 3 wk with prednisone was approved as standard front-line chemotherapy for CRPC by FDA in 2004 and the European Medicines Agency (EMA) in 2005.

Although docetaxel plus prednisone extended survival compared to mitoxantrone, the overall benefit was modest, with most patients experiencing disease progression within 7 mo. Hence, the focus since 2004 has been on trying to improve clinical outcomes by exploring alternative chemotherapy agents, novel targeted agents, and sequential and combination regimens. Within the past year, several promising agents with widely varied mechanisms of action and therapeutic targets have demonstrated efficacy, and four new drugs were FDA approved for the treatment of patients with CRPC (cabazitaxel, sipuleucel-T, denosumab, and abiraterone acetate). Our understanding of advanced PCa has changed in parallel with the expansion of our repertoire of therapeutic options (Fig. 1, Table 1).

1.1. The biology of castration-resistant prostate cancer

Identification of new therapeutic targets for CRPC has largely resulted from an improved understanding of tumor biology. Tumor-derived factors, host factors, and tumor microenvironment are all essential contributors in sustaining prostate tumor growth and progression of metastases, triggering clinical development of novel therapeutics, including those targeting hormonal signaling, angiogenesis, bone-derived factors, cell cycle checkpoints, activated tyrosine kinases, and host immune surveillance.

Although patients with CRPC have, by definition, castrate levels of circulating testosterone, most tumors continue to remain dependent on androgen and on signaling from the androgen receptor (AR). This may occur through constitutive activation of the AR (gene amplification, alternative splicing [8], AR-activating gene mutations), intratumoral production of androgen, promiscuity of the AR (and binding of other hormones), activation of downstream targets by dysregulation of transcription factors (eg, binding of the frequently rearranged and overexpressed ETS oncogenic factors to androgen-regulated promoters) [9], and alternative yet unidentified mechanisms. Preclinical research has validated these concepts, and this validation has served as the basis for the translation of novel, potent AR-targeted therapies into clinical trials. Hence, it is generally accepted that most CRPC tumors are not truly hormone refractory.

Eventually, CRPC may evolve into a truly androgen-independent (and hormone-refractory) tumor that does not express AR, PSA, or other androgen-regulated genes, and these tumors frequently display a predominance of neuroendocrine features. These AR-independent tumors, termed *anaplastic* or *neuroendocrine prostate cancer* (NEPC), typically have an aggressive clinical course, and most patients survive <1 yr [10]. The diagnosis of NEPC is often made clinically, in the setting of progressive disease despite a low PSA, visceral metastases, and/or elevated serum markers of neuroendocrine differentiation.

Our enhanced understanding of tumor biology, including the role of tumor, host, and hormonal signaling, has led to rational development of new therapies for CRPC leading to FDA and/or EMEA approval of several novel drugs with different mechanisms of action (Table 1). The purpose of

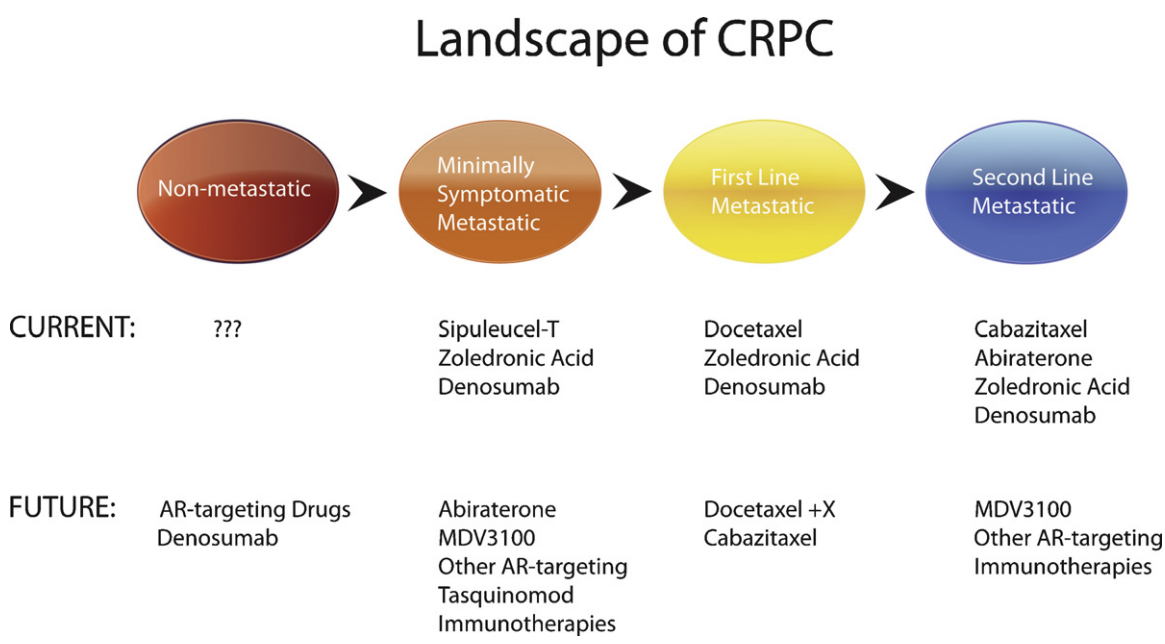

Fig. 1 – Landscape of castration-resistant prostate cancer. AR = androgen receptor.

this review is to discuss new therapies for CRPC, with an emphasis on efficacy and safety.

2. Evidence acquisition

Electronic databases, relevant journals, and conference proceedings were searched manually for preclinical studies, clinical trials, and biomarker analyses focused on the treatment of CRPC. Information pertaining to current studies was searched through trial databases and discussed with key opinion leaders.

3. Evidence synthesis

Therapies for CRPC are discussed, with a focus on efficacy and safety. Although discussing every tested agent is beyond the scope of this review, we focus on approved agents (Table 1), promising therapies that have proceeded to phase 3 evaluation (Table 2), and those that have enhanced our understanding of CRPC tumor biology. Biomarkers are considered in the context of novel targeted agents and immunotherapy.

3.1. Docetaxel combinations

Several agents have been studied in combination with docetaxel and prednisone in attempts to improve the efficacy of first-line therapy and/or decrease toxicity.

3.1.1. Docetaxel plus bevacizumab

Bevacizumab is a humanized monoclonal antibody that targets tumor angiogenesis through inhibition of vascular endothelial growth factor (VEGF) receptor. Although single-agent bevacizumab lacked significant activity in PCa, the encouraging results of combination therapies in other solid tumors led to the phase 2 Cancer and Leukemia Group B (CALGB) 90006 trial assessing bevacizumab in combination with chemotherapy [11]. Seventy-nine patients receiving docetaxel, estramustine, and bevacizumab showed an encouraging 77% PSA-ORR rate (decline $\geq$50%), time to progression (TTP) of 9.7 mo, and OS of 21 mo [11]. Based on these results, a phase 3 trial (CALGB 90401) evaluating docetaxel plus prednisone with bevacizumab versus placebo was pursued. Although there was a significant increase in PFS (9.9 mo vs 7.5 mo; $p < 0.0001$) and tumor response rate (53.2% vs 42.1%; $p = 0.01$; PSA-ORR 69.5% vs 57.9%; $p = 0.0002$), CALGB 90401 was negative for the primary end point of OS (22.6 mo vs 21.5 mo; $p = 0.91$) [12]. The addition of bevacizumab was also associated with higher morbidity, with 74.8% of patients experiencing greater than grade 3 toxicity (vs 55.3%; $p < 0.001$), and 4.4% suffered treatment-related deaths (vs 1.1%; $p = 0.001$). Toxicities associated with bevacizumab therapy include hypertension, proteinuria, bleeding, and thrombosis. Although overall a negative trial, there is some debate whether bevacizumab maintenance (and chronic VEGF suppression) may have yielded better outcomes, such as has been seen in other tumor types.

3.1.2. Docetaxel plus aflibercept (vascular endothelial growth factor trap)

Aflibercept is a soluble VEGF fusion protein composed of the extracellular domains of VEGF receptors 1 and 2 fused to the constant region of immunoglobulin G (IgG) that binds to and neutralizes VEGF. A phase 1 study of aflibercept in combination with docetaxel was safe [13], and the main grade 3–4 toxicity was hypertension (15%). Grade 2 toxicities were proteinuria (12%), epistaxis (8%), and dysphonia (2%). A

Table 1 – Approved drugs for castration-resistant prostate cancer

Drug	Versus	Author/yr	Patients	OS	PFS	PSA-ORR	Radiologic-ORR	Grade 3-4 toxicites	Other
Chemotherapy									
Mitoxantrone/ prednisone Mitoxantrone/ Hydrocortisone	Steroids	Tannock et al, 1996 [6] Kantoff et al, 1999 [7]	First-line metastatic CRPC	($p = 0.27$); 12.3 vs 12.6 ($p = 0.77$)	43 wk vs 18 wk ($p < 0.001$) 3.7 mo vs 2.3 mo ($p = 0.02$)	33% vs 22% ($p = 0.11$); 18.7% vs 16.6%	29% vs 12% ($p = 0.01$) 31% vs 27%	N/V (0.5%), myelosuppression (25%), cardiac toxicity (5 of 34 patients who received cumulative dose >100 mg/m3)	Pain improvement: 29% vs 12% ($p = 0.01$) Duration 43 wk vs 18 wk ($p < 0.001$)
Docetaxel/ prednisone Docetaxel/ estramustine	Mitoxantone/ prednisone	Tannock et al, 2004 [3] Petrylak et al, 2004 [4]	First-line metastatic CRPC	18.9 mo vs 16.5 mo ($p = 0.009$) 17.5 vs 15.6 mo ($p = 0.02$)	6.3 mo vs 3.2 mo ($p < 0.001$)	45% vs 32% ($p < 0.001$) 50% vs 27% ($p < 0.001$)	12% vs 7% ($p = 0.11$) 17% vs 11% ($p = 0.3$)	Overall: 26% vs 20%; 12.5% vs 16.1% ($p = 0.22$) Neutropenia: 32% Nausea/vomiting: 42% Cardiovascular events: 14%	Tannock et al: pain improvmeent in 35% vs 22% ($p = 0.01$) QoL improvement: 22% vs 13% ($p = 0.009$)
Cabazitaxel	Mitoxantone/ prednisone	de Bono et al, 2010 [33]	Postdocetaxel metastatic CRPC	15.1 mo vs 12.7 mo ($p < 0.0001$)	8.8 mo vs 5.4 mo ($p < 0.0001$)	39.2% vs 17.8% ($p = 0.0002$)	14.4% vs 4.4% ($p = 0.0005$)	Overall:82% vs 58% Neutropenia, febrile neutropenia, diarrhea; toxic death rate: 5% vs 2%	–
Immunotherapy									
Sipuluecel-T	Placebo	Kantoff et al, 2010 [52] Higano et al, 2009 [54]	Predocetaxel asyptomatic or minimally symptomatic metastatic CRPC Visceral metastases excluded	25.8 mo vs 21.7 mo ($p = 0.03$)	3.7 mo vs 3.6 mo ($p = 0.63$)	2.6% vs 1.3%	NR	Overall:31% vs 35% Infusion reaction: 54% Cerebrovascular event: 2.4% vs 1.8%	–
AR-targeting									
Abiraterone/ prednisone	Placebo/ prednisone	de Bono et al, 2010 [33]	Postdocetaxel metastatic CRPC	14.8 mo vs 10.9 mo ($p < 0.0001$)	5.6 mo vs 3.6 mo ($p < 0.0001$)	38% vs 10% ($p < 0.0001$)	NR	Overall: 3.8% vs 0.8% Hypokalemia: 1.3% vs 0.3% Hypertension	–
Supportive care									
Zoledronic acid	Placebo	Saad et al, 2004 [61]	CRPC with bony metastates	546 d vs 464 d ($p = 0.091$)	Same (84 d)	Same	5.2% vs 4.6% PR in bone	Hypocalcemia: 2% Renal failure: 3.3%	SRE rate: 33.2% vs 44.2% ($p = 0.021$)
Denosumab	Zoledronic acid	Fizazi et al, 2011 [62]	CRPC with bony metastates	Not significant (HR: 1.03)	Not significant (HR: 1.06)	NR	NR	Overall:66% vs 72% Osteonecrosis of jaw: 2% vs 3% Hypocalcemia: 6% vs 13%	Time to first on study SRE: 20.7 mo vs 17.1 mo ($p = 0.008$)
Strontium	Placebo	Lewington et al, 1991 [64]	CRPC with bony metastates	NR	NR	NR	NR	Myelosuppression	Pain relief: 67% vs 20% at 5 wk 22% pain free at 3 mo
Samarium	Placebo	Serafini et al, 1998 [65]	CRPC with bony metastates	NR	NR	NR	NR	Myelosuppression: 9%	Pain relief: 62–72%, with complete relief in 31% at 4 wk

OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; ORR = objective response rate; CRPC = castration-resistant prostate cancer; QoL = quality of life; NR = not reported; AR = androgen receptor; FDA = US Food and Drug Administration; PR = partial response; SRE = skeletal related event; HR = hazard ratio.

Table 2 – Ongoing phase III trials

Trial	Control	Experimental	Mechanism of action	Patients	Primary endpoint(s)	Secondary endpoints
VENICE	Docetaxel/ prednisone	Docetaxel/prednisone plus aflibercept	Soluble VEGF fusion protein comprised of extracellular domains of VEGF receptors 1 and 2 fused to IgG. Binds to and neutralizes VEGF.	Metastatic CRPC	OS	PSA, pain, SRE
MAINSAIL	Docetaxel/ prednisone	Docetaxel/prednisone plus lenalidomide	Immunomodulatory and anti-angiogenic	Metastatic CRPC	OS	PFS, RR, safety
SWOG 0421	Docetaxel/ prednisone	Docetaxel/prednisone plus atrasentan	Endothelin receptor antagonist	Metastatic CRPC with symptomatic skeletal metastases	OS, PFS	Pain, QOL, toxicity, RR, PSA-P
ENTHUSE 33	Docetaxel/ prednisone	Docetaxel/prednisone plus zibotentan	Endothelin receptor antagonist	Metastatic CRPC	OS	PFS, safety, SRE, PSA-P, pain, QOL, RR
READY	Docetaxel/ prednisone	Docetaxel/prednisone plus dasatinib	SRC kinase inhibitor (targets stromal–epithelial interactions)	Metastatic CRPC	OS	Change in urinary N-telopeptide, SRE, pain, PSA-P, safety
SYNERGY	Docetaxel/ prednisone	Docetaxel/prednisone plus OGX-11	Antisense oligonucleotide that inhibits clusterin (cell survival protein)	Metastatic CRPC	OS	PFS, safety, PSA-RR
SATURN	Docetaxel/ prednisone	Docetaxel/prednisone plus OGX-11	Antisense oligonucleotide that inhibits clusterin (cell survival protein)	Metastatic CRPC	Pain	Time to pain progression, safety
PROSELICA	Cabazitaxel 20 mg/m^2 plus prednisone	Cabazitaxel 25 mg/m^2 plus prednisone	Taxane chemotherapy (discrupts microtubule function)	Metastatic CRPC post-docetaxel	OS	PFS
FIRSTANA	Docetaxel/ prednisone	Cabazitaxel 25 mg/m^2 or 20 mg/m^2 / prednisone	Taxane chemotherapy (discrupts microtubule function)	Metastatic CRPC	OS	PFS
NCT0123431	Placebo	Tasquinimod	Anti-angiogenic	Asymptomatic or minimally symptomatic metastatic CRPC	PFS	
COU-AA-302	Placebo/ prednisone	Abiraterone acetate/ prednisone	CYP17 inhibitor (inhibits androgen biosynthesis)	Chemotherapy Naïve Asymptomatic or minimally symptomatic metastatic CRPC	OS, PFS	
AFFIRM	Placebo	MDV3100	Inhibits androgen receptor binding, translocation to nucleus, and DNA binding	Metastatic CRPC post-docetaxel	OS	
PREVAIL	Placebo	MDV3100	Inhibits androgen receptor binding, translocation to nucleus, and DNA binding	Chemotherapy naïve metastatic CRPC	OS, PFS	SRE, time to initiation of cytotoxic chemotherapy
C21005	Placebo/ prednisone	TAK-700/prednisone	Inhibits 17,20 lyase (androgen biosynthesis)	Metastatic CRPC post-docetaxel	OS	PSA-RR, pain, radiologic PFS
C21004	Placebo/ prednisone	TAK-700/prednisone	Inhibits 17,20 lyase (androgen biosynthesis)	Chemotherapy naïve metastatic CRPC	Radiologic PFS, OS	PSA-RR, changes in CTC count, time to pain progression
PROSPECT	Placebo	PROSTVAC +/- GM-CSF	Recombinant vaccinia viral cassette that expresses PSA gene and costimulatory molecules, followed by fowlpox booster.	Asymptomatic or minimally symptomatic chemotherapy naive metastatic CRPC	OS	PFS, pain, initiation of chemotherapy
CA-184-095	Placebo	Ipilumimab	Human monoclonal antibody that blocks CTLA-4 (T cell receptor)	Asymptomatic or minimally symptomatic chemotherapy naive metastatic CRPC	OS	PFS, TTP, time to non-hormonal therapy, safety
CA-184-043	Placebo	Ipilumimab	Human monoclonal antibody that blocks CTLA-4 (T cell receptor)	Metastatic CRPC post-docetaxel	OS	PFS, pain, safety
'147	Placebo	Denosumab	Monoclonal antibody against RANKL (protein that promotes boen resorption)	Non-metastatic CRPC	Bone metastasis-free survival	Time to occurrence of bone metastases, OS
ALASYMPCA	Placebo	Radium-223	Radioisotope that emits alpha radiation	Metastatic CRPC with symptomatic skeletal metastases	OS	Time to disease event, PSA-P, TTP in total ALP, safety, QOL

VEGF = vascular endothelial growth factor; IgG = immunoglobulin G; CRPC = castration-resistant prostate cancer; OS = overall survival; PSA = prostate-specific antigen; SRE = skeletal related event; PFS = progression-free survival; ORR = objective response rate; SWOG = Southwest Oncology Group; QoL = quality of life; CTC = circulating tumour cell; TTP = time to progression; RANKL = receptor activator of nuclear factor-κB ligand; ALP = alkaline phosphatase.

phase 3 trial of docetaxel and prednisone with or without aflibercept has completed accrual [14]. The primary end point is an improvement in OS.

3.1.3. Docetaxel plus lenalidomide

Thalidomide is an immunomodulatory agent that inhibits angiogenesis and has demonstrated efficacy in combination with weekly docetaxel for patients with CRPC, with a significant improvement in 18-mo OS compared to docetaxel alone seen in a randomized phase 2 trial of 60 patients with CRPC (69.3% vs 47.2%; $p < 0.05$) [15]. Side effects included gastrointestinal toxicity and depression, and the incidence of thromboembolism was significantly higher with the addition of thalidomide (20% venous thromboembolism, 7% transient ischemic attack, and none seen with docetaxel alone). Lenalidomide, a more potent immunostimulatory and antiangiogenic derivative of thalidomide, demonstrated manageable toxicity in combination with docetaxel in phase 1 evaluation, with a PSA-ORR of 47% in chemotherapy-naïve patients and 50% in previously treated patients [16]. Based on these findings, a phase 3 trial comparing docetaxel plus prednisone versus docetaxel, prednisone, and lenalidomide has begun enrollment [17].

3.1.4. Docetaxel plus endothelin receptor antagonists

Endothelins are peptides produced both by the tumor and the microenvironment, are overexpressed in CRPC, and facilitate formation of blastic metastases in preclinical models. A phase 1 trial of atrasentan, an endothelin receptor antagonist, was safe and suggested antitumor activity as well as improved pain control for patients with CRPC [18]. However, two subsequent phase 3 trials were negative for PFS benefit [19,20]. Exploratory analyses suggested that men with bone metastases potentially derived the greatest benefit; thus, a phase 3 trial evaluating docetaxel plus prednisone with or without atrasentan in patients with bony metastases (S0421) was launched and has completed accrual [21]. Zibotentan, another endothelin receptor antagonist, initially demonstrated an OS benefit for mildly symptomatic metastatic CRPC in a randomized phase 2 trial compared to placebo [22], although this significance was lost at longer follow-up (23.9 mo versus 19.9 mo; $p = 0.1$). Based on initial OS data, three phase 3 trials were launched. A phase 3 trial of docetaxel with or without zibotentan (ENTHUSE M1C) has completed accrual [23], but the phase 3 trials of zibotentan versus placebo in asymptomatic metastatic and nonmetastatic, chemotherapy-naïve CRPC were subsequently halted because of inactivity. Endothelin receptor antagonists are generally well tolerated but have been associated with an increased incidence of cardiac problems and even myocardial infarction (MI), especially in patients with underlying heart disease.

3.1.5. Docetaxel plus tyrosine kinase inhibitors

Several activated tyrosine kinases have been implicated in promoting prostate tumor growth and survival, and phase 2 trials evaluating various small-molecule tyrosine kinase inhibitors in combination with or following docetaxel chemotherapy have been conducted. Two agents have proceeded to phase 3 evaluation (dasatinib and sunitinib). Dasatinib, a potent inhibitor of the Src (sarcoma) family of kinases that targets stromal–epithelial interactions, has demonstrated efficacy in combination with docetaxel and prednisone in phase 1/2 evaluation, with a 49% PSA-ORR, 42% partial soft tissue ORR, and a 28% reduction in bony metastases [24]. Three of 16 patients (18.7%) evaluated experienced grade >3 toxicity, including one pleural effusion. The most common grade 1/2 toxicities were fatigue, dysgeusia, diarrhea, and skin disorders. A phase 3 trial of dasatinib in combination with docetaxel has completed recruitment, and results are pending (the READY trial) [25]. The phase 3 trial evaluating sunitinib, a multitargeted VEGF and platelet-derived growth factor inhibitor, in combination with prednisone versus placebo/prednisone for men with CRPC who have progressed after docetaxel was recently halted at interim analysis because of lack of efficacy (the SUN trial).

3.1.6. Docetaxel plus OGX-011

OGX-011 is a second-generation antisense oligonucleotide that inhibits production of clusterin, a cell survival protein overexpressed in CRPC and associated with disease progression and treatment resistance. In a randomized phase 2 trial of first-line docetaxel with or without OGX-011, OS was dramatically improved with the combination (23.8 mo vs 16.0 mo; hazard ratio [HR]: 0.61); on multivariate analysis, patients treated with docetaxel plus OGX-011 had a 51% lower death rate than patients treated with docetaxel alone (HR: 0.49; $p = 0.012$) [26]. Grade ≥3 adverse events were similar overall in both groups, except for a higher incidence of lymphopenia with OGX-11 combination (50% vs 22%). Grade 1–2 neuropathy, fevers, chills, and elevated creatinine were also more common with OGX-011. Two phase 3 trials of docetaxel with or without OGX-011 are under way (SYNERGY [27] and SATURN [28]). One of these trials focuses on survival and the other on symptom relief.

3.1.7. Docetaxel plus DN-101

Calcitriol, the principal metabolite of vitamin D, demonstrated antitumor effects and synergy with docetaxel in preclinical models [29]. In a randomized phase 2 trial (ASCENT-1), high-dose calcitriol (DN-101) in combination with weekly docetaxel did not significantly improve PSA-ORR compared to weekly docetaxel plus placebo (63% vs 52%; $p = 0.07$) but did improve OS (24.5 mo vs 16.4 mo) [30]. Based on this result, a phase 3 trial was performed to compare DN-101 plus weekly docetaxel versus docetaxel every 3 wk (ASCENT-2). Of the 953 men enrolled, there were increased deaths in those who received DN-101 (OS: 16.8 mo vs 19.9 mo; $p = 0.01$) [31]. The inferior survival and increased side effects, such as thromboembolic events, are difficult to explain. This study is also an example of how large, randomized phase 2 trials can often be poor predictors of results in phase 3 trials.

In summary, no combination to date has been proven in phase 3 evaluation to enhance the activity of docetaxel and prednisone as first-line chemotherapy for men with CRPC. It is worth noting that patients are doing better with standard

docetaxel plus prednisone than was historically seen (eg, OS of docetaxel plus prednisone was 21.5 mo in CALGB 90401 vs 19.2 mo in TAX327), perhaps because of better patient selection and earlier initiation of chemotherapy.

3.2. Other cytotoxic chemotherapies

3.2.1. Cabazitaxel

Cellular resistance to taxanes, among other mechanisms, is mediated by P-glycoprotein multidrug resistance or microtubule alterations, and resistance to one taxane does not confer complete clinical resistance to other taxane agents. In addition, patients who stop responding to docetaxel may respond again when reintroduced at a later date, suggesting that resistance may also be overcome with time [32]. Cabazitaxel is a potent taxane with activity in docetaxel-resistant preclinical models; it also has low affinity for P-glycoprotein. The TROPIC trial, a phase 3 trial comparing cabazitaxel and prednisone to mitoxantrone plus prednisone for patients with CRPC who had progressed after first-line docetaxel, led to FDA approval of cabazitaxel as postdocetaxel therapy for CRPC in 2010 [33]. There was a 30% reduction in risk of death (HR: 0.70; $p < 0.0001$) and a 2.4-mo improvement in median OS favoring cabazitaxel (15.1 mo vs 12.7 mo). Grade 3/4 toxicities included neutropenia (81.7%), febrile neutropenia (7.5%), infections (10.2%), vomiting (1.9%), and diarrhea (6.2%). Deaths resulting from adverse events were 4.9% with cabazitaxel (primarily because of neutropenia) compared to 1.9% with mitoxantrone. Of note, the dose of cabazitaxel in the TROPIC trial was higher than was recommended from phase 1 evaluation (25 mg/m^2 vs 20 mg/m^2), and a follow-up phase 3 trial is now planned to directly compare cabazitaxel 25 mg/m^2 and 20 mg/m^2. Another phase 3 trial will evaluate cabazitaxel in the first-line setting versus docetaxel.

3.2.2. Epothilones

The epothilone derivatives—ixabepilone, patupilone, and sagopilone—act similar to taxanes in their microtubule-stabilizing effects, and each has been evaluated in phase 2 trials as second-line therapy for patients with CRPC progressing on docetaxel [34]. PSA-response rates were modest at approximately 20–45%, and phase 3 trials are not being pursued. Major toxicities related to epothilones include neutropenia, fatigue, diarrhea, and neuropathy, with grade 3/4 adverse events occurring in approximately 45% of patients.

3.2.3. Platinum chemotherapy

Satraplatin, an orally administered platinum agent, underwent phase 3 evaluation as a second-line therapy in combination with prednisone versus prednisone and placebo for patients who progressed after one line of chemotherapy. The trial showed a 46% improvement in the time to pain relief, a 33% increase in PFS (HR: 0.69; $p < 0.00001$), and PSA and tumor ORR (25% vs 12%; $p = 0.00007$; 7% vs 1%; $p < 0.002$) but no statistically significant improvement in OS (14.3 mo vs 14.3 mo; HR: 0.98; $p = 0.80$) [35]. FDA declined to approve satraplatin for men with CRPC on the basis of these results.

Carboplatin has also been combined with taxanes (docetaxel, paclitaxel) as a second-line therapy in several phase 2 trials, with a PSA-ORR of approximately 20%, duration of response of 6 mo, PFS of 3 mo, and OS of 12 mo [36]. Because neuroendocrine differentiation and progression to pure NEPC may occur in late-stage CRPC, many hypothesize that this subgroup of patients might benefit from platinum therapy. An ongoing phase 2 trial is evaluating carboplatin and docetaxel for patients with known or suspected anaplastic or NEPC [37].

3.3. Tasquinimod

Tasquinimod is an orally administered antiangiogenic drug that significantly improved PFS compared to placebo in a randomized phase 2 trial of 206 metastatic CRPC patients (24.7 wk vs 12.9 wk) [38]. Side effects were rare though severe in some patients, including vascular events (ie, MI, heart failure, stroke) in 3% and deep vein thrombosis in 4% of patients receiving tasquinimod (and none seen with placebo). Other common adverse reactions were gastrointestinal issues, fatigue, and musculoskeletal pain, with greater than grade 3 toxicity seen in 38% of patients with tasquinimod (vs 10% receiving placebo). A phase 3 trial comparing tasquinimod and placebo for men with asymptomatic or minimally symptomatic metastatic CRPC prior to chemotherapy was launched in 2011 [39].

3.4. Targeting the androgen axis

Some men with CRPC may respond to multiple secondary hormonal manipulations with antiandrogens, estrogen, or ketoconazole in combination with hydrocortisone, but responses tend to be transient. Based on our recent understanding of the importance of AR signaling in CRPC, several new drugs have been developed that more potently block androgen synthesis from adrenal and intratumoral sources or inhibit androgen binding to AR and downstream signaling.

Abiraterone acetate is an inhibitor of the androgen biosynthesis enzyme CYP17 (17-α-hydroxylase and C17,20-lyase) and is more potent and selective and less toxic than ketoconazole. Several phase 2 trials have been conducted of abiraterone in combination with prednisone, with a PSA-ORR of 51–85% and durable radiologic responses seen in both chemotherapy-naïve and docetaxel-pretreated CRPC patients [40–42]. A phase 3 trial in 1195 patients of abiraterone plus prednisone versus placebo plus prednisone was conducted for patients with CRPC who previously received docetaxel. Based on a 4-mo improvement in OS found at interim analysis (14.8 mo vs 10.9 mo) as well as significant improvements in PFS (5.6 mo vs 3.6 mo) and ORR (38% vs 10%), abiraterone was FDA approved in April 2011 for metastatic CRPC post-docetaxel [31,43]. Toxicity was minimal and mainly related to mineralocorticoid excess, including fluid retention (30.5%) and hypokalemia (17.1%), but grade >3 hypokalemia (17.1%) or hypertension (1.3%)

were infrequent. Low doses of steroids (prednisone 5 mg twice daily) are added to abiraterone to optimize the safety profile [42]. A phase 3 trial of abiraterone acetate versus placebo (both plus prednisone) in men with CRPC who have not received prior chemotherapy has completed accrual [44].

MDV3100 is a potent anti-androgen that inhibits AR receptor binding, translocation to the nucleus, and DNA binding [45]. In a phase 1/2 evaluation of 140 patients, antitumor effects were seen in both chemotherapy-naïve and docetaxel-pretreated patients (PSA-ORR: 56%; soft-tissue ORR: 22%) [46]. Median TTP was 47 wk. The most common toxicity was reversible dose-dependent fatigue (11%), and the dose-limiting toxicity was seizures, though they were not observed at lower effective doses. A phase 3 trial for docetaxel-pretreated patients has completed enrollment (AFFIRM) [47], and another phase 3 trial in chemotherapy-naïve CRPC patients is ongoing (PREVAIL) [48].

TAK-700 is a selective nonsteroidal inhibitor of 17,20 lyase. Phase 1 data were encouraging, with all of the 26 treated patients achieving significant declines in PSA [49]. Of patients receiving $\geq$300 mg for three or more cycles, the PSA-ORR was 80%. Toxicities included fatigue, nausea/vomiting, constipation, and anorexia, but there were no dose-limiting toxicities. Two phase 3 studies are underway comparing TAK-700 plus prednisone versus placebo and prednisone for men with CRPC who are chemotherapy naïve [50] and in those who have progressed after docetaxel chemotherapy [51]. Other potent next-generation anti-androgens are also in clinical development, including the dual antiandrogen and CYP17 inhibitor, TOK-001.

3.5. Immunotherapies

Sipuleucel-T is a form of cellular immunotherapy consisting of autologous dendritic cells isolated from leukopheresed peripheral blood mononuclear cells and activated ex vivo with a recombinant fusion protein composed of prostatic acid phosphatase linked to granulocyte-macrophage colony stimulating factor (GM-CSF). Sipuleucel-T is infused every 2 wk for a total of three infusions and is thought to activate host antigen-specific T cells. Three phase 3 trials of sipuleucel-T compared to placebo were conducted for patients with metastatic asymptomatic or minimally symptomatic CRPC (D9901, D9902, IMPACT) [52–54]. Although not the primary endpoint for D9901 or D9002, a combined analysis of all three trials demonstrated a survival benefit; hence, sipuleucel-T was approved by FDA for this indication in 2010. Sipuleucel-T reduced the risk of death from any cause by 26.5% and extended median OS by 3.9 mo. Although OS was prolonged, the control arm had an unusually poor survival (21.7 mo), and there was no increase in either PSA-ORR or PFS. It is possible that PSA-ORR and PFS are not the best determinants of response for patients receiving immunotherapy. Lack of availability (especially in Europe), complexity of administration, and cost issues have limited clinical utilization of sipuleucel-T.

PROSTVAC-VF, a recombinant vaccinia viral expression cassette engineered to express the human *PSA* gene and costimulatory molecules, followed by a fowlpox virus booster, was designed to enhance and sustain host antitumor immune response. Three phase 1 trials demonstrated minimal toxicity, and a phase 2 trial in nonmetastatic CRPC was promising (53% PSA-PFS >6 mo and 78% metastases-free survival at 24 mo). The subsequent randomized phase 2 trial comparing PROSTVAC-VF with placebo did not meet its primary end point of PFS (TTP: 3.9 mo vs 3.7 mo), but an 8.5-mo OS benefit was seen (25.1 mo versus 16.6 mo) despite 50% patient crossover to active treatment [55]. This apparent discrepancy between PFS and OS recapitulates that seen with sipuleucel-T and again raises the question of how to measure biologic effects with immunotherapeutics. Critics suggest that it may be that we see an artifactual or overestimated OS benefit resulting from the poorer-than-expected survival seen in the control arms. A phase 3 trial to reevaluate these results has been initiated.

GVAX is a vaccine composed of inactivated PCa cell lines (PC-3, LNCaP) genetically engineered by adenoviral transfer to secrete GM-CSF, resulting in efficient tumor antigen presentation. Two phase 2 trials of GVAX in asymptomatic metastatic CRPC showed promising antitumor effects [56,57], but subsequent phase 3 trials were closed at interim analysis based on lack of efficacy. Vaccine therapies are generally well tolerated, with the most common adverse effects being infusion reaction or reversible flu-like symptoms within the first few days after treatment.

Ipilimumab is a human monoclonal antibody that blocks CTLA-4, an inducible receptor expressed by T cells that plays a role in tolerance to "self." In a randomized phase 2 trial, patients treated with ipilimumab plus androgen ablation were more likely to have undetectable PSA levels by 3 mo compared to androgen ablation alone (55% vs 38%), and significant clinical responses were also seen [58]. The most common grade 3–4 adverse events were colitis (4.5%) and diarrhea (4.5%), and 27.7% of patients experienced cutaneous changes. Preliminary data from a phase 1/2 trial in combination with radiation therapy for CRPC also suggests efficacy (21% PSA-ORR; median duration: 4.8 mo), and two phase 3 trials are underway [59,60].

3.6. Bone-targeted agents

Until recently, bisphosphonate treatment with zoledronic acid has been the only FDA-approved drug for prevention of SREs in patients with castration-resistant bone metastases, acting through inhibition of osteoclast-mediated bone resorption. In a phase 3 trial of 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases, zoledronic acid (4 mg every 3 wk) resulted in fewer SREs compared with placebo (33.2% vs 44.2%; $p = 0.021$) and also increased the median time to first SRE (488 d vs 321 d; $p = 0.009$) [61].

Denosumab, a monoclonal antibody that blocks receptor activator of nuclear factor-κB ligand (RANKL), a protein that promotes bone resorption through osteoclast activation, was FDA approved in 2010 for prevention of SREs in men with metastatic CRPC and bony metastases. A phase 3 study

of 1904 men with CRPC and bone metastases comparing denosumab (120 mg subcutaneously every 4 wk) versus zoledronic acid (4 mg intravenously [IV] every 4 wk) favored denosumab, with an increase in time to first on-study SRE (20.7 mo vs 17.1 mo; $p = 0.008$) and reduced rate of multiple SREs ($p = 0.004$) [62]. OS and TTP were similar between the groups. SREs were defined as radiation or surgery to bone, cord compression, or pathologic fracture, albeit many of them were asymptomatic and discovered by serial imaging. Adverse event rates were similar and primarily fevers, constipation, and joint pain; the incidence of hypocalcemia was 13% with denosumab (vs 6% with zoledronic acid), and osteonecrosis of the jaw was 2.3% (vs 1.3% with zoledronic acid; $p = 0.09$). Although cataracts have been associated with denosumab in non-metastatic PCa patients receiving androgen-deprivation therapy [63], cataracts were not reported in this study. Other advantages of denosumab include ease of subcutaneous administration (as opposed to IV zoledronic acid) and the lack of nephrotoxicity or need to monitor serum creatinine. Whether zoledronic acid and denosumab should be used sequentially after drug failures, duration of effect, and optimal frequency of administration remain unanswered. Notably, preliminary analysis of a phase 3 trial examining the utility of denosumab versus placebo in delaying time to bony metastases in men with nonmetastatic CRPC is reported to be positive, with a 4.2-mo difference seen, and final results are awaited to see if this will translate into improvements in patient outcome.

Strontium-89 and samarium-153 are FDA-approved bone targeting radionuclides for the treatment of pain from osseous metastases resulting from CRPC. They rely on selective uptake and prolonged retention at sites of increased osteoblastic activity and deliver local radiation through emission of beta particles. Palliation occurs within 2–3 wk after a single injection and typically lasts at least 3 mo. Phase 3 trials have demonstrated superior pain relief in 75–80% of patients compared with placebo [64,65], with primary toxicity being reversible myelosuppression. Radium-223 is a newer radioisotope that emits alpha radiation, which has higher energy and travels a shorter distance than beta emission. In a randomized phase 2 trial compared with placebo, radium-223 did not significantly affect time to SRE or pain control but did result in improved PFS (26 wk vs 8 wk) and a 41% improvement in OS (65 wk vs 46 wk). Toxicity of radium-223 was mild, with $< 1\%$ grade 4 and $< 5\%$ grade 3 hematologic toxicity. Other adverse events included nausea (33%), bone pain (30%), fatigue (26%), diarrhea (26%), vomiting (20%), and constipation (20%) [66,67]. A phase 3 trial evaluating OS of best standard of care plus either radium-223 or placebo in patients with symptomatic CRPC with bone metastases is ongoing (ALSYMPCA) [68].

3.7. Measuring efficacy and clinical biomarkers

Although clearly not a surrogate for clinical benefit or tumor response, many clinical trials consider a PSA decline $>50\%$ as a marker of response to therapy, and PSA PFS at 3 mo [69], rate of PSA decline, pain response, and tumor ORR may be associated with OS. However strategies that are not anticipated to cause substantial cell death (such as immunotherapy) may not produce declines in total PSA or changes in scans despite demonstrating a survival benefit, and other drugs may be associated with an initial rise in total PSA or tumor flare before clinical benefit is seen. Furthermore, as some tumors progress towards neuroendocrine differentiation, they may stop producing PSA. Therefore, understanding the limitations of PSA and radiographic testing and incorporating alternative biomarkers in evaluating therapeutic response are essential, especially in the era of molecularly targeted therapies.

Ninety percent of patients with metastatic CRPC have bone metastases, and they are the only site of known disease in up to 70% of cases. Unfortunately, bone scans are suboptimal in distinguishing tumor progression from response to therapy, and Response Evaluation Criteria in Solid Tumors (RECIST) considers blastic bone metastasis a nontarget lesion; therefore, they cannot be used to define progression. To address this, the Prostate Cancer Clinical Trials Working Group defines *radiologic progression* as the development of two or more new lesions on bone scan compared with a prior scan and requires additional confirmation of two additional lesions on a subsequent scan [70]. This methodology is being examined prospectively in several phase 3 trials. Functional imaging with positron emission tomography (PET) has not shown consistent results with the standard PET tracer, 18F-fluorodeoxyglucose, and is not recommended. Alternative radiolabels, such as 18F-fluoro-5α-dihydrotestosterone, a radiolabeled analogue of dihydrotestosterone, are under investigation and may be useful in the context of AR-targeted agents.

Prognostic markers in metastatic CRPC that have been reported to predict OS include pretreatment lactate dehydrogenase, PSA, alkaline phosphatase, Gleason score, performance status, hemoglobin, pain, and the presence of visceral disease [71]. Isolation of circulating tumor cells (CTC) based on epithelial surface markers and quantification using the CellSearch platform was FDA approved in 2008 as a prognostic biomarker in CRPC when measured at diagnosis and while on therapy. In 231 men with CRPC, patients who had a CTC count >5 detected in 7.5 ml of blood had an OS of 11.5 mo (unfavorable), compared to an OS of 21.7 mo in patients with CTC <5 in 7.5 ml (favorable) [72]. In addition, if on serial measurement of CTC patients converted from the unfavorable group to the favorable group on therapy, prognosis was better and similar to those patients who started in the favorable risk group. Similarly, if the CTC count converted from <5 in 7.5 ml to >5 in 7.5 ml, prognosis was worse than those who maintained a CTC <5 in 7.5 ml of blood. Several ongoing phase 3 trials have incorporated CTC end points into their trial design to prospectively validate CTCs as surrogates of response and survival.

The notion that we can effectively isolate prostate tumor cells from the circulation also led to the exciting possibility that we may be able to gain important molecular information about the underlying tumor from CTC analysis. Attard et al and others have shown that fluorescence in situ hybridization can be performed on CTCs for ERG fusion status, AR or MYC amplification, and phosphatase and

tensin homologue deletion [73]. However, several questions remain unanswered: are CTCs dormant? Are they responsible for disease relapse? What is the relationship between CTCs and the primary or metastatic tumors? Can they serve as diagnostic or predictive biomarkers? Current efforts are aimed toward developing novel microfluidic cell-capture devices designed to improve CTC yield, purity, and viability as well as our ability to perform molecular studies [74,75]. Prospective clinical trials incorporating molecular analyses using CTCs are ongoing in attempts to gain a better understanding of tumor biology and potentially identify and validate new biomarkers to help guide therapy.

4. Conclusions

CRPC has many targets. Four new agents with different mechanisms of action have recently been approved in the United States for CRPC: cabazitaxel, sipuleucel-T, denosumab, and abiraterone acetate. With our improved understanding of tumor biology and the incorporation of new prognostic and molecular biomarkers into clinical trials, we are making progress in the management of patients with CRPC.

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Study concept and design: Beltran, Beer, Carducci, de Bono, Gleave, Hussain, Kelly, Saad, Sternberg, Tagawa, Tannock.
Acquisition of data: Beltran, Beer, Carducci, de Bono, Gleave, Hussain, Kelly, Saad, Sternberg, Tagawa, Tannock.
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